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Anxiety and depressive symptoms effects on cortisol trajectories from pregnancy to postpartum: Differences and similarities between women and men

Ana Conde [a,b,*,1], Raquel Costa [c,d], Bárbara Figueiredo [b]

[a] INPP – Portucalense Institute for Human Development, Portucalense University, Porto, Portugal
[b] Psychology Research Center, School of Psychology, University of Minho, Braga, Portugal
[c] Universidade Europeia, Lisboa, Portugal
[d] EPIUnit, ISPUP - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal

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ABSTRACT

Anxiety and depressive symptoms may influence cortisol trajectories in women and men during pregnancy and the postpartum period. Using a multilevel approach, anxiety and depressive symptoms effects on 24-hour urinary free cortisol trajectories from the 2nd trimester to 3-months postpartum were examined in a sample of 66 women and 65 men with no known psychosocial or medical risk (N = 131; 33 (50%) of them were couples that participated in the same assessment waves). Results showed that both anxiety and depressive symptoms influence women's and men's cortisol trajectories from mid-pregnancy to 3-months postpartum. Women with high depressive symptoms and men with high anxiety or high depressive symptoms exhibited less accentuated variations in the 24-hour urinary free cortisol trajectories compared with women with low depressive symptoms and men with low anxiety or depressive symptoms, respectively. These effects were significant for women's cortisol trajectories from the 2nd to the 3rd pregnancy trimester and for men's cortisol trajectories throughout the entire period. The effect of anxiety and depressive symptoms on HPA axis functioning and cortisol production during pregnancy and postpartum, seems to be sex-specific. Reproductive-related alterations (associated with gestation, parturition and lactation) in women's HPA axis functioning may explain these sex-specific effects.

1. Introduction

Pregnancy and the postpartum are challenging periods for both women and men, associated with both anxiety and depressive symptoms (e.g., Don et al., 2014; Figueiredo and Conde, 2011a; Underwood et al., 2016) and hormonal changes (e.g., Conde and Figueiredo, 2014; Kane et al., 2014). Anxiety and depressive symptoms paths over pregnancy and the postpartum periods are generally similar in women and men: higher levels of anxiety at the 1st and 3rd pregnancy trimesters compared to the 2nd trimester (e.g., Figueiredo and Conde, 2011a; Lee et al., 2007), followed by a decline after childbirth (e.g., Andersson et al., 2006; Canário and Figueiredo, 2017; Don et al., 2014), and a decrease in depressive symptoms from the 1st to the 3rd pregnancy trimester (e.g., Figueiredo and Conde, 2011a; Tendais and Figueiredo, 2016) and at 3 to 6 months postpartum compared to mid-pregnancy (e.g., Andersson et al., 2006; Figueiredo and Conde, 2011a; Heron et al., 2009). Nevertheless, there are sex differences in the severity of psychopathological symptoms (e.g., Figueiredo and Conde, 2011a; Parfitt and Ayers, 2014; Rollè et al., 2017). Women have increased anxiety and depressive symptoms during pregnancy and childbirth (Figueiredo and Conde, 2011a; Teixeira et al., 2009) but not in the postpartum (Figueiredo and Conde, 2011b) compared to men.

Stage-specific differences in cortisol levels are also generally similar in women and men: increase during pregnancy with a peak in labor and decrease during the postpartum period (Cheng and Pickler, 2010; Conde and Figueiredo, 2014; Jung et al., 2011; Storey et al., 2000). Evidence suggests that in women the mechanisms underlying cortisol changes are influenced by the reproductive status (Handa and Weiser, 2014).

* Corresponding author at: INPP – Portucalense Institute for Human Development, Portucalense University, Rua Dr. António Bernardino de Almeida, 541, 4200-072 Porto, Portugal.
E-mail address: anac@upt.pt (A. Conde).
[1] Affiliation where the study was conducted: Psychology Research Center, School of Psychology, University of Minho, Braga, Portugal. Present affiliation: INPP – Portucalense Institute for Human Development, Portucalense University, Porto, Portugal.

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Alterations in the Hypothalamic-pituitary-adrenal (HPA) axis functioning can be triggered by gestation, fetal development, and parturition phenomena (Glynn et al., 2013; Kammerer et al., 2006; Murphy et al., 2006). During the postpartum period, the decline in cortisol release is associated with the placenta expulsion and continuity of hypertrophy of the adrenal glands (Cheng and Pickler, 2010; Glynn et al., 2013; Jung et al., 2011). These changes may have adaptive functions including: regulation of parental behavior (Carter and Porges, 2012), facilitation of energy conservation required for lactation, buffer from stress-associated inhibition of lactation, and improvement of the immune function (e.g., Glynn et al., 2013; Hahn-Holbrook et al., 2011). Modifications in HPA axis function persist over the postpartum period and best estimates suggest that it takes at least two to three months for the HPA axis to return to pre-pregnancy functioning pattern (Glynn et al., 2013; Jung et al., 2011; Magiakou et al., 1996; Owens et al., 1987).

