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Diurnal cortisol throughout pregnancy and its association with maternal depressive symptoms and birth outcomes

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ABSTRACT

Background: Depression during pregnancy is a common complication that can negatively affect fetal health and birth outcomes. Cortisol is believed to be a key mediator of this association. Although pregnancy entails a natural increase in cortisol levels, preclinical depression could alter its circadian rhythm, producing excessively high overall diurnal cortisol levels that might be harmful for the fetus and future offspring development.
Objectives: Using a prospective longitudinal design, we aimed to study (i) trimestral cortisol circadian rhythm and its overall levels throughout pregnancy in healthy women, (ii) the extent to which maternal depressive symptoms influence both cortisol rhythmicity and overall levels, and (iii) the possible adverse consequences of elevated maternal cortisol on the offspring's weight and gestational age at birth.
Study design: 112 healthy pregnant women from the general Spanish population were recruited before their first pregnancy. To assess cortisol circadian rhythm, participants provided four saliva samples at each trimester of pregnancy (at awakening, 30 min after awakening, before lunch and before going to bed). Overall cortisol levels were calculated with AUCg approximation. Depressive symptoms were evaluated in each trimester and defined according to EPDS cut-off values (1st trimester, EPDS $\geq$ 11; 2nd and 3rd trimesters, EPDS $\geq$ 10). At birth, the risk for low weight, prematurity and weight birth percentile was retrieved for 100 infants. Mixed models and simple effects were employed to study changes of maternal cortisol circadian rhythm and overall levels throughout pregnancy and the possible influence of maternal depressive symptoms. Finally, logistic regressions were performed to assess the associations between maternal overall cortisol levels in each trimester of pregnancy and birth anthropometrics.
Results: Although overall diurnal cortisol levels increase throughout pregnancy, cortisol circadian rhythm is preserved in all trimesters [1st ($F(3110)= 92.565$, $p < .001$), 2nd ($F(3,85)= 46.828$, $p < .001$) and 3rd ($F(3,90)= 65.555$, $p < .001$)]. However, women with depressive symptoms showed a flattened cortisol circadian pattern only during the second trimester, characterized by a blunted awakening peak and reduced evening decline ($F(3,85)= 4.136$, $p = .009$), but not during the first ($F(3,11)= 1.676$, $p = .176$) or the third ($F(3,90)= 1.089$, $p = .358$) trimesters. Additionally, they did not show a cortisol increase from second to third trimester ($p = .636$).

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Finally, higher maternal cortisol levels in second and third trimesters seemed to be associated with increased risk of prematurity (adjusted OR −0.371, 95% CI 0.490–0.972, p = .034) and low birth weight percentile (adjusted OR −0.612, 95% CI 0.348–0.846, p = .007) respectively.

Conclusion: Maternal cortisol levels increased throughout pregnancy, although cortisol circadian rhythm was preserved in all trimesters of pregnancy. However, prenatal depressive symptoms were associated with flattened maternal cortisol circadian rhythm in mid-pregnancy. Therefore, it seems that women with depressive symptoms tended to increase less gradually their cortisol levels from mid to late pregnancy. Finally, higher maternal cortisol levels in mid and late-pregnancy seem to be associated with poorer birth anthropometrics Early detection of depressive symptoms in general population could help to prevent putative obstetrical and birth adverse outcomes.

1. Introduction

Pregnancy is a sensitive period for the expectant mother in which multiple psychological and physiological changes occur. During this period, it is common that women experience depressive symptoms. In fact, while major depression is present in up to 11.9% of pregnant women, the prevalence of subclinical depressive symptomatology is higher, although it often remains undetected (Woody et al., 2017; Yonkers et al., 2009). Depression during pregnancy has been associated with an increased risk of adverse birth and child outcomes, including prematurity, low birth weight, neurodevelopmental delays and adult psychiatric disorders (Davis et al., 2007; Deave et al., 2008; Glover, 2011; Grigoriadis et al., 2013; Osborne et al., 2022; Plant et al., 2015). A key potential mediator linking maternal depression and offspring's developmental alterations is the flow of abnormally high levels of maternal cortisol, which can cross the placental barrier and compromise fetal development (Buss et al., 2012; Reynolds, 2013; Vlenterie et al., 2022).

Cortisol is the end effector of the Hypothalamic-Pituitary-Adrenal (HPA) axis and it plays a crucial role in homeostatic regulation during stress situations (Godoy et al., 2018). Cortisol is also responsive to normal daily activities and is involved in the proper functioning of multiple physiological systems (Spencer and Deak, 2017). Cortisol secretion follows a circadian rhythm in healthy individuals, with a maximum peak approximately 30 min after awakening, followed by a decline across the day, reaching the lowest levels at night (Debono et al., 2009; Weitzman et al., 1971). Over the course of pregnancy, maternal cortisol increases two to four-fold due to the release of other hormones such as estrogen and placental corticotrophin-releasing hormone (CRH), that interact with maternal HPA axis stimulating cortisol secretion (Jung et al., 2011; Qureshi et al., 2007; Sandman et al., 2006). Despite the increasing circulating levels of cortisol, its circadian rhythmicity seems to be maintained throughout pregnancy (Entringer et al., 2011).

In utero, the fetus is partly protected from excessive cortisol exposure thanks to the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which metabolizes cortisol into inactive cortisone (Murphy et al., 1974). Although 11β-HSD2 rises in parallel with maternal cortisol during pregnancy, about 10–20% of maternal cortisol still makes it through the placenta, reaching fetal circulation and playing a role in fetal development and organ maturation (Murphy et al., 2006; Trainer, 2002). In addition to these naturally occurring maternal endocrine fluctuations, it has been shown that maternal depression can cause a short term increase in cortisol levels, further increasing fetal exposure to this hormone (Duthie and Reynolds, 2013). In that sense, excessive cortisol levels could influence in infant birth outcomes, reducing birth weight by inducing the vasoconstriction of the uterine artery, diminishing the flow of nutrients and oxygen, and shortening the gestation by stimulating the production of placental CRH (Field and Diego, 2008). Moreover, according to Krontira et al. (2020), an elevated glucocorticoid signaling in utero may dysregulate fetal HPA axis through alterations on the epigenetic landscape, predisposing children to worse emotional outcomes (Krontira et al., 2020; Monk et al., 2016; Morsi et al., 2018).

