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Hair cortisol concentrations across pregnancy and maternal postpartum depressive symptoms - The ELFE cohort

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ABSTRACT

Postpartum depression and depressive symptoms have a major impact on maternal and infant health and well-being, yet to date their aetiology remains unclear. One hypothesis suggests a link between these symptoms and variations in prenatal cortisol levels, but existing evidence is limited and inconclusive. This study aims to provide additional evidence to disentangle the relationship between prenatal cortisol concentrations and subsequent occurrence of postpartum depressive symptoms. Cortisol for all three trimesters of pregnancy was extracted from the hair of 775 women participating in the French ELFE cohort. Depressive symptomatology at two months postpartum was assessed through the Edinburgh *Postpartum* Depression Scale (EPDS). Associations between prenatal cortisol levels and EPDS scores were tested using propensity-score weighted logistic regression models to control for confounders. An increase in mean cortisol concentrations was observed from the first to the third trimester of pregnancy.

No significant differences in hair cortisol concentrations were found during the first and second trimesters between women who experienced postpartum depressive symptoms and those who did not. However, an association was observed between third trimester hair cortisol concentrations and depressive symptoms at two months postpartum. Women whose cortisol concentrations fell within the second quartile had a higher risk of subsequent PPDS (aOR = 2.67, 95%CI [1.01, 7.08]).

Using a large sample from the general population, we observed an association between hair cortisol levels during the third trimester of pregnancy and postpartum depressive symptoms. Nevertheless, our results suggest that future studies could benefit from investigating other biomarkers of the reactivity of the corticotropic axis.

1. Introduction

In perinatal psychopathology research, much attention is devoted to understanding the exact role of the maternal stress-responsive hypothalamic-pituitary-adrenal (HPA) axis and its end product cortisol. Throughout pregnancy, the HPA-axis undergoes essential adaptations for a successful gestation, resulting in a continuous escalation of HPA-axis hormone levels until childbirth (Kofman et al., 2019). Several biological, lifestyle-related, and social factors have been linked to higher levels of gestational cortisol, including younger maternal age, nulliparity, lower pre-pregnancy body mass index (BMI), higher levels of C-reactive protein (CRP), carrying a female foetus, non-smoking status,

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adequate sleep, and unemployment (Bleker et al., 2017), some of which are also risk factors for postpartum depressive symptoms (PPDS).

The link between perinatal mental health and cortisol as its potential biomarker is a research field in expansion and some studies have found an association between high cortisol in pregnancy and depressive symptoms prenatally (Mustonen et al., 2019; Seth et al., 2016). However, despite the plausible role the HPA-axis may play in perinatal mental health, there is no consensus in the literature regarding the interplay between cortisol concentrations during pregnancy and subsequent development of PPDS. Postpartum depression (PPD) is a major public health concern, with an estimated global prevalence of 17.2% (Wang et al., 2021). It has a significant impact on new mothers, including degraded social relations and increased risky health behaviours, such as smoking (Slomian et al., 2019). Severe cases can also lead to suicide, which contributes to as much as 20% of maternal deaths worldwide (Lindahl et al., 2005). In addition, PPD is negatively associated with several infant outcomes, including behaviour, health concerns, quality of sleep, and cognitive and language development. (Slomian et al., 2019). Finally, PPD in mothers is also associated with depressive symptoms, stress and anxiety in their partners (Moore Simas et al., 2019).

Several studies indicate that PPD or PPDS may be related to variations in HPA-axis activity during pregnancy. For instance, low blood cortisol levels in the third trimester have been linked to higher early postpartum depression scores (Yavuz et al., 2023). Likewise, Jahangard et al. observed significantly lower hair cortisol levels, both before and after birth, in women experiencing PPD twelve weeks after delivery compared to those without PPD (Jahangard et al., 2019). Additionally, cortisol levels remained consistently low from pregnancy to postpartum in women with PPD, whereas non-depressed women had high cortisol levels during pregnancy that dropped significantly after placental expulsion. Similarly, another study found that the expected post-pregnancy decrease in hair cortisol levels was absent in mothers with PPDS, for whom cortisol levels remained stable from the last trimester of pregnancy to twelve weeks postpartum, unlike mothers without PPDS (Stickel et al., 2021). Although these studies seem to indicate an association between underactivity of the HPA-axis and PPDS, other reports highlight that PPDS may be linked to a hyperactivity of the HPA-axis. Indeed, Laurent et al. showed that elevated salivary cortisol levels, reflecting acute rather than chronic cortisol levels found in hair, predict a more pronounced increase in depressive symptoms from pregnancy to one year postpartum (Laurent et al., 2018), while Caparrós-González et al. found an association between high hair cortisol levels in the first and third trimesters of pregnancy and PPDS (Caparros-Gonzalez et al., 2017). The authors also noted a consistent increase in hair cortisol levels throughout pregnancy in non-depressed women, whereas women with PPDS experienced a decrease from the first trimester to the second, followed by an increase in the third trimester. Finally, in contrast with the aforementioned studies, others found no discernible association between prenatal cortisol levels and PPDS. For instance, Galbally et al. reported no link between hair cortisol levels in the third trimester of pregnancy and symptoms of depression at twelve months postpartum (Galbally et al., 2019). Similarly, another study using serum cortisol levels found that prenatal cortisol levels were not associated with depressive symptoms 4–11 weeks after delivery (Gillespie et al., 2018). Khoury et al. could not evidence any significant relationship between hair cortisol during pregnancy and depressive symptoms at 4 months postpartum (Khoury et al., 2020). Altogether, relationships between prenatal cortisol levels and PPDS thus appear to be inconsistent (Mlili et al., 2023; Seth et al., 2016).