Reports from neuroendocrine research conducted in adults, although not in the perinatal period, show an association between anxiety and depressive symptoms and a dysregulation of the HPA axis (Kofman et al., 2019), determining alterations in cortisol release (Elnazer and Baldwin, 2014; Oldehinkel and Bouma, 2011). In individuals with anxiety and depressive symptoms, the HPA axis seems to be hyperactive, with increased 24-hour urinary free cortisol levels (Hess et al., 2007; Kathol et al., 1989; Maes et al., 1998). These alterations seem to be sex-specific, since women with major depressive disorders or anxiety disorders exhibit a blunted cortisol response to psychosocial stress compared to controls, whereas men with major depressive disorders or anxiety disorders exhibit an elevated cortisol response (Zorn et al., 2017). Specifically, during pregnancy and postpartum periods, changes in gonadal steroid hormones can compromise the HPA axis ability to respond to environmental stimuli, since reproduction is regulated by a neuroendocrine axis, the Hypothalamo–pituitary–gonadal (HPG) axis, involving the hypothalamus, anterior pituitary gland and gonads (Handa and Weiser, 2014). Blunted plasma cortisol to acute stressors driven by anxiety during pregnancy suggests that the rising circulating levels of HPA axis hormones and placental corticotropin-releasing hormone (CRH) influence the endocrine response to challenges (De Weerth and Buitelaar, 2005; Serati et al., 2016). This is also consistent with clinical study reports showing non-significant or low associations between stress and cortisol levels in women (e.g., Giesbrecht et al., 2012; O'Connor et al., 2014). Depressed women during pregnancy exhibit higher cortisol levels, lower wake-up, flattened, less sharply declining diurnal pattern (O'Connor et al., 2014), and elevated night-time (Peer et al., 2013) cortisol levels. In the postpartum period depression is associated with a dysregulated HPA axis activity (Glynn et al., 2013), reflected in a lack of a cortisol morning rise (Taylor et al., 2009), reduced cortisol diurnal variation (de Rezende et al., 2016) and elevated evening salivary cortisol levels when compared to healthy controls (Iliadis et al., 2015).

The majority of the studies conducted so far are cross-sectional, focused on women and on the association between psychological symptoms and cortisol levels at specific time points, without controlling for individual differences in cortisol levels. Recent studies suggest that a longitudinal approach and multilevel analysis are necessary to clearly describe the potential effects of psychological symptoms on cortisol levels (Giesbrecht et al., 2012; Kane et al., 2014). Cortisol-related research also involves a variety of methods for biological samples collection, including blood, urine and saliva (Sarkar et al., 2013), depending on the aim of the study. The 24-hour urinary free cortisol is considered a moderately stable indicator of adrenocortical output, therefore the best way to assess the overall or long-term HPA axis activity during pregnancy and postpartum, namely in non-acute experimental situations (Yehuda et al., 2003). As far as we know, no studies have been published on the association between men's anxiety or depressive symptoms and cortisol levels during the prenatal and postpartum period.

Using a multilevel approach, the current study examines anxiety and depressive symptoms effects on women's and men's 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester (20 to 24 weeks) to 3-months postpartum, adjusting for parity. Parity was adjusted in the analysis due to differences between first and second-time parents (2nd child or beyond) in anxiety and depressive symptoms (Chen et al., 2019; Figueiredo and Conde, 2011a; Skari et al., 2002) and in cortisol levels (Conde and Figueiredo, 2014) over pregnancy and postpartum period. We hypothesize that both anxiety and depressive symptoms effects on cortisol trajectories in women may be different from those observed in men, not only because the HPA axis functioning is different in women and men (Helpman et al., 2017), namely in the presence of a psychiatric disorder (Zorn et al., 2017), but also because the reproductive and lactation phenomena interferes with the HPA axis functioning (Altemus et al., 1995; Handa and Weiser, 2014).

2. Methods

2.1. Participants

A sample of 66 women and 65 men ($N = 131$) with no known psychosocial or medical risk ($N = 131$) were included in this study. The majority of the participants were aged between 30 and 39 years old (women: $M = 29.54$, $SD = 5.60$, min = 16, max = 41; men: $M = 30.84$, $SD = 6.80$, min = 13, max = 48), married, lived with the partner (and children), completed the secondary level of education and were employed. More than a half were first-time parents (women: 55.6%; men: 55.7%), and most women (83.3%) were exclusively breastfeeding at 3 months postpartum (Table 1).

2.2. Measures

This study is part of a larger research project, therefore measures have already been described elsewhere (Conde and Figueiredo, 2014).

2.2.1. Sociodemographic questionnaire

Participants' sociodemographic data were collected using a questionnaire developed by the research team. Information included age, sex, marital status, household, occupational status, education and

Table 1
Sociodemographics.

	Women ($n = 66$)	Men ($n = 65$)	Total ($N = 131$)
	%	%	%
Age (years)			
<18	3.2	1.6	2.4
18–29	41.2	41.0	41.0
30–39	52.4	47.8	50.2
≥40	3.2	79.6	6.4
Marital status			
Cohabiting	19.0	21.3	20.2
Married	73.1	72.1	72.5
Single	7.9	6.6	7.3
Household			
With the partner (and children)	82.5	82.0	82.3
Alone	1.6	0	0.8
With the larger family	6.4	6.6	6.4
With the family and the partner	9.5	11.5	10.5
Occupational status			
Employed	82.5	90.2	86.3
Unemployed	9.5	6.6	8.1
Housekeeping/student	8.0	3.2	5.6
Education (years)			
<9	27.0	34.4	30.6
9–12	41.2	47.5	44.5
>12	31.8	18.1	24.9

parity.

