

Original Article



Prenatal stress and infants' development: association with cortisol and leptin levels in cord blood and saliva

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Abstract

Introduction: Stressful events during pregnancy may affect cognitive and somatic development in infants and increase the risk of developmental disorders in future. This study aimed at assessing the correlation between prenatal stress with salivary cortisol and leptin levels with a focus on infant development.

Methods: In this prospective correlative study, 80 infants whose mothers were admitted to clinics during pregnancy were evaluated. The pregnant women were included during 24-28 weeks of pregnancy and assessed using the perceived stress scale until delivery. Following delivery, growth and development of infants were evaluated using the Ages and Stages Questionnaire (ASQ) at birth as well as 2, 4 and 6 months after birth. For assessing leptin and cortisol levels, cord blood and salivary samples were collected at birth and 6 months after birth, respectively.

Results: The mean perceived stress score (PSS) during pregnancy was associated with infant development and weight at 2 and 6 months of age, respectively. Moreover, there was a negative association between leptin level at 6 months of age and infant height at 2, 4 and 6 months after birth. Finally, a negative correlation was observed between cortisol level at 6 months of age and infant height at 2 months following birth.

Conclusion: The results indicated that the PSS of the mothers negatively correlated with the infants' growth, development and cortisol and leptin levels. Thus, prenatal stress probably affects growth and development in infancy through effects on the neuroendocrine system. Leptin might be an appropriate biomarker for determination of growth and development in infancy.

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Keywords:

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Introduction

Early life stress may cause neuropsychiatric disorders in adulthood and impair health and neurodevelopment of organisms (Hosseini-Sharifabad and Sabahi, 2014). Studies suggest that

maternal prenatal psychosocial stress not only can affect the mental health during childhood, but also contributes to mental disorders later in life (Oates, 2002). Other complications of prenatal stress (PS) in offspring include impaired function of hypothalamus-pituitary-adrenal axis (HPA), depression symptoms in

adolescence and development of asthma in children (Van den Bergh et al., 2005; Cookson et al., 2009). Moreover, according to studies, perturbations in the maternal environment are transferred to the embryo through placenta. Thus, defects of placenta may cause problems in offspring growth and development which can negatively affect brain maturation and mental capabilities (Bronson and Bale, 2016). PS may cause preterm labor which is a risk factor for cerebral palsy and learning disabilities and also results in intrauterine growth retardation (Black et al., 2013; Abedi et al., 2017). Studies conducted in England and Sweden estimated that prevalence of PS is about 33-37% and 5-7%, respectively (Woods et al., 2010).

HPA axis is activated in response to stress, which can lead to an increase in blood cortisol level in long term (Kudielka et al., 2004). Previous studies reported high cortisol and corticosterone concentration long after parturition following maternal stress during pregnancy (Gholipour et al., 2017; Saboori et al., 2019). In humans, cortisol is the main glucocorticoid following HPA-axis stimulation in blood and saliva (Taddio and Katz, 2005). Although accurate information is not available, particularly in children under six months of age, the mechanism of cortisol secretion varies with age, and also physical and environmental stresses can exacerbate its secretion (Zijlmans et al., 2013). Changes in blood cortisol can alter cortisol level in saliva and salivary cortisol is an indicator of blood free cortisol or active biological cortisol (Alpers et al., 2003; Kudielka et al., 2004). Assessing saliva cortisol is more beneficial than measuring it in serum or plasma as its sampling is cheaper and non-invasive (Adam and Kumari, 2009). Moreover, studies suggest that there is a positive relationship between stress and salivary cortisol levels (Vedhara et al., 2003).

Further, glucocorticoids and adrenocorticotrophic hormone (ACTH) provoke synthesis and secretion of leptin which affects adrenal function (Lee et al., 2007; Eftekhari et al., 2015). The effect of HPA-axis on leptin secretion is controversial (Nishii et al., 2006). After birth, the mean serum and placental leptin levels of infants correlate with their arm fat mass and birth weight, respectively (Briffa et al., 2015). Although numerous studies have been conducted on PS as well as on leptin and cortisol levels in neonates, the correlation between leptin and cortisol

levels with stress during pregnancy and the effects of these hormones on neonatal development are still unknown. Therefore, this study aimed to assess the correlation between PS with salivary cortisol and leptin levels with a focus on introducing an appropriate biomarker for growth and development of infants.

