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Effect of maternal cortisol levels on fetal heart rate patterns in primiparous pregnant women in the third trimester

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SUMMARY

OBJECTIVE: This study aimed to determine whether maternal cortisol levels affect fetal heart rate patterns in primiparous pregnant women in the third trimester.

METHODS: This cross-sectional descriptive study included 400 primiparous pregnant women with uncomplicated pregnancies between November and December 2022. The study included primiparous pregnant women over 18 years old in the third trimester who had not exercised for at least 2 h before the fetal heart rate monitoring and had a healthy pregnancy without consuming any food or drink. Fetuses with decelerating heartbeats and pregnant women who showed uterine contraction and cervical dilation during the fetal heart rate monitoring were excluded from the study. Research data were collected with the data collection form. The fetal heart rate data were collected using a cardiotocograph. At least two accelerations during the 20-min nonstress test period were the basis for diagnosing a reactive nonstress test. About 5 mL of maternal saliva for cortisol measurements was collected before fetal heart rate monitoring. Research data were analyzed with IBM SPSS Statistics for Macintosh, Version 28.0. A p-value of <0.05 was considered significant.

RESULTS: There were no significant differences in the comparison of the groups in terms of education and income status, family type, fetal gender, pregnancy planning status, BMI and age averages, or gestational week averages (p>0.05). The number of at least two accelerations required for the diagnosis of reactive NST was also higher in Group 1 (maternal salivary cortisol level ≤24.20). A moderately positive relationship between fetal heart rate and maternal salivary cortisol was observed (r=0.448, p=0.000). In total, 11.9% of the total change in fetal heart rate level is explained by maternal cortisol (R^2=0.119). Maternal cortisol increases fetal heart rate level (ß=0.349).

CONCLUSION: These findings suggest that stress in primiparous pregnant women with high cortisol levels may influence fetal heart rate patterns. It was revealed that the increase in cortisol level, considered a stress hormone, may be a harbinger of fetal tachycardia.

KEYWORDS: Heart rate, fetal. Hydrocortisone. Pregnancy. Saliva.

INTRODUCTION

The mental health of women during the perinatal period is affected by many factors[1]. Especially in primiparous pregnancies, pregnancy, and birth unknowns due to a lack of information can cause stress and anxiety[2]. Since pregnancy brings significant alterations in the levels and function of key endocrine systems, the role of endocrine changes across the perinatal period has been widely investigated as an influence on maternal mood and behavior as well as fetal and child development[3]. During pregnancy, dramatic changes in the functioning of the maternal hypothalamic-pituitary-adrenal (HPA) axis are observed because the placenta expresses the genes for human corticotropin-releasing hormone (hCRH) and the precursor for adrenocorticotropic hormone (ACTH) and beta-endorphin (proopiomelanocortin). Placental corticotropin-releasing hormone (pCRH) production increases dramatically over gestation, and pCRH plays a central role in the regulation of fetal maturation and the timing of parturition[4].

Stress experienced in the prenatal period can cause negative maternal and neonatal outcomes[5]. Stress and anxiety disorders experienced during pregnancy not only cause adverse effects on the course of the pregnancy but also affect the neurodevelopment of the baby[6,7]. Furthermore, stress is associated with negative outcomes such as prematurity and low birth weight in newborns[8]. Cortisol is released in response to stress and is a critical physiological marker for activation of the stress response. Cortisol is a glucocorticoid steroid hormone synthesized from cholesterol in the adrenal cortex, and its release is regulated via the HPA system[9]. Typically, in response to the cognitive appraisal of significant stressors, CRH is produced in the paraventricular nucleus of the hypothalamus and released into the pituitary gland. CRH then stimulates the release of ACTH in

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the anterior pituitary, which subsequently results in the adrenal cortex releasing several glucocorticoids, including cortisol, in humans[4,9]. Consequently, pCRH and cortisol in maternal plasma increase exponentially across pregnancy, and maternal levels can be 60 to 700 times higher than before pregnancy[10]. Cortisol can be measured through different substrates (blood, saliva, hair, and urine), and measurements of cortisol concentrations may vary based on the substrate being used[11].