2.2.2. Anxiety symptoms

State-Trait Anxiety Inventory (STAI-S; Spielberger et al., 1983). The STAI is a self-report questionnaire that includes two subscales, the state anxiety subscale and the trait anxiety subscale, each one involving 20 items and scores ranging from 20 to 80. In this study we only used the state anxiety subscale that related to anxiety symptoms felt at the moment and is conceptualized as a transient emotional condition of the individual, characterized by subjectively experienced feelings of tension, together with a heightened activity of the autonomous nervous system. Higher scores on this subscale indicate higher anxiety symptoms. The Portuguese version of the STAI-S showed an excellent internal consistency for pregnancy and postpartum (Cronbach's $\alpha = 0.91$ and 0.92, respectively). The optimal cut-off to consider clinically significant symptoms is 40 for pregnancy and 34 during the postpartum period (Tendais et al., 2014). In this study, low anxiety was considered for scores one standard deviation below the grand mean and high anxiety was considered for scores one standard deviation above the grand mean.

2.2.3. Depressive symptoms

Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). The EPDS is a self-report questionnaire used to assess depressive symptoms. It is composed of 10 items in a Likert scale of 4 points (0–3). This scale covers the severity of depressive symptoms in the last seven days. The Portuguese version of the EPDS showed good internal consistency for pregnancy and postpartum (Cronbach's $\alpha = 0.82$ and 0.88). The optimal cut-off to consider clinically significant symptoms is 9 for pregnancy and 7 during the postpartum period (Tendais et al., 2014). In this study, low depression was considered for scores one standard deviation below the grand mean and high depression was considered for scores one standard deviation above the grand mean.

2.2.4. 24-Hour urinary free cortisol

The collection of the urine produced during a 24-hour period was requested to the participants following these instructions: 1) registering the day and time of the first urine collection, 2) collecting and storing the urine produced in a cool and dark place, and 3) collecting the last urine sample 24 h after the first urine collection. After collection, the participants informed the research team and a team member picked up the urine samples immediately. For each assay, the total volume of urine produced during a 24-hour period was registered. The urine samples were kept frozen at −20 °C and analyzed in the laboratory. Cortisol assay was implemented by a certified clinical lab (APCER n° 2004/CEP, 2395), following the clinical laboratory procedure manual (Bayer Diagnostics ADVIA Centaur Assay Manual, Revision AT). According to the cortisol ADVIA Centaur Assay Manual, five samples were assayed 6 times, in each of 24 runs, on 6 systems ($n = 144$ for each sample), over a period of 2 days in order to calculate the precision performance characteristics of the ADVIA Centaur cortisol assay. The within-run % CV ranged between 2.89 and 3.82 and the run-to-run % CV ranged between 1.86 and 5.45. The total % CV ranged between 4.22 and 6.58. Assay procedure included: 1) taking a 20 nl sample; 2) adding 50 nl of Lite reagent and 250 nl of Solid Phase before incubating at 37 °C for 5 min; 3) separating, aspirating and washing the recipient with reagent water; 4) adding the same amount of acid and basic reagent to initiate the chemiluminescent reaction (Bayer Diagnostics ADVIA Centaur Assay Manual). Following the guidelines established in the manuals of the Bayer Diagnostics ADVIA Centaur, total volumes lower than 750 ml of urine were excluded from the analysis to guarantee valid determination of cortisol levels (2nd trimester - two samples from men; 3rd trimester - six women's and five men's samples; 3-months postpartum - thirteen women's and twelve men's samples).

Among the general population, the reference range of 24-hour urinary free cortisol levels registers between 55.5 and 286.0 μg/24 h (Bayer Diagnostics ADVIA Centaur Reference Manual).

2.3. Procedures

This study is in accordance with the Declaration of Helsinki, and is part of a larger study in which preferentially couples were recruited. After institutional approval, couples were asked to take part in the study at their first medical appointment (prior to 14 weeks of gestation) in a public antenatal obstetric unit. Nonetheless, the participation of one member of the couple was allowed regardless of the participation of the other member. Inclusion criteria required participants to be able to read and write Portuguese, have a single gestation and no medical/obstetric risk. The aims and the procedures were fully explained and an informed consent form was signed by participants or their legal representatives. The socio-demographic questionnaire was separately filled by the women and men during the first half of pregnancy. Repeated measures of anxiety symptoms (STAI-S), depressive symptoms (EPDS) and 24-hour urinary free cortisol levels were obtained at the 2nd (20 to 24 weeks) and 3rd (30 to 34 weeks) pregnancy trimesters and at 3-months postpartum (10 to 12 weeks). This information was provided by women and men separately, therefore, measures for woman and man within a couple may not have been collected on the exact same day on each time point.