Materials and methods

In this prospective correlative study, we randomly evaluated 80 infants younger than 6 months whose mothers were admitted (as regularly scheduled check-ups) to the Health Center No.1, Miandoab, West Azerbaijan Province, Iran, from March 2016 to March 2017. The sample size of the study was determined according to the sample size of a study conducted by Salari et al. (2013) considering correlation coefficient of 0.312 between stress score and cortisol level, significance level of 0.05 and power of 80%. Inclusion criteria comprised 24-28 weeks of pregnancy; singleton pregnancy; negative history of cardiovascular, renal, pulmonary, psychiatric and autoimmune diseases; negative history of diabetes during and prior to pregnancy and negative history of neuroleptic drugs consumption. Moreover, exclusion criteria encompassed unwillingness to be included in the study.

Ethical approval

All procedures were reviewed and approved by the Ethics Committee at the Urmia University of Medical Sciences, Urmia, Iran (IR.UMSU.RIC.1394;205). The procedures were consistent to the guidelines of Declaration of Helsinki (2008). Appropriate informed consent was obtained from all the cases.

At first, the perceived stress scale (PSS) was filled out for the cases and their demographic characteristics were obtained. Then, the cases were followed up every 4 weeks. The first follow-up was conducted on the weeks 28-32, the second one was done on the weeks 32-34 and finally the last follow-up was done in the labor room prior to delivery. In all these follow-ups, we filled out PSS for the cases. In the labor room, cord blood samples were collected in order to determine cortisol and leptin levels of the neonates. At birth as well as 2, 4 and 6 months after birth, we measured weight, head circumference and height of the infants and also assessed infants' development using the Ages and Stages

Questionnaire (ASQ). At 6 months of age, approximately 3ml of infants' saliva were collected between 9 and 11 am. The mothers were asked not to breastfeed their infants at least one hour prior to sampling. Then, the samples (both saliva and blood) were centrifuged at 1000g for 10min. Finally, cortisol (DiaMetra, Italy) and leptin (BioVendor, Czech Republic) levels were checked using the ready to use ELISA kit.

Tools

1. Cohen's Perceived Stress Scale (PSS): it was firstly designed by Cohen et al. in 1983. PSS consists of 14 items evaluating thoughts, emotions and perceived general stress of people in the past. Scaling is according to 5-point Likert scale including never (0), almost never (1), sometimes (2), often (3) and almost always (4). The lowest point possible is 0 and the highest is 56. Higher score indicates higher perceived stress (Cohen et al., 1983).

2. For evaluating infant development at 2 months after birth, we used a developmental status checklist designed by the Ministry of Health, Islamic Republic of Iran. These checklists are currently used in health centers and are according to the questionnaire of infant developmental status filled out using parents' expressions. The questionnaire consists of 5 items including smiling, making noise, getting calm with mother's voice, using fingers and 45-degree head elevation. Possible answers include yes and no and in case of negative answer, the infant is admitted to higher levels of the health system for further investigation.

3. The Ages and Stages Questionnaire (ASQ): this questionnaire evaluates developmental status of children aged 4-60 months in 19 different age groups and 5 developmental areas including gross movement, fine movement, communication, solving problem and personal-social skills by comparison with determined cutoff points. Thirty questions have been designed for each age group, 6 questions for each area. The highest achievable score for each question is 10 (60 for each area) and the lowest is 0. Scores for each area are collected and then compared with cutoff points of that area. Infants with a score lower than cutoff-SD in at least one field are considered to have problems and are admitted to higher levels of the health system. Several studies have demonstrated ASQ as a trustable screening

method, even in translated and localized versions (Richter and Janson, 2007; Yu et al., 2007; Kapci et al., 2010). In a study conducted in 18 countries located in Asia, Africa, Europe as well as North and South America in 2007, sensitivity and specificity of this method were measured 88% and 82.5%, respectively (Altman et al., 2002; Yu et al., 2007).

4. The questionnaire designed by the researcher: it includes demographic information (age, education and occupation of parents), pregnancy information (number of pregnancies, number of deliveries, delivery types and infant sex) and infant physical characteristics (age, weight, sex, height and head circumference).