Fetal heart rate (FHR) monitoring is the primary clinical technique for assessing fetal well-being and is one of the most valuable techniques for investigating fetal neurodevelopment. The nonstress test (NST) measures the FHR in response to fetal movement over time. NST test results are reported as reactive and non-reactive NST. A regular test (reactive NST) is usually associated with a neurologically sound and sufficiently oxygenated fetus. An abnormal test (non-reactive NST) is associated with negative fetal or neonatal outcomes[12,13].

Although there are results about stress levels and outcomes for pregnant women in the literature, there are no studies evaluating the effect of cortisol levels on fetal heart patterns in primiparous pregnant women in the third trimester. The present study aimed to determine whether maternal cortisol levels affect FHR patterns in primiparous pregnant women in the third trimester.

METHODS

This cross-sectional descriptive study included 400 primiparous pregnant women (Group I (n:203), maternal saliva cortisol level≤24.20 nmol; Group 2 (n:197), maternal saliva cortisol level>24.21 nmol) with uncomplicated pregnancies and a single fetus recruited from a private hospital in Istanbul, Turkey, between November 2022 and December 2022. The STROBE checklist was used in the study design's planning, implementation, and reporting[14].

The minimum sample size required in the study was decided by power analysis (G*Power Version 3.1.9.2). In the calculation, the effect size was taken as 0.35 (as the primiparous mother rate)[15]. Type 1 error rate (α)=0.05, and the power of the study (1-β) was 0.95 (Type II error=0.05). Accordingly, the minimum number of samples to be reached was calculated as a total of 356. It aimed to reach 392 samples considering the 10% loss risk, and the research was completed with 400 participants. After maternal saliva analyses, based on the mean daytime saliva concentrations (24.20 nmol/L) of pregnant women between the 31st and 37th gestational weeks[7], pregnant women with maternal saliva averages ≤24.20 nmol/L were evaluated as group 1 (n:203), >24.21 nmol/l, and pregnant women with 2 (n:197).

The study included primiparous pregnant women over 18 years old in the third trimester who had not exercised for at least 2 h before the FHR monitoring and had a healthy pregnancy without consuming any food or drink. In all patients, the well-being and growth of the fetus were normal, and the amniotic fluids were also normal. Fetuses with decelerating heartbeats and pregnant women who showed uterine contractions and cervical dilation while the NST procedure was in progress were excluded from the study (n=12).

Research data were collected with the data collection form. The data collection form included 10 questions in total on the socio-demographic characteristics (BMI, age, education status, family type, and income status) of women and their obstetric history (gestational week, fetal sex, pregnancy planning status, NST result, and the number of accelerations).

After collecting the data collection, the pregnant woman was asked to give a saliva sample into a 5-mL Eppendorf tube. The sampling time took 3–5 s. Saliva for cortisol measurements was collected between 08:00 and 10:00. The salivary cortisol samples were taken into Eppendorf tubes and centrifuged at 3,000 RPM for 10 min, and the supernatant portions were stored in a –80°C cabinet for 7 days. The samples were delivered to the biochemistry laboratory of a private university for weekly analysis. Cortisol values in supernatant samples were determined by ELISA-based commercially available kits [Human Salivary Cortisol ELISA kit (DRG International, Inc., USA, Cat Num:SLV-2930); Human Adrenocorticotropic Hormone (ACTH) ELISA kit (Elabscience Inc., USA, Cat Num:E-EL-H0137)] and were measured on a microplate reader (Thermo Scientific Multiskan FC, 2011-06, USA).

The FHR data were collected using a cardiotocograph (Philips Avalon FM20, Koninklijke Philips Electronics N.V., The Netherlands). Pregnant women admitted to the clinic before the research were checked routinely by the obstetrician in the clinic. The researcher included pregnant women who met the inclusion criteria in the study and voluntarily participated. Philips Avalon FM 20 brand NST Device US probe (where the fetal heartbeat is taken) and Toco probe (uterine fundus) were placed. All pregnant women were rested in the left lateral semi-fowler position in a quiet room for 30 min before the study to avoid being affected by external factors that cause stress. The NST process was continued in the quiet room where the pregnant women were resting and in the left lateral semi-fowler position in all groups. At least two accelerations (elevation of basal rhythm over 15 beats for 15 s) during a 20-min NST period were the basis for diagnosing reactive NST. The patients who did not meet the criteria for normal cardiotocography considered by the researchers continued to receive routine care.