The evidence of an association between maternal depression and cortisol levels has been controversial, partially due to the variability of cortisol collection during pregnancy and analytic approaches, but also to the definition of maternal depressive condition (Dunkel Schetter, 2011; Orta et al., 2018). Although cortisol can be measured in different tissues (e.g.: blood, hair, and urine), it has been commonly measured in saliva due to its ability to identify subtle fluctuations in concentrations across the day, and its non-invasive easy access. Despite multiple samples are needed to capture cortisol diurnal patterns, most of the studies collect salivary samples only in the morning, which does not allow to assess diurnal variation (Orta et al., 2018; Vlenterie et al., 2021). Furthermore, most of the studies linking maternal adverse conditions and cortisol have been performed in the third trimester of pregnancy (Bublitz et al., 2019; Fassaie and McAloon, 2020; Orta et al., 2018). To the best of our knowledge, only three articles have assessed cortisol levels at different time points throughout the day and in different moments of pregnancy, showing contradictory results. While two studies observed that cortisol diurnal pattern was flatter in depressed women in all trimesters (Murphy et al., 2022; O'Connor et al., 2014), the other study did not show any association between maternal depressive symptoms and cortisol circadian rhythm (van den Heuvel et al., 2018). Additionally, a recent review indicates that maternal depression correlates with cortisol concentrations in only 24 out of 47 studies reviewed (Seth et al., 2016). In this line, an independent meta-analysis found no consistent relationships between self-reported stress or depression and hair cortisol levels in pregnant women (Stalder et al., 2017).

In order to clarify the association between maternal depression, cortisol and birth anthropometrics, the aims of the current research were: (1) to study how cortisol diurnal patterns and overall levels vary over the three trimesters of pregnancy, (2) to explore how maternal depressive symptoms impacts on her cortisol rhythmicity and overall levels, and (3) to study the influence of overall maternal cortisol levels on infant's weight, weight percentile and gestational age at birth. Based on previous literature, we hypothesized that diurnal cortisol levels would increase throughout pregnancy, especially at the evening. Additionally, we expected that pregnant women with depressive symptoms would show higher overall cortisol concentrations since the beginning of the pregnancy, when compared to control women. Finally, the offspring of women with higher cortisol levels will have and increased risk of low weight, prematurity and/or low weight for gestational age.

2. Materials and methods

The current sample includes 112 healthy primiparous pregnant women from the general Spanish population, recruited from May 2016 to March 2020 in the ongoing "Intramural Maternal Epi-Project". Participants were recruited before their first ultrasound from the maternity units of two public Spanish general hospitals (Hospital Clinic of Barcelona and Hospital Universitario Central de Asturias). Inclusion criteria included: (1) less than thirteen weeks of pregnancy, (2) age between 18–40 years, (3) first pregnancy, (4) no history of physical, neurological, or mental diseases, and (5) singleton pregnancy. Multiple pregnancies and health conditions were discarded to avoid possible biases. This study was approved by the medical ethical committee of the local hospitals and was conducted in full compliance with Helsinki declaration.

After providing their written informed consent, participants were interviewed by a trained psychologist three times during pregnancy, coinciding with the ultrasounds offered by the Spanish Public Healthcare system: between 11th–13th weeks (first trimester), between 20th–22nd weeks (second trimester) and between 32nd–34th weeks (third trimester). At the end of each interview, participants were instructed to collect four salivary samples at home. At birth, perinatal outcomes of 100 infants were obtained.

The protocol of the project is summarized in Fig. 1.

2.1. Data collection

2.1.1. Depressive symptoms

The Edinburgh (Postnatal) Depression Scale E(P)DS (Cox et al., 1987) is a screening scale for depressive symptoms during pregnancy and postpartum (Cox et al., 1996). This hetero-administered questionnaire consists of 10 questions, measured on a Likert scale from 0 to 3, regarding woman's emotions on the previous 7 days. The total score ranges between 0 and 30. Following Bergink et al. (2011) recommendations, the cutoff-values for depressive symptoms considered for this study were 11 or greater in the first trimester and 10 or greater in second and third trimesters. Depressive symptoms through pregnancy were defined as the presence of depressive symptoms at least in one trimester.

2.1.2. Body Mass Index (BMI)

maternal BMI was calculated using self-reported measures of weight and height at first trimester of pregnancy.

2.1.3. Cortisol circadian rhythm measures

Participants were given four specially designed test-tubes (Salivette®, Sarstedt, Germany) at the end of each trimester's interview for self-saliva collection, following a protocol highly used and accepted in the literature(Sørensen et al., 2021). Moreover, to avoid possible biases, clear written instructions for salivary self-collection were given (Section 1.1, Supplementary material). Samples must be taken immediately after awakening (B1), 30 min after awakening (B2), before lunch (B3), and before going to bed (B4). Participants were instructed to store their saliva samples in their freezer until they delivered them to the research center in the next trimestral appointment and then samples were stored at −25 ºC until analysis.

Salivary cortisol was determined using a highly sensitive enzyme-linked immunosorbent assay (ELISA) (commercial kit Salimetrics, LLC, State College, PA; Table S1, Supplementary material).

2.1.4. Birth anthropometrics

Weight at birth, gestational age at birth and offspring's birth weight percentile were retrieved. The cutoff-value for low weight was <2.500 kg, for preterm birth was <37 0/7 weeks according with the World Health Organization (2014) and the American College of Obstetricians and Gynecologists(American College of Obstetricians and Gynecologists, 2013), respectively. Offspring birth weight percentile was calculated with an online tool based on the clinical growth charts developed by the World Health Organization (WHO) for infants and children ages 0 to 2 years of age (Kiserud et al., 2017). Weight percentile was calculated according to gestational age (in days) and offspring sex. The total score ranges between 1 and 99 and the cutoff-value for low weight percentile was <10.