5. Salivary cortisol and leptin measurement kits: leptin levels were measured using BioVendor kits made in Czech Republic with sensitivity of 0.2ng/ml and specificity of 100%. Moreover, cortisol levels were measured using DiaMetra kits made in Italy with sensitivity of 2.44ng/ml and specificity of 100%.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) and descriptive analyses and frequency tables were conducted using this application. The Kolmogorov-Smirnov test was used to determine the normality of distribution. Quantitative variables were reported as mean±SD and qualitative data were presented in terms of rates and proportions. The statistical analyses were conducted using t-student and Pearson tests. *P*-value <0.05 was considered statistically significant.

Results

Demographic and reproductive information of participants is showed in Table 1. Among the infants studied, 41 percent was girl. Among the mothers, 21.3% experienced their first delivery. Finally, 70% of the mothers had vaginal delivery.

To address the effect of newborn's sex on proposed variables, data related to stress score, leptin and cortisol were compared between boys and girls. Although the leptin levels were higher in girls than boys, there was no significant difference between two sexes on any items. Also, we checked these variables between normal delivery and cesarean section. There was no significant difference between two types of delivery; therefore, all data were

Table 1: Demographic and reproductive information in research units

Variable	Category	Percent(frequency)
Mother's age (year)	≤18 years	7.5(6)
	19-34	78.7(63)
	≥35	13.8(11)
Mother's education	Elementary	40(32)
	Middle school	42.5(34)
	Collegiate	17.5(14)
Mother's job	Housewife	97.5(78)
	Employed	2.5(2)
Father's education	Elementary	38.8(31)
	Middle school	48.7(39)
	Collegiate	12.5(10)
Father's job	Unemployed	10(8)
	Employed	90(72)
Parity	no	21.3(17)
	1	50(40)
	2 or more	28.8(23)
Newborn sex	boy	58.7(47)
	girl	41.3(33)
Type of delivery	vaginal delivery	70(56)
	cesarean section	30(24)

combined and analyzed together.

Mean cortisol concentration (ng/ml) in the cord blood samples at birth (307.57±12.56) and the saliva samples at 6 months of age (312.36±82.43) were detected. Also, mean leptin concentration (ng/ml) in the cord blood at birth and the saliva samples at 6 months of age were 23.23±10.18 and 65.77±77.11, respectively. We observed a significant relationship between leptin and cortisol levels at 6 months of age ($r=0.272$ and $P=0.022$).

Table 2 demonstrates weight, head circumference and height of the infants at birth and 2, 4 and 6 months after birth. As observed in the Table, 7, 11 and 10 infants had developmental problems at 2, 4 and 6 months of age, respectively. Moreover, the mean PSS of the mothers during pregnancy was 26.85±2.65. We observed a significant correlation between maternal PSS and infant weight at 6 months of age ($P=0.012$). Moreover, the level of saliva cortisol at 6 months of age was significantly correlated with infant height at 2 months after birth ($P=0.034$). Finally, there was a significant negative association between leptin level at 6 months after

birth and infant height at 2 ($P=0.004$), 4 ($P=0.001$) and 6 ($P=0.001$) months of birth (Table 3).

There was a negative relationship between infant development at 2 months of age and maternal PSS during pregnancy ($P<0.001$), but no association was observed between PSS and infant development at 4 ($P=0.509$) and 6 ($P=0.747$) months of age (Table 4). Additionally, cortisol and leptin levels at birth and 6 months after birth were not significantly correlated with infant development at 4 and 6 months of age. Finally, no significant relationship was observed between PSS with cortisol and leptin levels at birth and 6 months after birth.

Discussion

In the current study, we found a negative correlation between maternal PSS and infant's weight at 6 months of age. In a study conducted by Bazr Afshan and Mahmoodi (2009), they showed that women's anxiety during pregnancy caused low birth weight in offspring. Studies have also shown that women experiencing stress during pregnancy are more likely to have preterm deliveries (Punamäki et al., 2006). It