From the initially recruited participants ($N = 246$; 123 women and 123 men), those with at least one cortisol urine sample and that filled in at least one STAI-S and/or one EPDS questionnaire were included in the analyses ($N = 131$; 66 women and 65 men; 33 (50%) of them were couples that participated in the same assessment waves). Some participants' 24 hour urine volume did not accomplished the minimum required volume and some have refused to provide urine samples, so ninety-six cortisol samples (50 women and 46 men) are available for the 2nd trimester, 103 (53 women and 50 men) for the 3rd trimester and 81 (41 women and 40 men) for 3-months postpartum. STAI-S is available for 63 women and 63 men at the 2nd trimester, 64 women and 62 men at the 3rd trimester, 57 women and 56 men at 3-months postpartum. EPDS is available for 64 women and 63 men at the 2nd trimester, 63 women and 63 men at the 3rd trimester, 56 women and 56 men at 3-months postpartum. The remaining participants did not complete the STAI-S or the EPDS. Non-participants were more likely to be younger ($t(220) = -5.280$, $p < 0.001$), married ($\chi2^2(3) = 24.864$, $p < 0.001$), and to live with the family and the partner ($\chi2^2(5) = 20.921$, $p < 0.01$). There were no significant differences between participants and non-participants concerning occupational status.

2.4. Statistical analysis

Descriptive statistics (means and standard deviations) were conducted for anxiety and depressive symptoms and for 24-hour urinary free cortisol at the 2nd and 3rd pregnancy trimesters and at 3-months postpartum. A piecewise growth model (time 1, from the 2nd to the 3rd pregnancy trimester and time 2, from the 2nd pregnancy trimester to 3-months postpartum) was tested in order to analyze if changes in anxiety or in depressive symptoms over time were significant. Pearson correlations were used to test the association between anxiety and depressive symptoms at the 2nd and 3rd pregnancy trimesters and at 3-months postpartum. Characteristics of participants and non-participants were compared using chi-square tests for categorical variables and independent samples *t*-test for continuous variables. The analysis of outliers revealed one outlier for women (182.7 μg/24 h) and one for men (206.4 μg/24 h) at 3 months postpartum, however these values were within the reference levels for 24-hour urinary free cortisol, so these data was included in the analyses (Bayer Diagnostics ADVIA Centaur Reference Manual).

Independent growth curve models (with maximum likelihood (ML) estimation) were performed in order to examine anxiety or depressive symptoms effects on women's and men's trajectories of 24-hour urinary free cortisol during pregnancy and the postpartum period. A person-period data set was used, resulting in 198 observations for women (66

participants by three time points) and 195 for men (65 participants by three time points) (total of 393 observations). This statistical approach enabled us to compensate for missing data at each time point. The effect size r^2 (Rosenthal et al., 2000) was estimated for all significant effects and interpreted according to Cohen's guidelines (Cohen, 1988).

Several steps were implemented in order to analyze anxiety or depressive symptoms effects on women's and men's trajectories of 24-hour urinary free cortisol during pregnancy and the postpartum. Firstly, an unconditional mean model was tested, with no predictors included. This model served as a baseline to examine individual variation in the outcome regardless to time. Through the calculation of the Intraclass Correlation Coefficient (ICC), the proportion of total outcome variation associated to interindividual differences was examined (amount of outcome variation explained by the predictors). In step 2, the unconditional growth curve model was tested in order to estimate the average within-person initial status and change rate over time. Predictors weren't included in this model (Shek and Ma, 2011). Taking into account the descriptive analysis of women's and men's 24-hour free cortisol levels, a piecewise growth model (time 1, from the 2nd to the 3rd pregnancy trimester and time 2, from the 2nd pregnancy trimester to 3-months postpartum) was tested. An important question to take into consideration in modeling growth curves is the scaling of time (Biesanz et al., 2004). Thus, for both models, Time 0 was defined as the date of the first assessment and the time variable was scored in weeks. In step 3, predictors were included in the growth curve model in order to analyze the fixed effects of anxiety or depressive symptoms (time-varying factors), as well as their interactions with time. Anxiety and depressive symptoms are highly correlated in this sample as expected. For that reason, when the anxiety symptoms effects were tested, parity [coded as −1 for first-time parenthood and 1 for second-time parenthood (that is to say, 2nd child or beyond)] and depressive symptoms were included in the model as covariates in order to adjust its effects. When the depressive symptoms effects were tested, parity and anxiety symptoms were included in the model as covariates in order to adjust its effects. Parity was adjusted in the analysis due to differences between first and second-time parents (2nd child or beyond) in anxiety and depressive symptoms (Chen et al., 2019; Figueiredo and Conde, 2011a; Skari et al., 2002) and in cortisol levels (Conde and Figueiredo, 2014) over pregnancy and postpartum period. The significant interactions of time with continuous predictors (anxiety/depressive symptoms) were interpreted and graphed using one standard deviation above (higher anxiety/depressive symptoms) and one standard deviation below (lower anxiety / depressive symptoms) the grand mean. In order to identify similarities and differences between women and men in the effects of anxiety or depressive symptoms on 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester to 3-months postpartum, sex (coded as −1 for men and 1 for women) and the interaction time * sex * anxiety symptoms or the interaction time * sex * depressive symptoms, respectively were included in the model and their effects tested.

Results are reported at a $p < 0.05$ significance level. Analysis was conducted using the IBM SPSS Statistics for Windows, version 23.0.

