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Third trimester physiological hypercortisolemia may protect from postpartum depression and stress

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Abstract. – OBJECTIVE: This study was aimed to evaluate the impact of physiological alterations in cortisol milieu on mood changes during late pregnancy and postpartum.

PATIENTS AND METHODS: A total of 77 healthy pregnant subjects were prospectively evaluated after 36 weeks of gestation and at 3-4 weeks postpartum. Free cortisol (FC) was calculated using Coolen's equation and the free cortisol index (FCI) was defined as serum Total cortisol/Cortisol-binding globulin. Concurrently, status of depression, anxiety and stress were graded using Beck Depression Inventory, Beck Anxiety Inventory and Perceived Stress Scale. Statistical analysis was performed and $p<0.05$ was considered statistically significant.

RESULTS: Higher FC levels during late pregnancy were associated with lower scores on stress and depression early postpartum, albeit the latter was not statistically significant. Additionally, as FCI increased during late pregnancy both the scores on stress and depression decreased during early postpartum.

CONCLUSIONS: Increased cortisol levels during the latter periods of pregnancy may have long-lasting protective effects. They may enable the mother to cope with the changing and demanding conditions during postpartum.

Key Words:
Pregnancy, Postpartum, Cortisol, Stress, Depression.

Introduction

Stress responses involve complex mechanisms, including various behavioral and endocrinologic adaptations. Pregnancy is a period during which changes in the steady state of various systems occur. It may be also a state of stress for the mother.

Pregnancy sets the stage for mood swings. Additionally, the hypothalamus-pituitary-adrenal axis (HPA) is subject to certain physiological changes during pregnancy[1]. Placental corticotropin-releasing hormone (pCRH) and increase in size of pituitary gland during pregnancy are responsible for increased cortisol levels[2]. How HPA changes during pregnancy affect the psychological status of females is still controversial[3-8]. The impact of cortisol levels on postpartum depressive symptoms has yet to be confirmed[1,5,7,9,10]. Although gestation is a state of hypercortisolism, and response to HPA is hampered during late pregnancy. During postpartum, the HPA axis recovers after an initial suppression of both hypothalamic CRH secretion and of adrenocorticotropin hormone (ACTH) response to CRH stimulation[1,11]. Thereafter, cortisol levels regress[11].

Previous studies in literature mostly evaluated gestational periods earlier than late pregnancy. Herein, we aimed to study the effects of physiological alterations in cortisol milieu on mood changes during late pregnancy and postpartum.

Patients and Methods

Ethical Approval

The study protocol was approved by the Ethics Committee of Istanbul University Cerrahapasa School of Medicine (Date: 10.02.2014, No.: A-01), and was performed in accordance with the ethical

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standards described in an appropriate revised version of the 1975 Declaration of Helsinki.

Patient Selection and Informed Consent

A total of 77 healthy pregnant subjects gave informed consent and were prospectively evaluated after 36 weeks of gestation and at 3-4 weeks postpartum. Subjects with an uncontrolled/chronic disorder, a major mood disorder or receiving exogenous steroid treatment were excluded.

Data Extraction

Demographic data, support mechanisms and a medical history were obtained from all subjects. Data on delivery, fetal status, weight and length of the newborn, and Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores were also included. APGAR scores were evaluated at one and five minutes (APGAR-1 and 5) of age based on heart rate, respiratory effort, muscle tone, reflex irritability and color of the newborn[12].

At each visit, blood samples were taken to determine the levels of total cortisol (TC) and cortisol binding globulin (CBG) at 8 am and were stored at -20ºC. Cortisol levels were determined using a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding (DRG Cortisol Enzyme Immunoassay Kit, DRG International, Inc., Springfield, NJ, USA) and CBG was also determined using ELISA (Sunred Biological Technology Co., Ltd, Shanghai, China). Free cortisol (FC) was calculated using Coolen's equation, where $FC=[(0.0167+0.182\ (CBG-TC))^2+(0.0122xTC)]^{0.5}-[0.0167+0.182(CBG-TC)]$. Free cortisol index (FCI) was defined as serum TC/CBG[13].