2.2. Statistical analysis

Analyses were conducted using SPSS 26.0 (IBM, Chicago, Illinois, USA) for Windows. Salivary cortisol concentrations were log10 transformed to fulfill the requirements for normal distribution.

Three set of analyses were conducted: (i) The DIURNAL-set examined maternal cortisol circadian rhythm, independently in each trimester, and the possible influence of maternal depressive symptoms. Thus, three mixed-effects models (one per trimester) were employed, in which the main factor time had four categories corresponding to the diurnal saliva collection moments (B1, B2, B3 and B4).

(ii) The PREGNANCY-set examined changes on daily cortisol secretion throughout pregnancy and explored if these changes differed regarding depressive symptoms. To have a measure of the total cortisol output during a day, the area under the curve with respect to ground (AUCg) was calculated for each trimester using the four log10 transformed cortisol concentrations. For this PREGNANCY-set, only one mixed-effect model was executed. The main factor time had three categories corresponding to each trimester of pregnancy.

For all mixed models, a random effect of intercept and a random

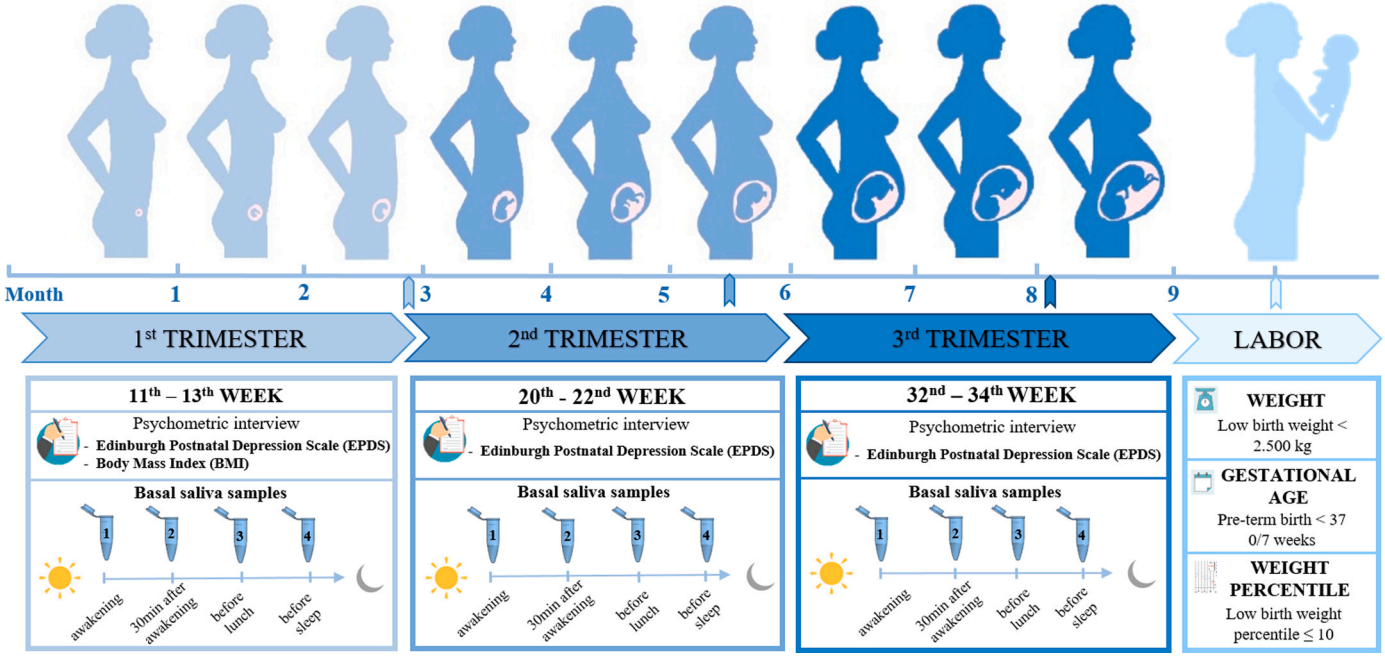

Fig. 1. Summary of the study protocol; EPDS, Edinburgh prenatal depression scale.

slope of time were employed to account for within-subject correlations, as recommended by Heisig & and Schaeffer (2019). The main effect of interest was the interaction between depressive symptoms and time, defined as four moments throughout one day for the DIURNAL-set and three trimesters for de PREGNANCY-set. Simple effects were also calculated to evaluate the specific time-point effect between groups. To account for possible confounders, maternal age, the gestational week in which salivary samples were collected, the time of first cortisol sample (awakening, B1) and maternal BMI were included as covariates for DIURNAL-set and maternal age for PREGNANCY-set.

(iii) The BIRTH-set explored the effect of diurnal total cortisol output (AUCg) in each gestational trimester in low weight, preterm birth and offspring birth weight percentile. For this set, logistic regressions were performed, crude and adjusting β coefficients with 95% confidence intervals. The following confounders were included: maternal age, the gestational week in which saliva samples were collected, maternal BMI and offspring's sex. The effect of maternal depressive symptoms (EPDS) in each gestational trimester in low weigh, preterm birth and low offspring birth weight percentile were also analyzed (see Section 2.6, Supplementary material).

All tests were two-tailed with significance defined as p-value <0.05. To correct for the testing of three different trimesters of pregnancy (DIURNAL-set) and the overall cortisol model (AUCg; PREGNANCY-set), a Bonferroni correction was applied in Table 2, by dividing the original alpha level ($p < .05$) by 4 (3 + 1) and obtained a new significance level of $p < .013$. Furthermore, to correct for the testing the three trimesters of pregnancy with birth anthropometrics (BIRTH-set), a Bonferroni correction was applied by dividing the original alpha level ($p < .05$) by 3 and obtained a new significance level of $p < .017$.