However, some of these conflicting results may be due to methodological issues. Studies on prenatal cortisol and PPDS have used relatively small samples (ranging from 44 to 279 subjects), with some authors recommending to increase sample size to gain better inference in this area (Galbally et al., 2019; Yavuz et al., 2023). Additionally, some studies used clinical samples recruited mostly among women participating in a mental health programme, thus limiting the generalizability of findings (Galbally et al., 2019; Laurent et al., 2018). Finally, most research has used minimal adjustment for confounding variables. Few studies have accounted for antenatal or earlier depression, and none have considered social support, which are all major risk factors for PPD (Ghaedrahmati et al., 2017).

The current study seeks to expand on existing literature by addressing some of these limitations. It aims to explore the association between prenatal hair cortisol levels in pregnant women during all three trimesters of pregnancy and the occurrence of postpartum depressive symptoms, using a large sample of women drawn from the general population and rigorously controlling for a wide range of potential confounding variables.

2. Methods

2.1. Study population

Participants were part of the ELFE cohort, which aims to longitudinally study factors impacting the development, health and socialisation of children from birth to adulthood. Data collection took place in 2011 in 320 maternity units in metropolitan France, corresponding to French territories on the European continent only, over four different waves (spring, summer, early autumn, late autumn). To be included in the cohort, single or twin live births had to occur over 33 weeks of gestation, mothers had to be 18 years old or older, with no plan of leaving metropolitan France within 3 years, and having signed an informed consent waiver alone (in which case the father was being informed of his right to deny consent for participation), or together with their partner. A total of 18,329 children were included at birth, and subsequently followed up at regular intervals. More details on the cohort and the recruitment of participants are described elsewhere (Charles et al., 2020). From the second wave of data collection (summer) onward, mothers' hair samples were collected at birth in 154 maternity units for those women who consented to biological sampling (n = 2956). From this population, a sample was selected including 834 participants for whom both prenatal cortisol levels and child outcomes at age 5 were available, as part of a larger study on prenatal stress and child development. Additionally, the final study population was constituted based on postpartum depression information availability. Women who did not answer the postpartum depression score were excluded (n = 59), leaving a final population of 775 women across trimesters (Fig. 1).

2.2. Measures

2.2.1. Exposure

Hair strands of 3 mm diameter were cut as close to the scalp as possible in the posterior vertex region with note of the root-tip orientation. Prenatal cortisol levels were extracted from a subsample of participants (n = 834). Assuming an average hair growth of 1 cm per month, the hair was segmented in three parts of 3 cm each, each section corresponding to a pregnancy trimester. After washing hair samples, cortisol was extracted using methanol incubation before online solid phase extraction (SPE) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) were performed on the samples to determine steroid concentrations. Such sensitive methods are recommended for detecting low hormone concentrations in hair. More details on the biological extraction process is explained elsewhere (Gao et al., 2013).

The inter- and intra-assay coefficients of variability were below 10%. No outlying values were removed from cortisol concentrations using data visualization, following recommendations (Marceau et al., 2020). Additionally, due to different hair lengths, cortisol levels were not available for 65 participants in the second trimester and 256 in the first one. These missing values were imputed along those of covariates using multivariate imputation by chained equations, as described further. We then categorized the three exposition variables representing cortisol