Concurrently, status of depression, anxiety and stress were graded using the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Perceived Stress Scale (PSS). BDI is a 21-question multiple choice self-report inventory which is helpful in evaluating symptoms in depression. The total score indicates the severity/seriousness of depression[14-16]. BAI is a self-report measure of anxiety. The sum of the scores obtained from each answer to the 21 items is used to calculate the total score[17,18]. PSS is an inventory used for measuring the perception of stress. PSS scores are obtained by reversing responses (0=4, 1=3, 2=2, 3=1, 4=0) to the four positively stated items, items 4-8, and then taking the sum across all scale items[19,20].

Statistical Analysis

Data were statistically analyzed with the SPSS 15.0 package program (SPSS Inc., Chicago, IL, USA). The Chi-square test was used for categorical variables. Sample distribution was evaluated with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were compared by using the Student's *t*-test. Continuous variables with non-normal distributions were compared by using the Mann-Whitney U test. Wilcoxon test was used to compare related variables. The Pearson's correlation coefficient was used for calculation of associations between variables. ROC Analysis was performed for associated variables and its performance on distinguishing states of pregnant. $p < 0.05$ was considered statistically significant.

Results

Data on delivery, fetal status, weight and length of the newborn, and APGAR scores are shown in Table I and II. TC levels during pregnancy significantly decreased after gestation in all 77 subjects [from 130.4 (IQR: 101.1-167.5) nmol/l to 53 (IQR: 41.7-73.1) nmol/l, ($p<0.001$)]. Also decreasing were FC levels [from 21.9 (IQR: 14.2-38.3) to 9.9 (IQR: 6.4-15.2) nmol/l ($p<0.001$)], CBG levels [from 31.6 (IQR: 28.3-36.7) to 15.1 (IQR: 12.9-19.7) mg/l ($p<0.001$)] and FCI [from 28.9 (IQR: 21.6-40.1) to 25.5 (IQR: 16.9-36.8) nmol/mg ($p=0.01$)].

The median BDI score of the subjects decreased substantially after pregnancy, from 9 (IQR: 6-14.5) to 7 (IQR: 3-11.5), ($p=0.006$). Similarly, the median total score on BAI, reflecting the level of anxiety, declined significantly [e.g.,

Table I. Demographic data of the subjects.

	Subjects (n=77)
Age (year)	28.5 ± 4.9
Educational level	
Primary-secondary school	44 (57%)
High school-University	33 (43%)
Occupational status	
Housewife	66 (86%)
Working	11 (14%)
Income level	
<500 USD	9 (12%)
>500 USD	68 (88%)
Medical History	
None	66 (86%)
Gestational diabetes	4 (5%)
Hypothyroidism	5 (6%)
Hyperthyroidism	2 (3%)
Wanted pregnancy	71 (92%)
Spouse and family support	77 (100%)

Table II. Data on delivery and fetal status.

	Subjects (n=77)
Gravida†	2 [1-3]
Parity†	1 [0-2]
Gestational week†	39 [IQR: 38-40]
Mode of delivery	
Vaginal	33 (43%)
C/S	44 (57%)
Complication	1 (1%)
Newborn	
Weight (gr)	3,384 ± 368.3
Height (cm)	50.3 ± 1.5
APGAR-1	7.8 ± 0.3
APGAR-5	9.9 ± 0.3

C/S: cesarean section. †The results are presented as median and interquartile range [IQR].

during pregnancy: 15 (IQR: 9-19), postpartum: 6 (IQR: 2-12), $p<0.001$]. The perception of stress, measured using PSS, was also significantly higher during pregnancy compared to postpartum [e.g., during pregnancy: 23 (IQR: 19-28.5), postpartum: 22 (IQR: 17-26), $p=0.02$].

TC levels during late pregnancy were positively correlated with APGAR 1 (r=0.2, $p=0.04$) but not with APGAR 5; neither FC nor FCI was correlated with APGAR scores. Cortisol levels and, depression, anxiety and perception of stress were not related to fetal status, including APGAR, weight and length. There was no statistically significant difference between cortisol measures and the scores on BDI, BAI or PSS based on any of the demographic data (insignificant data are not shown here).