3. Results

Out of 112 pregnant women initially recruited, 5 women dropped out of the study in the 1st trimester, 3 women dropped out in the 2nd trimester and 4 dropped out in the 3rd trimester of pregnancy (i.e., no cortisol and no questionnaire data available). Finally, birth information was retrieved for 100 dyads. For more information regarding missing data, see Section 2.1, Supplementary material.

When comparing the participants who dropped out the study and those included in the analysis, there were no significant differences in either maternal age ($p = .578$) and overall cortisol values in first trimester (AUCg) ($p = .634$). However, excluded participants exhibited significantly higher depressive symptoms than those included ($t = 3.90$ $p = .048$).

Maternal and neonatal characteristics are presented in Table 1 and information regarding cortisol samples is detailed in supplementary (Table S1). As expected, having depressive symptoms in the first trimester correlates with having depressive symptoms during the second ($r = .51$, $p < .001$) and third trimesters ($r = .67$, $p < .001$), indicating a time-stability of this subclinical condition.

3.1. Cortisol circadian rhythm across trimesters and maternal depressive symptoms

The DIURNAL-set indicated that cortisol levels fluctuated significantly throughout the day, showing a circadian rhythm in all trimesters [1st ($F(3110) = 92.565$, $p < .001$), 2nd ($F(3,85) = 46.828$, $p < .001$) and 3rd ($F(3,90) = 65.555$, $p < .001$)] (see Fig. 2).

Regarding maternal depressive symptoms, the second trimester-mixed model indicated that cortisol diurnal pattern differs between both groups ($F(3,85) = 4.136$, $p = .009$), surviving Bonferroni correction. While women without depressive symptoms showed significant differences between all the diurnal time-points ($p < .001$ between B1-B2, B2-B3, and B3-B4), women with depressive symptoms did not show the expected morning cortisol increase (between B1-B2) ($p = .214$) nor the evening decline (between B3-B4) ($p = .292$). These observations were more accentuated in women with severe depressive symptoms (see supplementary material). Cortisol diurnal pattern did not significantly differ between both groups in the first ($F(3110) = 1.676$, $p = .176$) and the third trimester ($F(3,90) = 1.089$, $p = .358$). However simple effects indicated that in the 1st trimester both morning cortisol increase, and evening decline were slightly blunted in women with depressive symptoms ($p = .224$ between B1-B2; $p = .145$ between B3-B4). (see Table 2 and Fig. 3).

For more details about simple effects and covariates, see Tables S3

Table 1
Demographics of the recruited sample (n pregnant women = 112, n offspring = 100).

Variables		Total sample
Maternal age (years) (M, S.D., range)		32.24 (4.43) [21–40]
Country of birth	Spain (*n, %*)	83 (74.1%)
	Other[a] (*n, %*)	29 (25.9%)
Level of education[b]	Low (*n, %*)	15 (13.4%)
	Moderate	31 (27.7%)
	High	66 (58.9%)
Pre-pregnancy BMI (kg/m^2) (M, S.D., range)		23.71 (4.24) [17.29-39.02]
EPDS 1st Trimester[c,d] (M, S.D., range)		6.87 (4.50) [0–19]
	Absence of depressive symptoms (*n, %*)	76 (71.0%)
	With depressive symptoms (*n, %*)	31 (29.0%)
EPDS 2nd Trimester[c,d] (M, S.D., range)		6.13 (5.16) [0–24]
	Absence of depressive symptoms (*n, %*)	79 (79.8%)
	With depressive symptoms (*n, %*)	20 (20.2%)
EPDS 3rd Trimester[c,d] (M, S.D., range)		6.25 (6.25) [0–23]
	Absence of depressive symptoms (*n, %*)	75 (77.3%)
	With depressive symptoms (*n, %*)	22 (22.7%)
Infant birth weight (kg)[e] (M, S.D., range)		3.29 (0.51) [1.80-4.51]
	Normal weight (*n, %*)	93 (93.0%)
	Low weight (*n, %*)	7 (7.0%)
Gestational Age at delivery (weeks)[f] (M, S.D., range)		39.75 (1.49) [32.86-42.57]
	Full term (*n, %*)	93 (93.0%)
	Pre-term (*n, %*)	7 (7.0%)
Offspring birth weight percentile[g] (M, S.D., range)		10.71 (28.42) [1–99]
	Appropriate for gestational age (*n, %*)	74 (74.0%)
	Low for gestational age (*n, %*)	16 (16.0%)
Infant sex	Male (*n, %*)	48 (48.0%)
	Female (*n, %*)	52 (52.0%)

Note: BMI, Body mass index; EPDS, Edinburgh prenatal depression scale

[a] Other includes Latin American (19.0%), Western Europe (5.7%) and Eastern Europe (1.6%)

[b] Low level of education includes no education, lower general secondary education and intermediate vocational education, Moderate level of education includes higher general secondary education, pre-university education and higher vocational education, High level of education includes university (degree, master or doctorate)

[c] Absence of depressive symptoms includes EPDS scores lower than 11 for 1st and lower than 10 for 2nd and 3rd trimester of gestation while depressive symptoms included EPDS scores equal or higher to 11 for 1st and equal or higher than 10 for 2nd and 3rd trimester of gestation

[d] n EPDS: 1st trimester (weeks 11–13) = 107, 2nd trimester (weeks 20–22) = 99, 3rd trimester (weeks 32–34) = 97