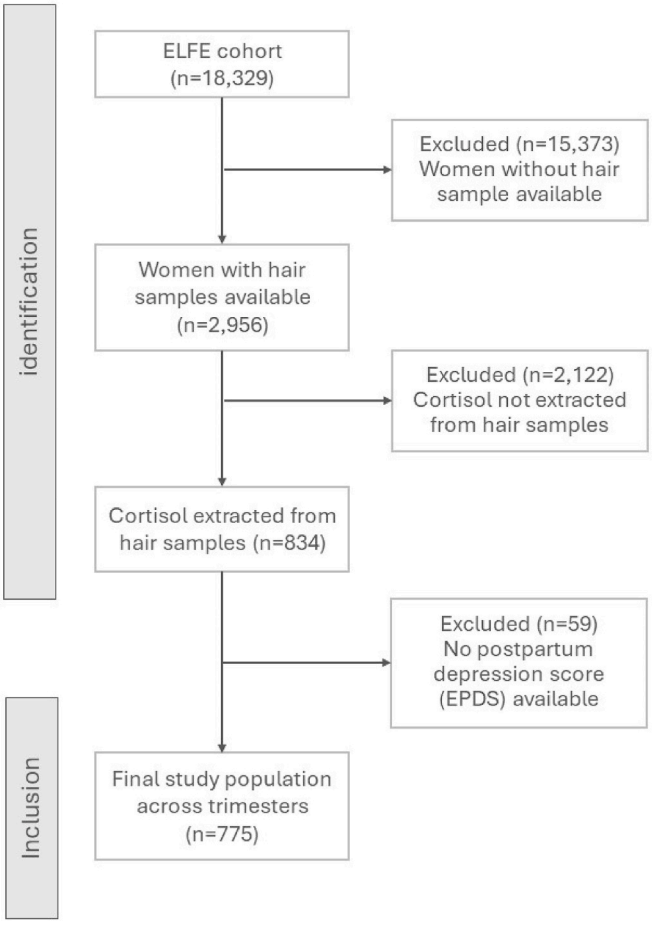

Fig. 1. Flowchart describing participant selection in the study population.

levels during each pregnancy trimester into quartiles within each imputed dataset. This not only aids in interpreting the results, but also allows for creating a propensity score including covariates, as described below. In the final study population (n = 775), 122 participants showed cortisol levels below the limit of detection (LOD) in the first trimester, 91 in the second and 49 in the last. These values were kept and included in the lowest quartile of cortisol as they represent very low cortisol levels.

2.2.2. Outcome

Postpartum depressive symptoms were assessed via a phone interview two months after delivery using the Edinburgh Postpartum Depression Scale (EPDS) (Cox et al., 1987), a scale consisting of 10 items, each scored between zero and three, validated in French settings (Guedeney and Fermanian, 1998). A total score out of 30 was then computed and the variable was subsequently dichotomized using a cut-off at >12 (Levis et al., 2020). The Cronbach's alpha of the scale for the study population was 0.77.

2.2.3. Covariates

Covariates were identified through the literature and discussed among the authors. Confounders in the regression models precede both the outcome and the exposure in time, and included *sociodemographic variables* such as maternal age at the time of the child's birth (18–24; 25–29; 30–34; 35–39; 40–45), highest educational level attained (higher education; no higher education), mother's occupation (in activity; unemployed; studying; other), migration background (French from birth or by reintegration; French by naturalisation, marriage, declaration at majority; foreigner or stateless), life partner (Mother lives with child's father or partner vs mother doesn't live with any partner), and social support (high; low). Other *variables related to pregnancy and delivery* included diabetes (no; chronic or during previous pregnancy) *Psychological variables* encompassed the occurrence of depression during a previous pregnancy (no; yes), psychological difficulties during ELFE pregnancy (no; yes), consultation for psychological difficulties before the ELFE pregnancy (no; yes), insults and hurtful remarks from partner during pregnancy (never; rarely or more), and intended pregnancy (yes; no or unsure). Lastly, other variables potentially *impacting hair cortisol* comprised parity, BMI at end of pregnancy, hypertension (no; chronic or previous pregnancy), child's sex (male; female), tobacco use (no; yes) and alcohol consumption during pregnancy (never; rarely or more), season at hair collection (summer; early autumn; late autumn), use of hairspray (never or rarely; one or several times a week; everyday), conditioner (never or rarely; one or several times a week; everyday), colouring products (never; rarely or more often), bleaching agents (never; rarely or more often), perm (never; rarely or more often), and chemical straightening (never; rarely or more often).