Statistical analysis

Research data were analyzed with IBM SPSS Statistics for Macintosh, Version 28.0. Mean, median, standard deviation, and interquartile range were used to evaluate statistical data. Kurtosis and skewness values were examined to determine whether the research variables showed a normal distribution. In the relevant literature, it is accepted as a normal distribution that the results regarding the kurtosis skewness values of the variables are between +1.5 and -1.5, +2.0 and -2.0[16,17]. Accordingly, it was determined that the data were distributed in accordance with the normal distribution. Chi-square analysis and independent groups T-test were used for parametric data. Pearson's correlation test was carried out to determine the relationship between the variables. A p-value of <0.05 was considered significant.

Ethical aspects

The Ethics Committee approval was obtained from XX University (Ethics Committee no: E-10840098-772.02-7253; date: 24/11/2022). The study was registered at ClinicalTrials.gov (identifier: NCT05503433). The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin. Written permission was obtained from the hospital where the research would be conducted. Written consent was retrieved from all participants before enrolment in the study.

RESULTS

The pregnant women who participated in the study were mainly primary school graduates (61.4%), lived in a nuclear family (79.5%), had an income equivalent to their expenses (61.4%), were pregnant women with a baby girl (63.6%), and planned their pregnancy (70.5%). Furthermore, their BMI averages were 25.50±4.36 (min: 23.34; max: 29.72). Their average age was 25.67±4.92 (min: 18; max: 35), and their gestational week average was 36.91±1.93 (min: 32; max: 41). There were no significant differences in the comparison of the groups in terms of education status, family type, income status, fetal gender, pregnancy planning status, BMI averages, age averages, and gestational week averages (p>0.05) (Tables 1 and 2).

In the analysis of the NST results of the groups, it was found that the reactive NST results were mostly seen in Group 1 (maternal salivary cortisol level ≤24.20), and there was a significant difference between the groups (p=0.000) (Group 1=97%; Group 2=51%). The number of at least two accelerations required for the diagnosis of reactive NST was also higher in Group 1. There was a significant difference between the intergroup acceleration averages and between the groups (p=0.000) (Table 2) (Group 1=97%; Group 2=52%). A moderately positive relationship between FHR and maternal salivary cortisol was observed (r=0.448, p=0.000) (Table 3).

Regression analysis to determine the cause-and-effect relationship between maternal cortisol and FHR was found to be significant (F=55.045; p=0.000<0.05). In total, 11.9% of the total change in FHR level is explained by maternal cortisol (R^2=0.119). Maternal cortisol increases FHR level (ß=0.349) (Table 4; Figure 1).

The regression analysis performed to determine the cause-and-effect relationship between maternal cortisol, BMI, age, gestational

Table 1. Socio-demographic and obstetric characteristics of pregnant women (n=400).

Characteristics	n	%
Education status		
Primary	245	61.4
High school	91	22.7
University and above	64	15.9
Family type		
Nuclear	318	79.5
Extended	82	20.5
Income status		
Income more than expenses	–	–
Income equal to expenses	245	61.4
Income less than expenses	155	38.6
Fetal sex		
Girl	255	63.6
Boy	145	36.4
Pregnancy planning status		
Planned pregnancy	282	70.5
Unplanned pregnancy	112	29.5
NST result		
Reactive	298	74.5
Nonreactive	102	24.5
Number of accelerations		
0–1	102	25.5
2 and above	298	74.5
	Min–max	$\bar{X}$±SD
BMI	23.34–29.72	25.50±4.36
Age (year)	18–35	25.67±4.92
GW	32–41	36.91±1.93
FHR	120.00–175.00	140.06±13.39
Cortisol (ng/mL)	16.98–29.70	23.70±3.30

Chi-square analysis; independent groups T-test; BMI: body mass index, GW: gestational week, IQR: interquartile range.

week, fetal sex, and FHR was found to be significant (F=13.513; p=0.000<0.05). In total, 13.6% of the total change in FHR level is explained by maternal cortisol, BMI, age, gestational week, and fetal sex (girl) (R^2=0.136). Maternal cortisol increases FHR level (ß=0.313). BMI does not affect FHR level (p=0.522>0.05). Age reduces the level of FHR (ß=-0,160). The gestational week does not affect FHR level (p=0.788>0.05). Fetal sex (girl) does not affect FHR level (p=0.585>0.05) (Table 5).