[e] The cutoff-value for low birth weight was <2.500 kg

[f] The cutoff-value for pre-term birth was <37 0/7 weeks

[g] The cutoff-value for low offspring birth weight percentile was <10

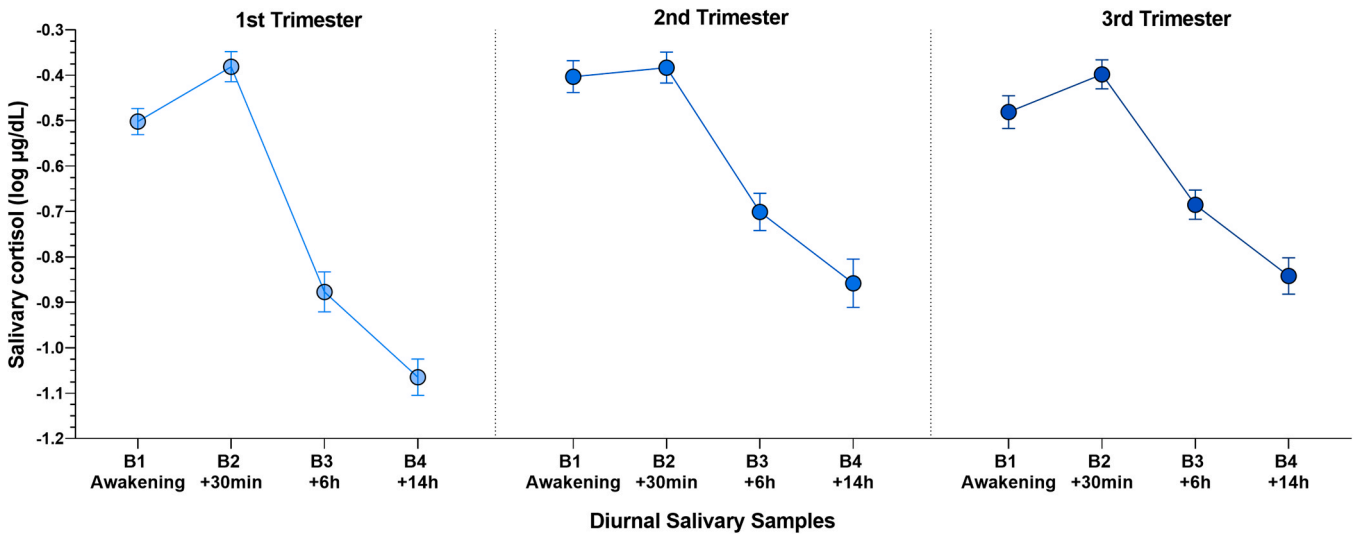

Fig. 2. Maternal salivary cortisol fluctuations throughout a day in each of the three trimesters of pregnancy (error bars SE). n analyses: T1 (weeks 11–13) = 93, T2 (weeks 20–22)= 91, T3 (weeks 32–34)= 81. Results of the DIURNAL-model indicate that cortisol significantly fluctuates during a day in all the three trimesters (1st trimester, F = 111.358, p < .001; 2nd trimester, F = 52.933, p < .001; 3rd trimester, F = 71.889, p < .001).

and 4, Supplementary material.

3.2. Overall cortisol levels throughout pregnancy and maternal depressive symptoms

The AUCg mixed model showed that overall diurnal cortisol varies across the three trimesters of gestation (*F(2101)= 15.393, p < .001*). When exploring simple effects, overall cortisol levels showed a significant increase from first to second trimester (*p < .001*) but did not vary from second to third trimester (*p = .551*), indicating a special increase in the first stages of pregnancy.

Interestingly, no significant differences between women with depressive symptoms and controls were found for overall diurnal cortisol throughout pregnancy (*F(1,87)= 0.948, p = .333*). However, simple analysis revealed that women with depressive symptoms only increased cortisol levels from first to second trimester, while control women tended to increase their cortisol levels gradually during pregnancy (see Table 2) (see Fig. S1 and Table S4, Supplementary material).

Regarding covariates, while maternal BMI did not significantly influence the AUCg (F(1,22)= 0.360, p = .360), maternal age was associated with higher AUCg throughout pregnancy (F(1,92)= 1.036, p = .024).

3.3. Maternal cortisol levels during pregnancy and birth outcomes

Regarding BIRTH-set, in the second trimester a significant association was observed between overall maternal cortisol levels (AUCg) and prematurity (adjusted odds ratio −0.371, 95% confidence interval 0.490–0.972, p = .034), although this result did not survive the conservative Bonferroni correction. In the 3rd trimester, higher maternal AUCg was associated with lower offspring weight birth percentile (adjusted odds ratio −0.612, 95% confidence interval 0.348–0.846, p = .007), surviving Bonferroni correction.

However, no associations were observed between maternal cortisol and birth anthropometrics in the 1st (See section 2.5, Supplementary material) and between covariates and birth anthropometrics in 1st, 2nd and 3rd trimester (See Table S5, Supplementary material). Interestingly, no associations were observed between maternal depressive symptoms in 1st, 2nd and 3rd trimesters and birth anthropometrics (See section 2.6., Supplementary material).

4. Discussion

The present study provides a deeper insight into the relationship between gestational maternal depressive symptoms, maternal cortisol fluctuations and birth anthropometrics. According to our results, cortisol circadian rhythm was preserved in all trimesters of gestation. However, women with depressive symptoms showed an attenuated cortisol circadian profile, presenting blunted morning cortisol increase and evening decline. These effects were apparent in the first trimester and significantly detectable in the second one, although not observable in the third. As expected, overall diurnal cortisol levels significantly increased during pregnancy in all women, even though women with depressive symptoms tended to present a milder increase from second to third trimester. Furthermore, higher cortisol levels in mid and late pregnancy seemed to be associated with prematurity and low weight percentile in newborns.

Previous studies have also linked HPA axis alterations and hypercortisolemia to clinical depression, in both pregnant women (Orta et al., 2018; Seth et al., 2016) and non-pregnant population (Mikulska et al., 2021; Nandam et al., 2020). Despite EPDS scale is used in all the above-mentioned studies, different cut-offs have been adopted, which might influence the number of depression cases identified and results interpretation. Particularly, our findings suggest that depressive symptoms are related to a flattening of the cortisol circadian rhythm in early-mid pregnancy, indicating that women with depressive symptoms (although not diagnosed) could be exposed to lowered morning and heightened evening cortisol levels in early mid pregnancy compared to their healthy peers. Moreover, we observed a significant effect between groups of severity, showing that 2nd trimester cortisol circadian rhythm flattening was more accentuated in women with severe depressive symptoms (see Fig. S2, Supplementary material). This is in line with previous literature (Murphy et al., 2022; O'Connor et al., 2014), reporting flatter diurnal cortisol patterns across all trimesters among pregnant women with anxious depressive disorders or exposed to early adverse life events. Moreover, Heuvel and colleagues (2018) identify a blunted cortisol awakening response (CAR) among pregnant women with somatic anxiety symptoms compared to controls; however, they did not observe associations regarding maternal diurnal rhythmicity and depression. Contrary, Osborne et al. (2022) did not find differences in cortisol diurnal rhythmicity nor in CAR regarding preconceptional depression diagnosis. To the best of our knowledge, our study is the first to analyze each trimester independently, while previous research

Table 2
Cortisol values log10 transformed in the three trimesters of pregnancy and cortisol secretion (AUCg) throughout pregnancy of the total sample and according to the presence of depressive symptoms.