2.3. Statistical analyses

First, descriptive and bivariate analyses were performed to compare women included in our final population to the rest of ELFE women, using Chi square tests for categorical variables and Fisher's test for continuous ones. To deal with missing data, we conducted multiple imputations with five iterations on all variables of interest except the study outcome, using multivariate imputation by chained equations with the R package *mice* (Buuren and Groothuis-Oudshoorn, 2011). In a second step, unadjusted logistic regressions explored the relationship between cortisol levels in the first, second, and third trimesters and dichotomized postpartum depression scores. These regressions and all ensuing regression analyses were performed on imputed datasets before results were pooled. Subsequently, to address potential confounding effects, adjusted regression analyses were performed at each pregnancy trimester with cortisol as exposure, and dichotomized EPDS as outcome. Given that our number of events only allows the inclusion of seven covariates in our logistic regression models, as recommended (Cepeda, 2003), we used propensity score weighting as a more robust approach to adjust on a large number of confounders. Weights based on propensity scores were calculated for each participant for each of the three exposures and mean differences and KS statistics were balanced at a threshold of 0.2 (Abdia et al., 2017). Propensity scores were performed on imputed data using the R package *MatchThem* (Pishgar et al., 2021). Distribution of propensity scores were plotted using love plots (Supplementary Figure 1). Moreover, an additional analysis was performed to observe whether the use of a cut-off in the EPDS scale was affecting results. Therefore, we used EPDS as a continuous score to perform unadjusted and adjusted linear regressions. This regression was adjusted using the previously described propensity scores. Additionally, both unadjusted and adjusted regressions were performed varying cortisol reference category as to observe a potential non-linear association between prenatal cortisol and dichotomous EPDS at two months. Lastly, the same analyses were performed on complete cases.

All statistical analyses were conducted in RStudio 2022.02.3 using R 4.2.1.

3. Results

3.1. Description of the population

Compared to participants with no available hair samples (n = 17,554), women who provided hair samples that were analysed for cortisol and who answered the EPDS (n = 775) had lower EPDS scores and higher levels of education. They were more likely to be aged between 30 and 39, be employed, have French nationality by birth or reintegration, live with a partner, consume alcohol during pregnancy, and give birth in late autumn, and engaged less in chemical hair straightening (Supplementary Table 1).

Among our final sample (n = 775), 62 women (8%) obtained an EPDS score above the threshold, and 713 (92%) had a score of 12 or below. The distribution of the score is skewed to the right with a maximum score reached of 24 (out of 30) while 79 women obtained a score of 0 (10.2%). The majority of women included in the final sample were aged 25–34 years at the time of the study, had received a higher education, were employed and had on average 1.81 children (SD = 1.00). In regard to their mental health, 7.5% of women experienced a depression during a prior pregnancy, 23.0% previously visited a health professional for psychological difficulties, and 13.1% reported psychological difficulties during the current pregnancy (Table 1 and Supplementary Table 1).

Compared to women who obtained an EPDS below the threshold, women who scored above 12 were less likely to be in professional activity, less likely to live with a partner, more likely to declare a low social support, more likely to have had a depression during a prior pregnancy and to have visited health professional for psychological difficulties prior ELFE pregnancy, less often declared never receiving insults and hurtful remarks from partner during pregnancy, and used hair bleaching agents more often (Table 1).

Table 1
Characteristics of women with and without depressive symptoms, ELFE cohort (Mean and SD or n and %).