3. Results

3.1. Anxiety and depressive symptoms trajectories in women and men from pregnancy to postpartum

High correlations between anxiety and depressive symptoms were found at the 2nd ($r = 0.699$, $p < 0.001$) and 3rd ($r = 0.694$, $p < 0.001$) pregnancy trimesters and at 3-months postpartum ($r = 0.733$, $p < 0.001$).

A piecewise growth model (time 1, from the 2nd to the 3rd pregnancy trimester and time 2, from the 2nd pregnancy trimester to 3-months postpartum) was tested in order to analyze if changes in anxiety or in depressive symptoms over time were significant. In women, there was a non-significant increase in mean levels of anxiety and of depressive symptoms from the 2nd to the 3rd pregnancy trimesters (anxiety symptoms: $\beta = 0.16$, $SE = 0.09$, $p = 0.06$; depressive symptoms: $\beta = 0.03$, $SE = 0.04$, $p = 0.36$), as well as a non-significant decrease from the 3rd pregnancy trimester to the 3-months postpartum (anxiety symptoms: $\beta = -0.12$, $SE = 0.06$, $p = 0.07$; depressive symptoms: $\beta = -0.04$, $SE = 0.02$, $p = 0.12$), suggesting a stability in women's symptomatology over this period. In men, there was a non-significant increase in the mean levels of anxiety symptoms from the 2nd to the 3rd pregnancy trimesters ($\beta = 0.08$, $SE = 0.08$, $p = 0.35$) and a significant decrease from the 3rd pregnancy trimester to the 3-months postpartum ($\beta = -0.09$, $SE = 0.04$, $p = 0.040$). Mean levels of men's depressive symptoms decreased significantly from the 2nd to the 3rd pregnancy trimesters ($\beta = -0.08$, $SE = 0.04$, $p = 0.026$) and remained stable from this time point until 3-months postpartum ($\beta = -0.03$, $SE = 0.02$, $p = 0.13$) (see Table 2).

3.2. 24-Hour urinary free cortisol trajectories in women and men from pregnancy to postpartum

In order to examine the amount of variance in the outcome that is attributed to differences between individuals, an unconditional mean model was tested. The ICC was calculated 204.27 / (204.27 + 1579.49) = 0.114, suggesting that about 11.4% of the total variation in 24-hour urinary free cortisol was due to interindividual differences (covariance parameters $p = 0.16$).

A piecewise growth curve model analysis was performed in order to predict 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester (baseline) until 3-months postpartum. The empty piecewise model corresponding to the estimative of these trajectories was significant for Time 1 (from the 2nd to the 3rd pregnancy trimester) ($\beta = 1.65$, $SE = 0.45$, $p < 0.001$, $r = 0.38$), but not for Time 2 (from the 3rd pregnancy trimester to 3-months postpartum) ($\beta = -0.44$, $SE = 0.38$, $p = 0.25$). The mean estimated initial status and growth rate for time 1 were 76.23 and 1.65, respectively. This suggests that the mean 24-hour urinary free cortisol was 76.23 and increased significantly from the 2nd to the 3rd pregnancy trimester.

As significant effects of time were found on 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester (baseline) to the 3rd pregnancy trimester, two growth curve models were implemented in order to test the independent prediction effect of anxiety and of

Table 2
Means and Standard Deviations of women's and men's 24-hour urinary free cortisol and anxiety and depressive symptoms during pregnancy and postpartum periods (N = 131).

Variables	Pregnancy				Postpartum	
	2nd trimester		3rd trimester		3-Months	
	M	*SD*	*M*	*SD*	*M*	*SD*
Women ($n = 66$)						
24-Hour urinary free cortisol	79.88	29.52	104.62	41.66	78.44	52.22
Anxiety symptoms	36.38	10.91	37.52	10.37	35.61	10.39
Depressive symptoms	6.59	4.33	6.97	4.48	6.07	4.49
Men ($n = 65$)						
24-Hour urinary free cortisol	70.17	26.43	78.94	33.46	90.98	56.30
Anxiety symptoms	32.80	8.50	33.93	8.04	32.31	8.87
Depressive symptoms	5.06	3.66	4.17	3.35	3.67	4.00
Total sample ($N = 131$)						
24-Hour urinary free cortisol	76.23	30.71	92.47	41.21	83.76	53.75
Anxiety symptoms	34.33	9.95	35.35	9.47	33.76	9.86
Depressive symptoms	5.71	4.02	5.48	4.16	4.85	4.39

[2] Effect size $r = \sqrt{[t^2 / t^2 + df]}$.

depressive symptoms on the shape of individual 24-hour urinary free cortisol growth trajectories. Both models were adjusted for parity as well as for depressive or anxiety symptoms, respectively.

3.3. Anxiety symptoms effect on 24-hour urinary free cortisol trajectories in women and men from pregnancy to postpartum

Table 3 presents the piecewise growth curve model predicting 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester until 3-months postpartum, taking into account the effects of anxiety, as well as the interaction effects with time and time * sex, adjusting for parity and depressive symptoms. The estimates in the top half of the table represent the degree to which each predictor showed effects on the intercepts. The estimates in the bottom half of the table represent the interaction effect between each predictor and time on 24-hour free cortisol.