		Total sample (Mean ± SD)	F (p)[a]	F (p)[b]	Depressive symptoms		
					Without depressive symptoms (Mean ± SD)	With depressive symptoms (Mean ± SD)	F (p)[c]
1st TRIMESTER (μg/dL Log transformed)	B1-T1st	-.502 ± .030	109.827 (<.001 ***)▲	0.688 (.409)	-.507 ± .026	-.498 ± .055	1.676 (.176)
	B2-T1st	-.396 ± .036			-.371 ± .031	-.421 ± .064	
	B3-T1st	-.881 ± .048			-.918 ± .042	-.844 ± .086	
	B4-T1st	-1.067 ± .043			-1.142 ± .037	-.993 ± .078	
2nd TRIMESTER (μg/dL Log transformed)	B1-T2nd	-.410 ± .037	84.603 (<.001 ***)▲	1.185 (.279)	-.455 ± .031	-.365 ± .067	4.136 (.009 **)▲
	B2-T2nd	-.395 ± .035			-.358 ± .029	-.433 ± .064	B1-B2 * **▲
	B3-T2nd	-.705 ± .043			-.753 ± .036	-.657 ± .077	B3-B4 * **▲
	B4-T2nd	-.859 ± .057			-.949 ± .047	-.769 ± .104	
3rd TRIMESTER (μg/dL Log transformed)	B1-T3rd	-.500 ± .037	89.710 (<.001 ***)▲	1.233 (.271)	-.431 ± .035	-.569 ± .065	1.089 (.358)
	B2-T3rd	-.412 ± .034			-.374 ± .032	-.450 ± .059	
	B3-T3rd	-.700 ± .034			-.679 ± .032	-.722 ± .060	
	B4-T3rd	-.851 ± .042			-.846 ± .040	-.857 ± .074	
AUCg throughout pregnancy	T1st	-12.086 ± 0.438	101.175 (<.001 ***)▲	0.948 (.333)	-12.291 ± 0.499	-11.882 ± 0.717	1.036 (.359)
	T2nd	-9.862 ± 0.366			-10.481 ± 0.416	-9.242 ± 0.599	
	T3rd	-9.515 ± 0.388			-9.661 ± 0.426	-9.569 ± 0.644	

Mixed-model analyses for cortisol diurnal slopes in the three trimesters of pregnancy and cortisol secretion (AUCg) throughout pregnancy according to maternal depressive symptoms.
Note: AUCg, area under the curve with respect to ground (indicating the total cortisol output); B1: basal sample at awakening, B2: basal sample 30 min after awakening, B3: basal sample before lunch, B4, basal sample before going to bed, T1st: 1st trimester, T2nd: 2nd trimester, T3rd: 3rd trimester
Mean time for saliva sample collection: 1st trimester [week 15.43 ± 3.26 (8-21)], 7:54 ± 1:09 (5:48–11:50) (B1-T1st); 8:28 ± 1:09 (6:30–12:30) (B2-T1st); 14:13 ± 1:10 (11:48–16:20) (B3-T1st); and 22:37 ± 1:40 [20:10–1:40(+1 day)] (B4-T1st); 2nd trimester [week 26.08 ± 4.50 (18-32)], 8:06 ± 1:08 (6:10–11:50) (B1-T2nd); 8:48 ± 1:19 (6:40–12:30) (B2-T2nd); 14:14 ± 1:03 (12:00–16:30) (B3-T2nd); and 22:40 ± 1:38 [20:00–1:48(+1 day)] (B4-T2nd); 3rd trimester [week 35.52 ± 2.81 (30-41)], 8:33 ± 1:08 (6:18–11:30) (B1-T3rd); 9:09 ± 1:07 (6:48–12:01) (B2-T3rd); 14:17 ± 0:47 (12:10–16:10) (B3-T3rd); and 22:41 ± 1:18 [19:00–1:30(+1 day)] (B4-T3rd)
Absence of depressive symptoms includes EPDS scores lower than 11 for 1st and lower than 10 for 2nd and 3rd trimester of gestation while depressive symptoms included EPDS scores equal or higher to 11 for 1st and equal or higher than 10 for 2nd and 3rd trimester of gestation
n depressive analysis (T1 = 93, Absence of symptoms = 70, With symptoms = 23; T2 = 91, Absence of symptoms = 71, With symptoms =20, T3 = 81, Absence of symptoms = 59, With symptoms = 22; Total pregnancy = 73, Absence of symptoms = 53, With symptoms = 20)
[a] Mixed-effects model for time
[b] Mixed-effects model for depressive risk
[c] Mixed-effects model for interaction between depressive risk and time. Values in superscript (B1-B2 and B3-B4) indicate the samples with significant differences in cortisol fluctuation regarding depressive symptoms in the simple effects test in the context of mixed-effect model.
The analyses include the following covariates: maternal age, weeks of gestation and time of awakening (for single cortisol measurements in all trimesters) and maternal age (for AUCg).
p values: **p < .01, and ***p < .001. ▲p ≤ .017 (as the Bonferroni-corrected level of significance for multiple testing (.05/4 = 0.013).

included the data of all trimesters in the same statistical analysis.