		Overall (n = 775)	No depressive symptoms (EPDS ≤12) (n = 713)	Depressive symptoms (EPDS >12) (n = 62)	*p*
EPDS score		5.5 (4.29)	4.67 (3.32)	14.95 (2.38)	
Sociodemographic variables					
Mother's age at childbirth	18–24	76 (9.8)	73 (10.3)	3 (4.8)	0.455
	25–29	237 (30.6)	216 (30.3)	21 (33.9)	
	30–34	295 (38.1)	272 (38.2)	23 (37.1)	
	35–39	139 (18.0)	128 (18.0)	11 (17.7)	
	40–45	27 (3.5)	23 (3.2)	4 (6.5)	
Educational attainment	No higher education	267 (34.5)	242 (34.0)	25 (40.3)	0.386
Mother's occupation	In activity	587 (75.7)	550 (77.1)	37 (59.7)	**0.004**
	Unemployed	94 (12.1)	80 (11.2)	14 (22.6)	
	Other (non-working, retired, other inactivity …)	80 (10.3)	69 (9.7)	11 (17.7)	
	Student, apprentice	14 (1.8)	14 (2.0)	0 (0.0)	
Migration background	French from birth or by reintegration	729 (94.6)	674 (95.1)	55 (88.7)	0.105
	French by naturalisation, marriage, declaration at majority	17 (2.2)	14 (2.0)	3 (4.8)	
	Foreigner or stateless	25 (3.2)	21 (3.0)	4 (6.5)	
Life partner	Mother lives with child's father or partner	751 (97.4)	695 (98.0)	56 (90.3)	**0.001**
	Mother doesn't live with any partner	20 (2.6)	14 (2.0)	6 (9.7)	
Social support	Low	60 (7.7)	45 (6.3)	15 (24.2)	**<0.001**
Variables related to pregnancy and delivery					
Diabetes	No	732 (97.6)	673 (97.5)	59 (98.3)	1.000
	Chronic or previous pregnancy	18 (2.4)	17 (2.5)	1 (1.7)	
Psychological variables					
Occurrence of depression during a prior pregnancy	Yes	58 (7.5)	49 (6.9)	9 (14.8)	**0.049**
Psychological difficulties during pregnancy	Yes	101 (13.1)	88 (12.4)	13 (21.3)	0.075
Health professional visit for psychological difficulties prior ELFE pregnancy	Yes	169 (23.0)	141 (20.8)	28 (48.3)	**<0.001**
Insults and hurtful remarks from partner during pregnancy	Never	694 (89.7)	647 (90.9)	47 (75.8)	**<0.001**
	Rarely or more often	80 (10.3)	65 (9.1)	15 (24.2)	
Intended pregnancy	No or unsure	44 (5.7)	37 (5.2)	7 (11.5)	0.082
Other variables potentially impacting hair cortisol					
Number of children		1.81 (1.00)	1.80 (1.00)	1.92 (1.08)	0.395
Mother's BMI at end of pregnancy		28.56 (4.69)	28.55 (4.66)	28.72 (5.00)	0.783
Hypertension	No	742 (97.8)	682 (97.7)	60 (98.4)	1.000
	Chronic or previous pregnancy	17 (2.2)	16 (2.3)	1 (1.6)	
Child's sex	Male	397 (51.2)	369 (51.8)	28 (45.2)	0.388
Tobacco consumption during pregnancy	Yes	153 (19.9)	141 (19.9)	12 (19.4)	1.000
Alcohol consumption during pregnancy	Yes	223 (29.0)	201 (28.4)	22 (35.5)	0.301
Season at hair collection	Late autumn	416 (53.7)	383 (53.7)	33 (53.2)	0.212
	Early autumn	155 (20.0)	138 (19.4)	17 (27.4)	
	Summer	204 (26.3)	192 (26.9)	12 (19.4)	
Use of hairspray	Never or rarely	537 (74.9)	500 (75.8)	37 (64.9)	0.138
	One or several times a week	113 (15.8)	99 (15.0)	14 (24.6)	
	Everyday	67 (9.3)	61 (9.2)	6 (10.5)	
Use of conditioner	Never or rarely	281 (38.9)	265 (39.8)	16 (28.1)	0.179
	One or several times a week	374 (51.7)	338 (50.8)	36 (63.2)	
	Everyday	68 (9.4)	63 (9.5)	5 (8.8)	
Use of hair colouring products	Never	430 (60.1)	404 (61.1)	26 (47.3)	0.061
	Occasionally or more often	286 (39.9)	257 (38.9)	29 (52.7)	
Use of bleaching agents	Never	655 (90.8)	608 (91.6)	47 (82.5)	**0.040**
	Occasionally or more often	66 (9.2)	56 (8.4)	10 (17.5)	
Getting a perm	Never	701 (97.4)	646 (97.4)	55 (96.5)	1.000
	Occasionally or more often	19 (2.6)	17 (2.6)	2 (3.5)	
Chemical straightening	Never	705 (97.5)	648 (97.4)	57 (98.3)	1.000
	Occasionally or more often	18 (2.5)	17 (2.6)	1 (1.7)	

EPDS: Edinburgh Postpartum Depression Scale.

3.2. Hair cortisol measures

An increase in mean cortisol concentrations was observed across trimesters (Fig. 2 and Table 2). Bivariate analyses between categorical cortisol at all three trimesters of pregnancy and all covariates of interest showed an association between cortisol during the first trimester and mother's BMI at end of pregnancy, season at hair collection, and use of hair colouring product. Associations between cortisol in the second trimester and mother's BMI at end of pregnancy, season at hair collection, and hypertension were also observed. Lastly cortisol in the third trimester was associated with mother's age at childbirth, mother's BMI at end of pregnancy, tobacco consumption during pregnancy, and season at hair collection **(Supplementary Table 2).**

3.3. Prenatal hair cortisol and postpartum depressive symptoms

Using EPDS as a dichotomous score, unadjusted and adjusted regression analyses showed an association between Q2 cortisol at the last pregnancy trimester and postpartum depression at 2 months (aOR = 2.67, 95%CI [1.01, 7.08]) (Table 3). An additional analysis using a continuous EPDS score in a linear regression was performed to exclude the possibility of having used an inadequate EPDS cut-off. This analysis revealed no significant associations between prenatal hair cortisol concentrations in any trimesters of pregnancy and an elevated risk of depressive symptoms 2 months postpartum (Table 4). Additionally, analyses varying cortisol reference categories confirmed the previous significant association with dichotomous EPDS at two months. Women whose cortisol concentrations fell withing the second quartile during the third pregnancy trimester had a higher risk of subsequent PPDS compared to those whose cortisol was within either the first or the fourth quartile (Supplementary Table 3). Lastly, unadjusted logistic regression analyses on complete cases revealed an association between dichotomous EPDS and both second and third quartiles of cortisol at the third pregnancy trimester. This association remained significant after adjustment with propensity scores, for both second (aOR = 4.58, 95%CI [1.57, 13.41]) and third quartiles of cortisol (aOR = 3.52, 95%CI[1.17, 10.62]). However, complete cases analyses showed no association between postpartum depressive symptoms and prenatal cortisol when using EPDS as a continuous score (adjusted or unadjusted) (Supplementary Table 4).