DISCUSSION

The fetal heart rate pattern is a parameter that is influenced by diurnal rhythm, gestational age, maternal pulse, and movements of the baby and also indicates fetal well-being[18]. In a study, it was determined that the basal fetal heart rate between the 37th and 40th gestational weeks was 143.10±.17[19]. Similarly, in another study, it was determined that the fetal heart rate in the third trimester was 134.5 (min 128.7; max 140.0) at week 36, 134.2 at week 37 (min 130.0; max 141.2), and 134.2 at week 38 (min 129.3; max 140.3)[20]. The mean gestational week of the pregnant women participating in the study was

Table 3. Correlation of fetal heart rate with body mass index, age, gestational week, and cortisol.

		BMI	Age	GW	Cortisol
FHR	r	-0.034	-0.216	0.261	0.349
	p	0.499	0.000	0.001	0.000

Pearson correlation test.

Table 2. Comparison of socio-demographic and obstetric characteristics according to cortisol levels (n=400).

Characteristics	Group I (n:203) Maternal saliva cortisol level ≤24.20		Group 2 (n:197) Maternal saliva cortisol level >24.21		p
	n (%)		n (%)		
Primary	128 (63)		117 (59)		0.128
High school	44 (21)		47 (23)		
University and above	31 (16)		33 (18)		
Family type					
Nuclear	158 (78)		160 (81)		0.347
Extended	45 (22)		37 (19)		
Income status					
Income equal to expenses	117 (58)		128 (64)		0.143
Income less than expenses	86 (42)		69 (36)		
Fetal sex					
Girl	130 (64)		125 (63)		0.456
Boy	73 (36)		72 (37)		
Pregnancy planning status					
Planned pregnancy	134 (66)		148 (75)		0.066
Unplanned pregnancy	69 (34)		49 (25)		
NST result					
Reactive	197 (97)		101 (52)		**0.000**
Nonreactive	6 (3)		96 (48)		
Number of accelerations					
0–1	6 (3)		96 (48)		**0.000**
2 and above	197 (97)		101 (52)		
	Min–max	X̄±SD	Min–max	X̄±SD	p
BMI	23.34–29.72	27.92±1.92	25.51– 29.41	27.92±1.33	0.232
Age (year)	21–30	24.36±3.13	19–27	22.36±2.61	0.372
GW	35.00–40.00	36.72±1.34	32.00–40.00	37.00±1.26	0.321
FHR	120.00–158.00	137.97±9.18	120.00–175.00	142.22±16.40	**0.027**

Chi-square analysis; independent groups T-test. Bold values indicate a statistically significant difference.

36.91±1.93, and the mean fetal heart rate was 140.06±13.39. Since the pregnant women participating in the study were in the third trimester, fetal neurological maturity was sufficient; thus, the fetal heart rate parameters were within normal limits.

Stress and anxiety during pregnancy are linked with differences in FHR and fetal movement and may have implications for future emotional development[21]. However, maternal anxiety seemed to affect the duration and variability of the FHR, with prolonged accelerations often fusing into sustained tachycardia[22]. Another study reported that the fetuses of mothers with depression had an elevated baseline FHR and a 3.5-fold delay in returning to baseline FHR after vibroacoustic stimulation (VAS)[23]. Thus, the maternal environment significantly influences the fetal autonomic nervous system and the central nervous system (CNS)[24]. It was found that the fetuses of women who had a cortisol increase following an arithmetic task had higher resting (HR) and less short-term HR variability (HRV) 20 min after the stressor task ended. There was a trend finding that participants who had a cortisol increase reported higher levels of life stress[25]. In other research, higher resting maternal cortisol during the third trimester was associated with greater fetal movement amplitude and amount (time spent) during a 50-min observation period[26]. In a study aimed to determine whether there were differences in FHR reactivity associated with the mother's psychiatric status as assessed by a psychological challenge, the Stroop color–word matching task, they reported that fetuses of women with high anxiety levels had more significant FHR increases than those with low anxiety levels[7,27]. Fetuses of pregnant women who report tremendous life stress have reduced parasympathetic or increased sympathetic activation, as measured by reduced FHR variability. Fetuses of highly stressed mothers, who also have a faster baseline heart rate, show reduced FHR variability and delayed maturation of the coupling between FHR and fetal movement, which is hypothesized to reflect a less mature CNS[7,27]. Elevated stress during pregnancy, specifically stress specific to being pregnant, is associated with greater fetal reactivity, as assessed at three time points during gestation. Fetuses of highly anxious women showed an increase in heart rate when their mother was exposed to psychological stress, while fetuses of low-anxiety women did not exhibit a change in heart rate[27]. Previous studies used the Stroop task to determine maternal stress levels; in the present study, stress was evaluated using the salivary cortisol level. In this study, it