Although the presence of depressive symptoms, moderate or severe, seem to be associated with subtle alterations on cortisol rhythmicity, flattening diurnal and evening responses, depressive symptoms are not able to completely dysregulate HPA axis functioning in early pregnancy. Furthermore, in late pregnancy no differences on cortisol circadian rhythm regarding maternal depressive symptoms were observed. This result is consistent with previous evidence reporting no differences in CAR among depressed and non-depressed pregnant women in late pregnancy (Hellgren et al., 2013). Of note, placental CRH increases especially during the last 6–3 weeks of pregnancy (Kammerer et al., 2006; Mastorakos and Ilias, 2003)[i], inducing the desensitization of pituitary CRH receptors (Thomson, 2013), and preventing women from hypercortisolemia (Grammatopoulos, 2007). In fact, Entringer et al. (2010) observed that cortisol responses to acute stress are attenuated only in the third trimester, suggesting that HPA axis functioning in late pregnancy may have a greater influence of hormonal perinatal environment rather than maternal stress conditions.

In accordance with previous studies, our results indicate that maternal overall cortisol levels significantly increase during pregnancy (Buss et al., 2012; Entringer et al., 2011; Orta et al., 2019; van den Heuvel et al., 2018). Interestingly, while control women show a gradual increase, women with depressive symptoms show a more pronounced increase of cortisol levels in mid-pregnancy. A pregnant woman goes throughout different metabolic, endocrine and immunological changes during the transition to motherhood. However, these changes are not completely gradual across pregnancy. Noticeably, the placenta is not fully formed until the second trimester. Thus, many changes associated

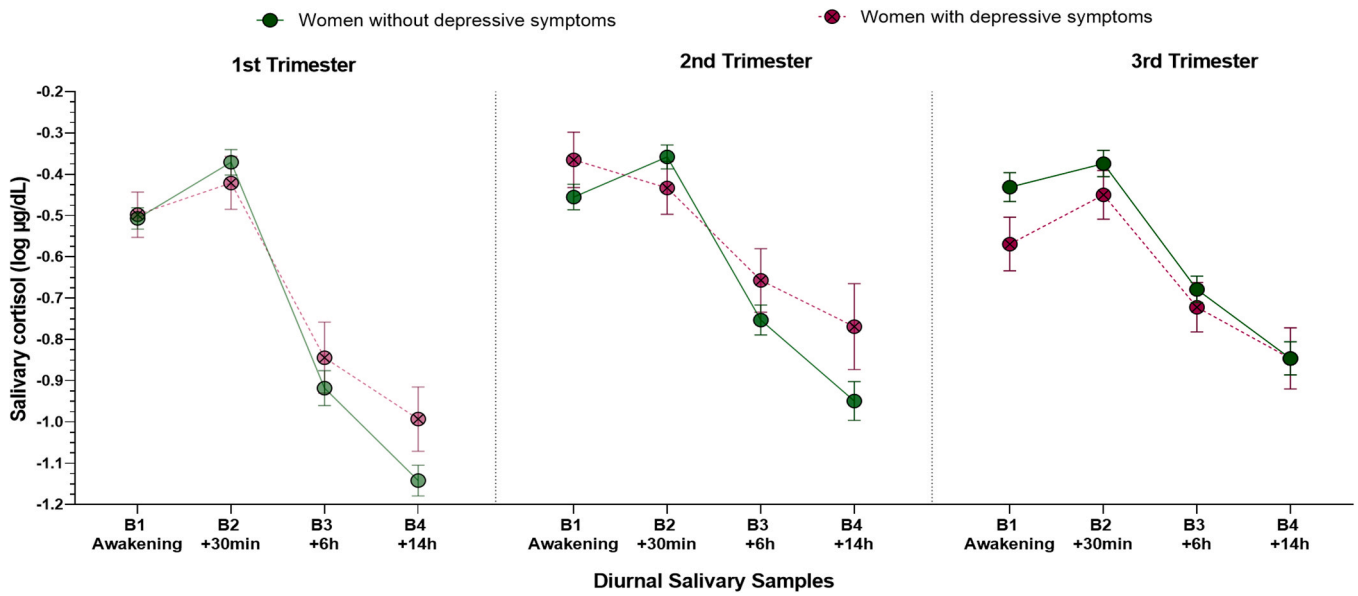

Fig. 3. Maternal salivary cortisol fluctuations throughout day in the three trimesters of pregnancy according to depressive symptomatology (error bars SE). Pregnant women with depressive symptoms (EPDS cut-off value ≥11 for 1st and ≥10 for 2nd and 3rd trimesters) are represented with dashed-pink lines and women with no depressive symptoms are represented with solid-green lines. n analyses: T1 (weeks 11–13) = 93 (Absence of symptoms = 70, With symptoms = 23), T2 (weeks 20–22) = 91 (Absence of symptoms = 71, With symptoms = 20), T3 (weeks 32–34)= 81 (Absence of symptoms = 59, With symptoms = 22). Results of the DIURNAL-model indicate that cortisol fluctuations during a day significantly differ between women with and without depressive symptoms only in second trimester (1st trimester, $F(3,11) = 1.676$, $p = .176$; 2nd trimester, $F(3,85) = 4.136$, $p = .009$,; 3rd trimester, $F(3,90) = 1.089$, $p = .358$).

to placental endocrine signals occur in this trimester, such as the increase in blood flow volume and maternal insulin resistance (Mayer and Joseph, 2013). Furthermore, hormonal fluctuations associated to placenta might be playing a role on the maternal brain reorganization occurring in pregnancy, increasing maternal susceptibility to depression (Servin-Barthet et al., 2023). Remarkably, although depressive symptoms seem to alter cortisol diurnal rhythmicity in mid-pregnancy, cortisol overall levels did not significantly differ between women with and without depressive symptoms. Although it seems contradictory, flatter diurnal cortisol contains elements of hypo and hyper-cortisolism (including low morning and high evening cortisol levels) which might explain this discrepancy and reinforces the idea that diurnal cortisol sampling protocol should include sampling at different time-points across the day.