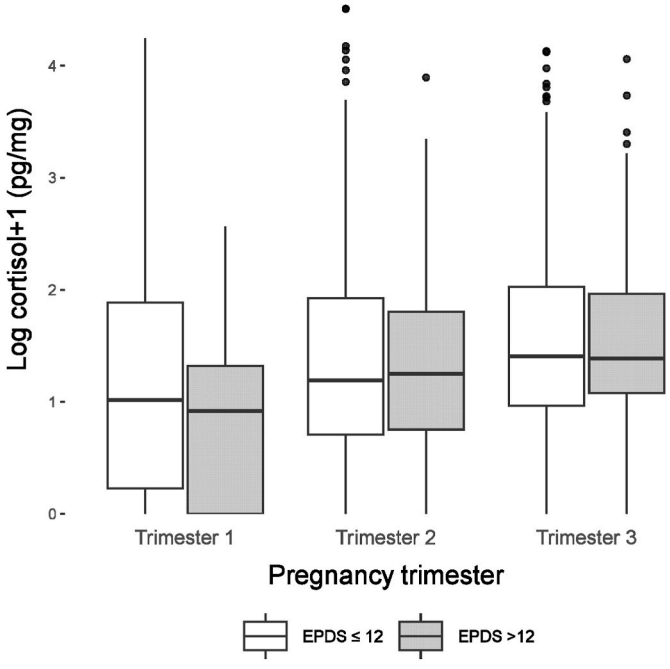

Fig. 2. Hair cortisol distribution of the ELFE study population per pregnancy trimester and by EPDS cut-off score.

4. Discussion

This study aimed to explore relationships between prenatal hair cortisol levels in pregnant women during different trimesters and subsequent postpartum depressive symptoms. Analysing a large cohort of French women from the general population, we observed an increase in mean hair cortisol concentrations from the first trimester to the third in both women with and without symptoms of postpartum depression. This increase throughout the course of pregnancy is in line with the current state of research reporting similar patterns (Khoury et al., 2023; Seth et al., 2016). However, one study observed a drop in cortisol concentrations during the second trimester among women with PPD symptoms (Caparros-Gonzalez et al., 2017). Nonetheless, neither our findings, nor previous research confirmed this drop during pregnancy among women with PPDS, indicating that this result may be specific to the data and could be explained by the small sample size of the study (n = 44).

We did not observe any noticeable differences in the overall pattern of hair cortisol concentrations during the first and second trimesters of pregnancy between women who later experienced postpartum depressive symptoms and those who did not, in both unadjusted and propensity score-adjusted analyses. These results align with those of several recent studies (Galbally et al., 2019; Gillespie et al., 2018; Khoury et al., 2020). However, we did observe an association between third trimester hair cortisol concentrations and depressive symptoms at 2 months postpartum. These outcomes corroborate certain previous findings reporting an association between lower third trimester cortisol levels and postpartum depressive symptoms (Jahangard et al., 2019; Yavuz et al., 2023). Nevertheless, our results should be interpreted with caution since only one quartile showed significance and sensitivity analysis using continuous EPDS scores did not confirm the association.

One explanation for the observed significant associations in the third trimester might be due to the fact that more recent hair strands are less prone to cortisol wash-out (Kirschbaum et al., 2009). It has been found that hair strands closest to the scalp offer more conclusive associations with cortisol than hair strands further down (Stalder and Kirschbaum, 2012). Hair collected at delivery, reflecting cortisol concentrations of the third trimester, is more reliable compared to hair strands further from the scalp, which reflect cortisol concentrations in earlier trimesters.