When the previous predictors were added to the piecewise model, a significant increase in 24-hour urinary free cortisol levels was found between the 2nd and 3rd pregnancy trimesters ($r = 0.20$) and a significant decrease was observed between the 3rd pregnancy trimester and 3-months postpartum ($r = 0.22$). Although not associated with the 24-hour urinary free cortisol levels at baseline, a significant effect of anxiety symptoms on 24-hour urinary free cortisol trajectories over these periods was found to be moderated by sex (between the 2nd and 3rd trimester: $r = 0.20$; between the 3rd trimester and 3-months postpartum: $r = 0.36$) (see Fig. 1). In men, both the cortisol increase from the 2nd to the 3rd pregnancy trimesters and the decrease from the 3rd pregnancy trimester to 3-months postpartum were significantly less accentuated for those with high anxiety compared to those with low anxiety, whereas for women, the cortisol variations were similar for women with high and low anxiety symptoms.

3.4. Depressive symptoms effect on 24-hour urinary free cortisol trajectories in women and men from pregnancy to postpartum

Table 4 presents the piecewise growth curve model predicting 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester until 3-months postpartum, taking into account the effects of depressive symptoms, as well as the interaction effects with time and time * sex, adjusting for parity and for anxiety symptoms. The estimates in the top half of the table represent the degree to which each predictor showed effects when predicting the intercepts. The estimates in the bottom half of the table represent the interaction effect between each predictor and time on 24-hour free cortisol.

Table 3
Women's and men's anxiety symptoms effects on 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester to 3-months postpartum (Piecewise growth curve model).

Fixed effects	24-Hour urinary free cortisol		
	B	*SE*	95% CI
Intercept	68.57	12.12	[44.52, 92.61]***
Time 1	4.23	1.88	[0.52, 7.95]*
Time 2	−3.00	1.36	[−5.69, −0.30]*
Sex	3.38	3.25	[−3.06, 9.83]
Parity	−5.33	2.61	[−10.51, −0.15]*
Anxiety symptoms	0.36	0.40	[−0.44, 1.15]
Depressive symptoms	−0.55	0.81	[−2.15, 1.06]
Time 1 * Anxiety symptoms	−0.08	0.05	[−0.19, 0.02]
Time 2 * Anxiety symptoms	0.08	0.04	[−0.001, 0.15]
Time 1 * Sex * Anxiety symptoms	0.03	0.01	[0.003, 0.06]*
Time 2 * Sex * Anxiety symptoms	−0.04	0.01	[−0.06, −0.02]**

Legend. Parity: −1 first-time parents, 1 second-time parents (2nd child or beyond). Sex: −1 men, 1 women.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

When the model was tested, baseline levels of cortisol were higher for women compared to men ($r = 0.37$) and a significant increase in 24-hour urinary free cortisol levels was found between the 2nd and 3rd pregnancy trimesters ($r = 0.39$), both in women and men. Although not associated with the 24-hour urinary free cortisol levels at baseline, depressive symptoms were a significant predictor of changes in 24-hour urinary free cortisol levels from the 2nd to the 3rd pregnancy trimester ($r = 0.28$). Women and men with high depressive symptoms had significantly lower increases in 24-hour urinary free cortisol levels from the 2nd to the 3rd pregnancy trimester compared to women and men with low depressive symptoms, respectively (see Fig. 2). An interaction effect of time * sex * depressive symptoms was also found between the 3rd pregnancy trimester and 3-months postpartum ($r = 0.25$). The cortisol decrease was significantly less accentuated for men with high depressive symptoms compared with men with low depressive symptoms, whereas for women the cortisol decrease was quite similar for those with high or low depressive symptoms.

4. Discussion

The current study examined the effects of both anxiety and depressive symptoms on women's and men's 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester to 3-months postpartum, adjusting for parity and depressive/anxiety symptoms. As hypothesized, both anxiety and depressive symptoms have sex-specific effects on cortisol trajectories. Men with high anxiety or depressive symptoms have significantly lower cortisol increases from the 2nd to the 3rd pregnancy trimesters and decreases from the 3rd pregnancy trimester to 3-months postpartum compared to men with low anxiety or depressive symptoms. For women, high depressive symptoms are associated with lower cortisol increases from the 2nd to the 3rd pregnancy trimester, whereas cortisol decreases from 3rd pregnancy trimester to 3-months postpartum are quite similar for women with high or low depressive symptoms.

No significant associations between anxiety or depressive symptoms and cortisol levels were found at the 2nd pregnancy trimester, sustaining findings of previous studies pointing out no associations between women's psychopathological symptoms and cortisol levels at specific time points in the perinatal period (Figueiredo and Costa, 2009; Harville et al., 2009; Shea et al., 2007; Voegtline et al., 2013) and extending these findings to men. Some reasons have been pointed out for this absent association, namely in women, including the fact that cortisol secretion seems to be primarily determined by reproductive phenomena (e.g., Glynn et al., 2013; Murphy et al., 2006). Therefore, these results seem to support the idea that cortisol production dissociates to a certain extent from environmental stressors in pregnancy, especially in women that are not under severe risk circumstances (Salacz et al., 2012), such as the ones in this sample. Moreover, high individual variability in cortisol levels (Kudielka et al., 2009; Radenbach et al., 2015) may also contribute to explain the absence of associations between anxiety or depression symptoms and cortisol levels at specific time points.