Higher cortisol levels in mid-late pregnancy seemed to increase the risk of low birth weight percentile and prematurity. These results suggest that the increment of cortisol in mid-pregnancy, associated with maternal depressive symptoms, could lead to poorer birth outcomes. Noticeably, cortisol is necessary for fetal organ's maturation in late pregnancy (Austin and Leader, 2000), as demonstrated by the use of corticosteroids in cases of growth restriction (McGoldrick et al., 2020). Nevertheless, an excess of maternal cortisol during early to mid-gestation has been reported to cause structural and functional changes on fetal nervous system and HPA axis and worse birth outcomes (Davis and Sandman, 2010; Howland et al., 2017; Vlenterie et al., 2022). Although the association between maternal cortisol levels during 3rd trimester and infant's weight percentile at birth was strong, the weak association observed in the 2nd trimester suggests that other routes could be playing a role in this association. For example, alterations in the diurnal cortisol slope haves been strongly associated with immune and inflammatory outcomes (Adam et al., 2017). The maternal immune system is adapted during pregnancy to protect the mother and the fetus from pathogens while to avoid detrimental immune responses against the fetus (Abu-Raya et al., 2020). However, perinatal maternal depression is associated with increases in peripheral inflammatory cytokines (IL-6, IL-1β), which might affect both maternal and fetal health. Pro-inflammatory activity might be responsible on functional and morphological changes in maternal brain structure (Servin-Barthet et al., 2023). Meanwhile, the activation of maternal inflammation could activate the inflammatory process in placenta, compromising fetal environment. Moreover, cortisol diurnal disruption might alter the pass of maternal cortisol to the fetus trough the placenta by altering epigenetic mechanisms associated with the gene encoding the enzyme 11β-HSD2 or other glucocorticoid pathway genes, such as *NR3C1* or *FKBP5* (Monk et al., 2016). Thus, might alter the functioning of this enzyme and, subsequently, the fetus could be exposed to higher cortisol levels although maternal cortisol levels are not considered excessively high.

According to a recent systematic review, there is a lack of consensus across European countries regarding the clinical recommendations for screening, diagnosing and managing peripartum depression (Motrico et al., 2022). In our cohort, the prevalence of depressive symptoms was about 22%, which almost doubles the number of pregnant women with a depression diagnoses (Woody et al., 2017). Considering the high prevalence of depressive symptoms and the putative maternal and fetal implications, it seems necessary to implement adequate strategies to detect depressive symptoms at least once at each trimester. This is especially important in early and mid-pregnancy since depressive symptoms seem to modify cortisol functioning, which might impact on birth anthropometrics. Moreover, this study opens up the possibility to implement cortisol as a universal biomarker for screening mothers at risk, particularly measuring its diurnal rhythmicity or at least morning and evening levels.

Future studies exploring depression in pregnant women should include not just categorical diagnosis but also the assessment of depressive symptoms, preferably explored in different moments along pregnancy. Although the role of cortisol is not yet completely understood in the earliest weeks of pregnancy nor the postpartum, we strongly recommend studying these time-points, preferably by the collection of at least four daily salivary measures. Given the tendency to low birth weight and prematurity among children exposed to higher prenatal cortisol levels in mid pregnancy, future studies with higher sample size could confirm this association and explore possible neurodevelopmental impairments in the offspring.

A major strength of our study was interviewing in different time-points along pregnancy and analyzing them separately to get a better insight of time sensitive windows for intervention. Additionally, we explored a healthy population in which depression screening is uncommon. Finally, four salivary samples were collected to capture different aspects of the cortisol circadian rhythm.

Regarding limitations, not all women did the interview and the collection of saliva in the same week, therefore some first trimester samples were collected at the beginning of the second trimester. To avoid bias, analyses were adjusted for the exact week of collection. Moreover, the assessment of cortisol concentrations just after conception would have provided valuable information about changes in the first stages of pregnancy. Additionally, attrition bias analysis revealed that women with depressive symptoms had a greater tendency to drop out the study. Dropouts are very common in longitudinal psychiatry studies and should be consider, as their data could impact in the final results (Mazumdar et al., 2007). When comparing cortisol patterns across trimesters, it should be also considered that not all participants completed the hole protocol in all the trimesters. Finally, combining EPDS administration and a diagnostic interview would have allowed to better characterize the severity of depressive symptoms.

5. Conclusions

Maternal cortisol levels gradually increased during pregnancy, although cortisol circadian rhythm was preserved in all trimesters of pregnancy. Depressive symptoms seem to be associated with blunted cortisol rhythmicity in mid-pregnancy, although there might be a physiological readjustment of cortisol levels in late pregnancy. Finally, maternal cortisol levels in mid and late-pregnancy could be associated with increased risk of prematurity and low gestational age at birth. This study highlights the importance of screening for symptoms of mental health issues throughout pregnancy, regardless the past or current history of psychiatric disorder, since it might have an impact on infant health.

CRediT authorship contribution statement

Conceptualization, A.C.-Q., E.E., F.C., M.P.G-P and L.F.; methodology, A.C.-Q., M.D-C, M.R.-B., A.M.-V., L.dlF.-T. and J.L.M.-G.; software, A.C.-Q.; validation, A.C.-Q., M.R.-B. and A.M.-V.; formal analysis, A.C.-Q.; investigation, A.C.-Q., H.P.-G., E.E., B.A., M.P.G.-P and L.F.; resources, E.E., F.C., M.P.G.-P.G. and L.F.; data curation, A.C.-Q. and J.L.M.-G.; writing—original draft preparation, A.C.-Q., M.R.-B., A.M.-V. and B.A.; writing—review and editing, A.C.-Q.,E.E., N.S.M-G., L.M.-F., H.P.-G., M.R.-B., A.M.-V., B.A., M.P.G.-P and L.F.; visualization, A.C.-Q. and L.F.; supervision, A.C.-Q., E.E., B.A., M.P.G.-P. and L.F.; project administration, A.C.-Q., E.E., M.P.G.-P and L.F.; funding acquisition, E.E., F.C., M.P.G.-P and L.F. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

Authors do not have any conflict of interest regarding the publication of this manuscript.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106930.

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