The lack of a clear association between prenatal cortisol concentrations and subsequent PPDS in our study and in the wider literature may be attributed to various factors. Firstly, methodological differences in cortisol and PPDS measurements may influence the observed outcomes. For instance, it is possible that the use of retrospective biological markers spanning several months does not reflect accurately the more transient measures of depressive symptoms. Secondly, previous studies have observed a cortisol drop at birth in women who do not experience PPDS, but stable cortisol concentrations up until 12 weeks postpartum in women experiencing depressive symptoms (Jahangard et al., 2019; Stickel et al., 2021). The lack of this anticipated cortisol drop warrants further investigation as a potential biological marker for the onset of postnatal depression. Since hair samples in this study were collected at birth, and thus only reflected the prenatal period, we were unable to identify the absence of a cortisol decrease after childbirth in our PPDS subsample. Finally, a recent review on psychological distress and prenatal cortisol argues for a disconnect between measured hair cortisol concentrations and the concept of self-reported distress (Khoury et al., 2023). This disconnect between prenatal cortisol and PPDS appears to be confirmed in a study that observed non-alignment of hair corticosteroid trajectories and mental health trajectories, leading the authors to advise against the use of hair corticosteroids as biomarkers in association with pregnancy mental health measures (Feng et al., 2024). More specifically, it has been suggested that cortisol in itself may not be a

Table 2
Hair cortisol concentration (pg/mg) characteristics for each pregnancy trimester, ELFE cohort.

	n	Min.	1st quartile	Median	Mean	SD	3rd quartile	Max.	Missing
Cortisol T1	775	0.00	0.23	1.76	4.47	7.34	5.56	68.67	256
Cortisol T2	775	0.00	1.03	2.33	5.26	8.84	5.81	89.72	65
Cortisol T3	775	0.00	1.68	3.09	5.80	7.77	6.57	61.20	0

T1: trimester 1; T2: trimester 2; T3: trimester 3.

Table 3
Unadjusted and propensity scores adjusted logistic regression analyses between prenatal hair cortisol quartiles at all three pregnancy trimesters and dichotomous EPDS.

		Unadjusted		Propensity score adjusted	
		OR	CI 95%	OR	CI 95 %
Trimester 1	Cortisol Q1	REF		REF	
	Cortisol Q2	0.95	0.41, 2.17	0.85	0.33, 2.20
	Cortisol Q3	1.10	0.49, 2.51	0.87	0.36, 2.14
	Cortisol Q4	0.78	0.31, 1.95	0.55	0.18, 1.66
Trimester 2	Cortisol Q1	REF		REF	
	Cortisol Q2	0.99	0.45, 2.17	1.07	0.45, 2.53
	Cortisol Q3	1.58	0.76, 3.26	1.78	0.77, 4.09
	Cortisol Q4	1.01	0.46, 2.23	0.76	0.29, 1.97
Trimester 3	Cortisol Q1	REF		REF	
	Cortisol Q2	**2.23**	**1.02, 4.88**	**2.67**	**1.01, 7.08**
	Cortisol Q3	1.65	0.73, 3.75	1.87	0.68, 5.14
	Cortisol Q4	1.55	0.68, 3.55	1.16	0.42, 3.20

EPDS: Edinburgh Postpartum Depression Scale.
Q1: quartile 1 (lowest); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4.

Table 4
Unadjusted and propensity scores adjusted linear regression analyses between prenatal hair cortisol at all three pregnancy trimesters and continuous EPDS.

		Unadjusted		Propensity score adjusted	
		exp B	CI 95%	exp B	CI 95%
Trimester 1	Cortisol Q1	REF		REF	
	Cortisol Q2	1.05	0.35, 3.15	0.95	0.33, 2.78
	Cortisol Q3	1.04	0.41, 2.65	0.96	0.34, 2.69
	Cortisol Q4	0.87	0.33, 2.25	0.72	0.24, 2.16
Trimester 2	Cortisol Q1	REF		REF	
	Cortisol Q2	1.07	0.44, 2.59	1.05	0.42, 2.59
	Cortisol Q3	2.04	0.83, 4.96	1.90	0.68, 5.30
	Cortisol Q4	1.24	0.50, 3.05	0.79	0.29, 2.16
Trimester 3	Cortisol Q1	REF		REF	
	Cortisol Q2	1.50	0.64, 3.54	2.14	0.82, 5.62
	Cortisol Q3	1.43	0.61, 3.38	1.66	0.64, 4.26
	Cortisol Q4	1.13	0.48, 2.67	0.85	0.35, 2.09

EPDS: Edinburgh Postpartum Depression Scale.
Q1: quartile 1 (lowest); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4.

reliable indicator of perinatal depression, possibly due to its involvement in numerous physiological mechanisms aside from the stress-response system (Mlili et al., 2023). For instance, the hair cortisol/cortisone ratio may be a more robust index as it can be quantified as an indirect marker of the enzymatic activity of 11b-hydroxysteroid-dehydrogenase type 2 (11β-HSD2) (Jaramillo et al., 2023). 11β-HSD2 converts cortisol into cortisone and reflects peripheral tissues' potential to metabolize corticosteroids. The intricate biological pathways leading to cortisol synthesis, influenced by various neurotransmitters and neuropeptides (such as noradrenalin and serotonin), may contribute to potential discrepancies between the body's biological reaction to stressors and the experienced stress at a subjective level.