From mid-pregnancy to 3-months postpartum, women with high depressive symptoms and men with high depressive or anxiety symptoms have less accentuated cortisol trajectories. The reasons underneath cortisol variations associated with psychopathological symptoms are largely unknown so far, especially considering men. Would these be a reflex of the HPA axis that becomes gradually less responsive to stress as a result of the exposure to chronic stress imposed by the challenges of pregnancy? And if so, why would this happen to a larger extent in individuals with more severe psychopathology symptoms? Studies on psychopathology and cortisol levels point in the exact opposite direction: women with major depressive disorders or anxiety disorders exhibit a blunted cortisol response to psychosocial stress compared to controls, whereas men with major depressive disorders or an anxiety disorder exhibit an elevated cortisol response (Zorn et al., 2017). Still those studies rely on cortisol reactivity whereas in the present study we

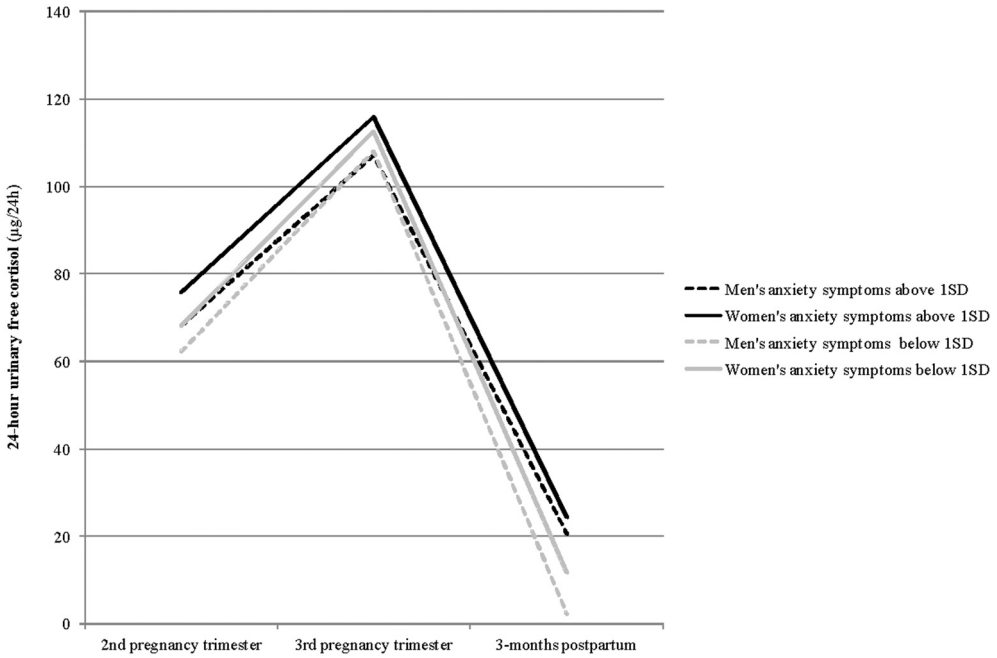

Fig. 1. Anxiety symptoms effects on women's and men's 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester until 3-months postpartum. Legend. High anxiety symptoms - One standard deviation above the grand mean/Low anxiety symptoms - One standard deviation below the grand mean.

Table 4
Women's and men's depressive symptoms effects on 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester to 3-months postpartum (Piecewise growth curve model).

Fixed effects	24-Hour urinary free cortisol		
	b	*SE*	95% CI
Intercept	68.95	8.63	[51.45, 86.44]***
Time 1	2.86	0.80	[1.27, 4.46]**
Time 2	−0.37	0.57	[−1.51, 0.76]
Sex	5.35	2.43	[0.38, 10.32]*
Parity	−3.50	2.08	[−8.67, 1.68]
Anxiety symptoms	0.03	0.29	[−0.59, 0.66]
Depressive symptoms	1.06	0.87	[−0.72, 2.84]
Time 1 * Depressive symptoms	−0.25	0.12	[−0.49, −0.006]*
Time 2 * Depressive symptoms	0.02	0.09	[−0.16, 0.20]
Time 1 * Sex * Depressive symptoms	0.08	0.07	[−0.06, 0.23]
Time 2 * Sex * Depressive symptoms	−0.14	0.06	[−0.27, −0.02]*

Legend. Parity: −1 first-time parents, 1 second-time parents (2nd child and beyond).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

analyzed the 24-hour urine circulating cortisol across the perinatal period. In women, increases in cortisol levels in the late gestation promote organ maturation and assist in time of labor (Rainey et al., 2004), therefore our findings of an effect of high depressive symptoms on lower cortisol increases in late pregnancy among women raises concerns regarding not only fetal maturation but also childbirth outcomes. Cortisol may be the link that explains evidence on the negative impact of prenatal depression on perinatal health and neonatal outcomes (Alder et al., 2007; Silva et al., 2018). Further studies focusing on the underlying mechanisms, as well as on the long-term effects of both women's and men's anxiety and depressive symptoms and hormonal changes on the behavior of the child would provide valuable insights both for research and clinical practice.