Correlations between cortisol measures and the scores on depression, anxiety and stress are shown in Table III. FC levels during late pregnancy tended to be negatively associated with the scores on depression during early postpartum period (r=-0.2, $p=0.06$) and it was negatively associated with the scores on stress (r=-0.2, $p=0.03$). There was also a significant negative association between FCI and both depression and stress perception (r=-0.3, $p=0.01$ and r=-0.4, $p=0.002$). There was no correlation between the change in cortisol levels and the change in the scores on BDI, BAI and PSS (Table III). ROC analysis showed a cut off could not be given for associated variables (AUC<0.5).

Table III. Correlation of the cortisol levels with the scores on BDI, BAI and PSS during late pregnancy and early postpartum periods.

		Late Pregnancy			Early Postpartum			Δ Values		
		BDI	BAI	PSS	BDI	BAI	PSS	BDI	BAI	PSS
Late Pregnancy	FCI	.04 .71	-.05 .65	.01 .96	**-.29** **.01***	-.13 .26	**-.36** **.00***	-	-	-
	FC	-.01 .94	-.10 .39	.00 .98	**-.21** **.06**	-.09 .46	**-.25** **.03***	-	-	-
	TC	-.05 .64	-.10 .30	-.04 .70	-.06 .58	.04 .76	-.09 .45	-	-	-
Early postpartum	FCI	-.01 .91	-.12 .32	-.07 .57	.02 .89	-.07 .55	.06 .62	-	-	-
	FC	.18 .13	-.03 .77	.10 .37	.03 .82	.02 .89	-.02 .85	-	-	-
	TC	.06 .63	-.09 .42	.01 .94	-.05 .65	-.10 .37	-.04 .71	-	-	-
Δ Values	FCI	-	-	-	-	-	-	0.09 0.39	0.06 0.56	0.08 0.45
	FC	-	-	-	-	-	-	0.13 0.26	-0.02 0.85	0.15 0.18
	TC	-	-	-	-	-	-	0.03 0.77	-0.1 0.38	0.06 0.55

*statistically significant correlations. Δ Delta, the change in the values from late pregnancy to the postpartum period. Pearson test was performed for correlation. FCI: Free cortisol index, FC: Free cortisol, TC. Total cortisol, BDI: Beck Depression Inventory BAI: Beck Anxiety Inventory PSS: Perceived Stress Scale.

Discussion

In the present study, levels of total and free cortisol declined after pregnancy. Likewise, the scores on the symptoms of depression, anxiety and perception of stress (reflected by Beck Depression Inventory, Beck Anxiety Inventory and Perceived Stress Scale) were significantly lower during postpartum than in late pregnancy. Free cortisol levels during late pregnancy were negatively correlated with the postpartum scores on BDI and PSS. The higher the free cortisol levels during late pregnancy, the fewer their symptoms of depression and perception of stress during postpartum.

Increased CBG levels during pregnancy lead to increased TC levels[21]. However, it is the free cortisol levels that cause the symptoms of hypercortisolemia[21]. During pregnancy, pituitary hypertrophy, placental and increased pituitary secretion of corticotropin-releasing hormone and increased estradiol result in higher free cortisol levels[11]. Peak cortisol levels, up to three times the normal levels, are seen during the third trimester of pregnancy. After delivery, hypercortisolemia recovers during postpartum[11]. Similarly, in the current study, TC, FC and FCI were higher during late pregnancy and decreased postpartum.

Maternal cortisol passes through the placenta and facilitates maturation of fetal organs, contributes to fetal survival in extrauterine environment and helps trigger the onset of delivery[22]. Although an increase in cortisol up to a certain level is necessary, higher than expected levels in pathologic conditions, including mood disorders, malnutrition or disease conditions, may be harmful for both the mother and the fetus and, even for the later adult life of the newborn[23]. On the other hand, in an animal model, Amugongo et al[24] demonstrated that increased cortisol levels, secondary to stress, accelerated fetal growth. In the present study, physiological increase in cortisol levels during pregnancy did not have a negative effect on fetal status. Even higher TC levels during late pregnancy were associated with higher APGAR 1 scores, however, it was not a strong correlation and free cortisol measures did not have such an association.