Biological and self-reported stress markers could be related to different constructs, or external factors could affect the two constructs differently, emphasizing the separation (Khoury et al., 2023). Indeed, self-reported distress measures a subjective experience that may not perfectly align with physiological responses. While an association between the two concepts is possible, individual variations in stress responses and coping mechanisms among pregnant women may contribute to the absence of a consistent pattern. For instance, some women may have higher resilience to stress than others, and similar levels of biological stress could have a different impact on different women. Additionally, following psychotherapy during or after pregnancy could help women cope with mental health difficulties and prevent the occurrence of PPDS (Valverde et al., 2023; Wang et al., 2023). Drawing from our results we support the idea that prenatal hair cortisol should not be used as a sole predictor of postpartum depression and that further studies are needed to understand how individual variations in stress responses and coping mechanisms may contribute to this association.

Nonetheless, this study holds several advantages. First, the use of hair cortisol, particularly concentrations extracted from hair strands closer to the scalp, reflects an accumulated or chronic exposition to cortisol in the corresponding period. Therefore, it is less susceptible to measurement errors than salivary or serum cortisol concentrations, representative of a more transient cortisol level (Khoury et al., 2023). Second, the study benefits from a larger sample size compared to recent research in the field, allowing for a more robust analysis. Previous studies on prenatal cortisol and PPDS typically involved samples sizes ranging from 44 to 279 participants, whereas the present study includes 775 women from the general population. Third, the longitudinal design of this study provides enough time for the effect of the exposure on the outcome to occur. Conversely, a cross-sectional study design would not allow us to conclude on any causal effect. Lastly, the use of propensity scores in weighted regressions allowed for the adjustment of a wide range of confounding variables, whether of a psychological nature or related to hair treatment. While enhancing the internal validity of the study, this methodology is still relatively uncommon in this research domain.

It is however important to account for certain limitations when considering our results. First, the hair samples were 9 years old at time of analysis and despite being stored away from direct sunlight at room temperature, time may have had an impact on molecules' stability, resulting in cortisol being under-detected. Second, it is worth noting that a large number of participants did not have hair samples representative of the entire pregnancy period merely because their hair was shorter than 9 cm. The proportion of missing hair samples reached as high as 33% in the first semester (hair furthest from the scalp) and dropped to 8% in the second semester. Third, the use of quantiles in cortisol may affect the results since one quantile can gather individuals with rather large discrepancies in cortisol amount. Fourth, 79 women in our sample obtained zero on the EPDS score. Null total depression score have been stated to be unlikely to obtain (Cox et al., 2014) and could be in fact suggestive of depressive symptoms (Field et al., 1991). Likewise, the EPDS authors suggested completing the questionnaire twice, two weeks apart, to improve validity. Therefore, the singular EPDS from ELFE participants might be prone to errors that a double completion could have averted. These issues might have resulted in that depressive symptoms were not captured accurately for some women, potentially leading to underreporting of postpartum depression in our sample. Moreover, even though the cut-off scores of the EPDS are generally reflective of a level of symptomatology corresponding to clinical

diagnoses, caution is needed when making any inferences on clinical diagnoses as they were not directly assessed. Lastly, given that our analytical sample presented overall more favourable characteristics (higher educational level, being employed or having French nationality) compared to the overall cohort, our results may not be generalizable to other populations that are more disfavored. Additionally, the fact that they had lower EPDS scores could have led us to underestimate a potential association.

5. Conclusion

In our study, we established an association between hair cortisol levels during the third trimester of pregnancy and PPDS at two months postpartum among a large sample of women from the French general population. These outcomes corroborate certain previous findings that report an association between lower third trimester cortisol levels and postpartum depressive symptoms. Nevertheless, our results, alongside previous research, suggest that future studies could benefit from investigating other biomarkers in the context of perinatal mental health. Investigating the CC ratio or exploring neurotransmitters and neuropeptides known to influence cortisol could offer valuable insights. Moreover, expanding measurements to encompass the early postnatal period and considering potential moderating factors could contribute to a more comprehensive understanding of the complex relationship between prenatal cortisol levels and postpartum depressive symptoms.

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CRediT authorship contribution statement

Charlotte Maguet: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Naomi Downes:** Writing – review & editing, Methodology. **Ketevan Marr:** Writing – review & editing. **Anne-Laure Sutter-Dallay:** Writing – review & editing. **Cédric Galéra:** Writing – review & editing. **Solène Wallez:** Writing – review & editing. **Clemens Kirschbaum:** Data curation. **Florence Gressier:** Writing – review & editing. **Maria Melchior:** Writing – review & editing. **Marie-Aline Charles:** Writing – review & editing, Project administration, Funding acquisition. **Muriel Koehl:** Writing – review & editing, Funding acquisition. **Judith van der Waerden:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.08.032.

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