Some limitations need to be acknowledged and results should be interpreted with caution. The small sample size is one of the major constraints that can hamper the final conclusions. Additionally, although sex, parity and depressive/anxiety symptoms were controlled in the analyses, many other factors with an important role in the HPA axis functioning (e.g., lactation, perceived stress, inhaled glucocorticoids, etc.) were not controlled for. Future studies with larger samples should be implemented in order to analyze the main and the interaction effect of these factors. The substantial attrition in our study is also a limitation that should be noted. Participants and non-participants differed in some socio-demographic characteristics (age, marital status and household arrangements), and may differ in terms of psychophysiological processes, which constrains the generalization of the findings. The replication of this study in a larger heterogeneous sample that allow taking into account exclusively participants with all measures in the several assessment time points would help to clarify and validate these findings. The validity of the cortisol measurement highly depended on the participants' compliance with the urine collection instructions and the environmental exposure to stressors or other elicitors of the HPA axis, such as contraceptives, corticosteroids or other drugs, that were not controlled for during the data collection period. Despite the above-mentioned limitations, this study is, as far as we are aware, the first analyzing the effect of both anxiety and depression on women's and men's cortisol trajectories during the perinatal period. It also has several other strengths, including a longitudinal design, repeated measures of cortisol, anxiety and depressive symptoms, growth curve analyses using multilevel modeling and consideration of intraindividual differences in cortisol levels. The inclusion of these aspects strengthens the understanding of the complex interplay between psychological and physiological factors that determine women's and men's adjustment during the transition to parenthood.

5. Conclusions

Both anxiety and depressive symptoms have sex-specific effects on cortisol trajectories from mid-pregnancy to 3-months postpartum. In men high anxiety or depressive symptoms are associated with less accentuated cortisol variations from the 2nd pregnancy trimester to 3-months postpartum, compared to those of men with low anxiety or depressive symptoms. For women, high depressive symptoms are associated with lower cortisol increases from the 2nd to the 3rd pregnancy

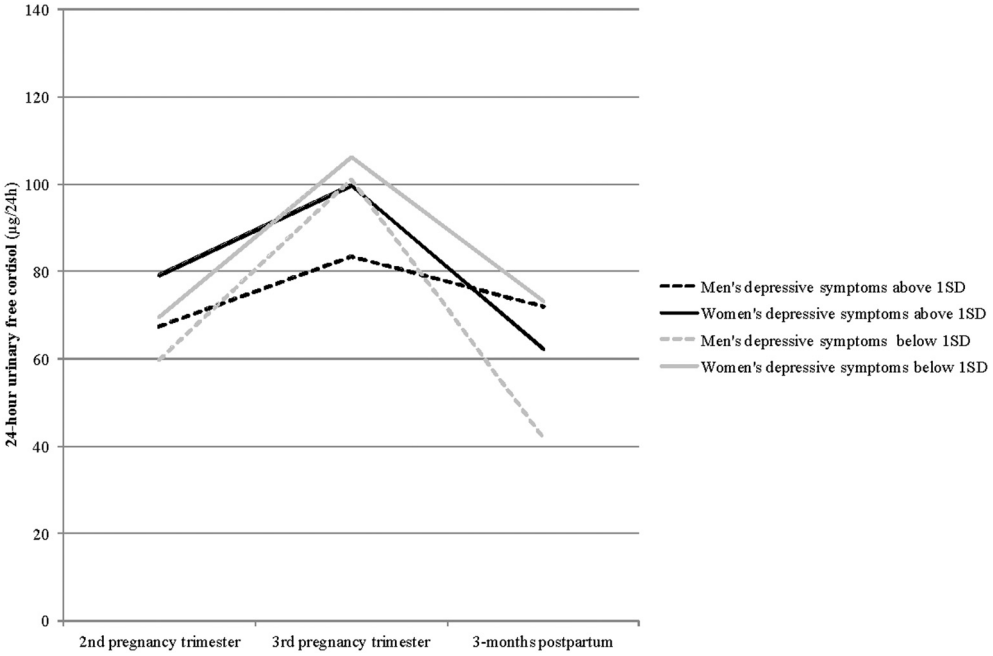

Fig. 2. Depressive symptoms effects on women's and men's 24-hour urinary free cortisol trajectories from the 2nd pregnancy trimester until 3-months postpartum. Legend. High depressive symptoms - One standard deviation above the grand mean/Low depressive symptoms - One standard deviation below the grand mean.

trimester whereas from the 3rd pregnancy trimester to 3-months postpartum the cortisol decrease is quite similar for women with high or low depressive symptoms. Alterations in the HPA axis functioning during the reproductive period may explain this sex-specific effect. Although the need for further studies focusing on the underlying mechanisms of the effects of anxiety and of depressive symptoms on women's and men's cortisol trajectories over pregnancy and postpartum, is undeniable, findings of this study seem to support the role of cortisol as a stress biomarker during this period, contributing to the identification of periods of increased psychological vulnerability for both women and men.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Data availability statement

Data is available upon request exclusively for the research purposes within the scope of this study, since the informed consent signed by participants implied using data for that purpose exclusively.

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