Furthermore, previous studies[25] conducted with severely depressed/stressed mothers reported the negative impact of mood disorders on the fetus/child. In the current study, the mean fetal weight, length and APGAR scores were within the normal limits for the newborn and the scores reflecting maternal depression, anxiety or stress during late pregnancy were not related to these measures. None of the scores on any of the scales was within the range that would indicate a major mood disorder. Therefore, we may conclude that although pathologic stress conditions hamper fetal development, physiological mood changes during pregnancy may not have a negative impact. However, the current study was not designed to draw a conclusion on fetal or infant development. Further studies may reveal a more certain conclusion on this subject.

The BDI or BAI scores, at late pregnancy and postpartum period, did not indicate the presence of a major mood disorder. However, there was still a dramatic decrease after pregnancy in the scores of depressive, anxiety and stress symptoms. Previous studies[4,6,10] on the relation of mood disturbances during pregnancy or postpartum with the cortisol levels have had conflicting findings. In the current study, TC, FC or FCI were not correlated to the concurrent scores on BDI, BAI or PSS. Additionally, the decline of cortisol levels was not associated with the decrease in the scores showing the status of depression, anxiety or stress of the subjects. Factors other than physiological hyperactivity of HPA may have a role in the status of mood during the concurrent period of pregnancy and postpartum.

Interestingly, during postpartum, the scores on depression tended to decrease and the scores on perception of stress significantly dropped as the FC levels increased during late pregnancy. Similarly, FCI was significantly and negatively correlated with both postpartum depression and stress perception. This means that as the FCI index in late pregnancy increased, both depressive symptoms and perception of stress decreased during the postpartum period. Although higher free cortisol levels during pregnancy did not affect the status of mood, they may later have a positive impact on both depressive symptoms and perception of stress during postpartum.

Postpartum may be a different and tough period for the mother and the change in lifestyle may also cause certain changes in mood[26]. Mood swings of pregnancy usually subside after 10 days of postpartum[27]. How long-term endurance of mood is maintained despite ongoing demanding conditions is inconclusive. In different populations, it has been shown[28,29] that reduced cortisol levels were associated with certain psychopathologies, including atypical depression, and avoidant coping mechanisms. A recent metanalysis[7] did not find an association between hypercortisolism and major depression during antenatal period. Additional-

ly, hypocortisolism was claimed[7] to be associated with chronic depressive states. Therefore, a particular level of cortisol may be necessary to develop certain coping mechanisms and to prevent some of the mood disorders. Likewise, based on our findings, physiologically high cortisol levels during late pregnancy may have ultimate benefits on mood. They may also render the postpartum status of mood more stable for the mother.

An increase in the number of participants involved might help finding a cut-off for FC and FCI to prediction of depression if the results with a greater volunteer population supports. In addition to this, the postpartum period was limited to first month in this study, a long lasting follow-up of postpartum women in future studies are needed to show if this association continues till the end of 42 days of the postpartum period.

Conclusions

This study contributes to what has been known for the role of hypercortisolemia during pregnancy. High basal cortisol levels especially during latest periods of pregnancy may prepare and support the mother for being able to cope with the changing and demanding conditions during postpartum.

Conflicts of Interest

The authors declare no conflicts of interest.

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Authors' Contributions

All of the authors contributed to the design of the study, data collection, statistical analysis and manuscript preparation.

Informed Consent

All patients were informed and gave their consent to participate in this study.

Ethics Approval

The study protocol was approved by the Ethics Committee of Istanbul University Cerrahapasa School of Medicine (Date: 10.02.2014, No.: A-01), had been performed in accordance with the ethical standards described in an appropriate revised version of the 1975 Declaration of Helsinki.

Availability of Data and Materials

The study data are available on request.

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