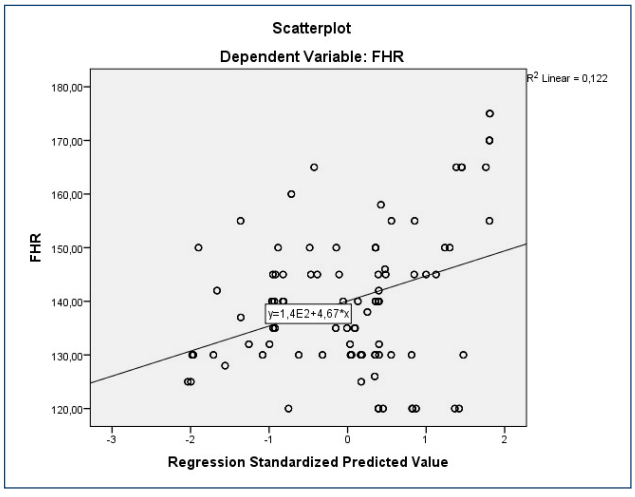

Figure 1. Effect of maternal cortisol on fetal heart rate.

Table 4. Effect of maternal cortisol on fetal heart rate.

Independent variable	Unstandardized coefficients		Standardized coefficients	t	p	95% confidence ınterval	
	B	SE	ß			Lower bound	Upper bound
Constant	106.573	4.558		23.383	0.000	97.612	115.533
Maternal Cortisol	1.413	0.190	0.349	7.419	**0.000**	1.038	1.787

Linear regression analysis; dependent variable=FHR; R=0.349; R^2=0.119; F=55.045; p=0.000; Durbin-Watson=0.442.

Table 5. Effect of independent variables on fetal heart rate.

Independent variable	Unstandardized coefficients		Standardized coefficients	t	p	95% confidence ınterval	
	B	SE	ß			Lower bound	Upper bound
Constant	114.497	13.734		8.337	0.000	87.496	141.498
Maternal cortisol	1.269	0.206	0.313	6.163	**0.000**	0.865	1.674
BMI	0.093	0.145	0.030	0.641	0.522	-0.192	0.378
Age	-0.434	0.132	-0.160	-3.286	**0.001**	-0.694	-0.174
Gestational week	0.094	0.350	0.014	0.269	0.788	-0.593	0.782
Fetal sex (girl)	0.697	1.275	0.026	0.547	0.585	-1.810	3.204

Linear regression analysis; dependent variable=FHR; R=0.383; R^2=0.136; F=13.513; p=0.000; Durbin-Watson=0.450.

was determined that FHR increased as maternal saliva cortisol levels increased. Following the literature, it can be thought that the cortisol rising with the increase in maternal stress level affects fetal reactivity, causes the acceleration of the fetal heartbeat, and therefore may be a harbinger of fetal tachycardia. In the study conducted by Kısa Karakaya et al.[28] 60–120 min after birth, it was found that maternal cortisol and fetal cord cortisol levels were affected by the mode of delivery, but there was no correlation between maternal cortisol and fetal cord cortisol levels (r=-0.192, p=0.336). According to these results, it can be said that maternal cortisol may cause fetal tachycardia in the intrauterine period, but it has no effect in the long term.

Strengths and limitations

Since there is no study evaluating FHR with cortisol levels in primiparous pregnant women who were previously in the third trimester, this study's findings will constitute the first result that will be reflected in clinical applications in this direction. The limitations are that, due to the nature of the research, the data obtained can only be generalized to primiparous pregnant women without uterine contractions, cervical dilation, or fetuses without decelerating heartbeats.

CONCLUSION

These findings suggest that stress in primiparous pregnant women with high cortisol levels may influence FHR patterns. It was found that the increase in cortisol level, which is considered a stress hormone, may be a harbinger of fetal tachycardia. To maintain fetal well-being, it is essential to minimize women's stress levels in the perinatal period.

AUTHORS' CONTRIBUTIONS

AT: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **CK:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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