Table 2: Descriptive data about growth and development of the infants

		At birth	2 months after birth	4 months after birth	6 months after birth									
Infant growth criteria (mean±SD)	Weight (g)	3231.25±576.89	5216±736.12	6660±881.39	7896±1016.39									
	Head circumference (cm)	34.42±2.18	38.31±1.93	40.60±1.80	42.45±1.59									
	Height (cm)	50.51±3.08	56.16±2.67	61.85±2.59	67.33±2.56									
Infant development criteria: (absolute and relative frequency)	2 months after birth		4 months after birth					6 months after birth						
	With problems	Without problems	With problems					Without problems	With problems					Without problems
			Problem solving	Communication	Gross motor skills	Fine motor skills	Personal-social		Problem solving	Communication	Gross motor skills	Fine motor skills	Personal-social	
	7	73	3	2	1	2	3	69	3	1	2	1	3	70
	8.7	91.3	3.8	2.5	1.3	2.5	3.8	86.3	3.8	1.3	2.5	1.3	3.8	87.5

The values related to infant growth criteria are mean±SD

was reported that PSS negatively correlated with birth weight, height and head circumference (Shayeghian and Tabatabaey, 2008) which can be partly resulted from low uterine blood supply due to stress-induced vasoconstriction (Osol and Mandala, 2009). This finding supports the results of our study. According to the findings of the current and some other studies, it can be inferred that stress during pregnancy might negatively affect infant growth (Ebrahimi et al., 2014; Heshmatian et al., 2010) and infants with growth problems could face growth retardation in different life stages (Kammerer et al., 2002; Robertson et al., 2004). Thus, although we observed no significant relationship between mother PSS during pregnancy with offspring height and head circumference in different life stages, our findings demonstrated that there was a negative correlation between PSS and growth criteria, which is in agreement with the findings of other studies.

According to our findings, there was a negative association between maternal PSS during pregnancy and offspring development at 2 months after birth. Studies have suggested that mothers experiencing stress during pregnancy may have offspring with delayed walking and speech, learning and memory deficits, sleep disorders and excitability, somatic disorders, increased excitatory reactions and seizure susceptibility, low mood and behavioral and affective

disorders (Kapoor et al., 2009; Glover, 2015). It is clear that the growth and behavior of the offspring can be altered by PS. Maternal stress exerts intense influences on offspring's development inducing abnormalities which extend from early to later life (Maccari et al., 2003). Therefore, our result, maternal PSS affected infant development after 6 month, is consistent with exiting literature. These short- and long-term consequences, at least in part, arise from some proven events: excess circulating maternal stress hormones alter the programming of fetal brain (HPA axis and others) and together with genetic factors, the postnatal environment and quality of maternal attention, express the growth, development and behavior of the offspring (Weinstock, 2008). In addition to PS, stress during postnatal period has also been observed to cause some of the mentioned disorders such as increased risk of epilepsy at older ages (Galic et al., 2008; Gholipour et al., 2013). Thus, pre and postnatal stresses have been suggested to play a key role in etiology of many childhood and adulthood disorders. As most of the studies are mainly focused on the effects of PS on offspring development, we suggest further studies to assess the impacts of postnatal, particularly early postnatal stress on neurodevelopment of offspring. Studies have shown that stress during late pregnancy is associated with lower cognitive development at 2

Table 3: Assessing correlation of infant growth with maternal perceived stress score (PSS) and infant cortisol and leptin levels

Variable	Weight				Height				Head circumference			
	At birth	2 months	4 months	6 months	At birth	2 months	4 months	6 months	At birth	2 months	4 months	6 months
Stress score	$P=.92$ $r=.01$.028 -.12	.096 -.19	.012* -0.28	.48 -.07	.76 -.03	.96 -.01	.83 -.02	.91 -0.12	.73 .038	.67 -0.04	.41 -.93
Cortisol level at birth	$P=.08$ $r=.44$.38 .09	.07 .20	.22 .14	.82 .02	.76 -.03	.21 .14	.19 .14	.11 .324	.31 -.12	.50 -0.07	.45 -.08
Cortisol level at 6 months after birth	$P=.25$ $r=.10$.064 -.22	.093 -.20	.23 -.14	.359 -.11	.034* -0.25	.826 .026	.733 .014	.121 .184	.59 .065	.77 .035	.88 -.018
Leptin level at birth	$P=.89$ $r=-.02$.61 .05	.08 -.03	.68 -.05	.317 .11	.36 .10	.82 -.02	.50 -.07	.94 .01	.56 .06	.23 .14	.12 .17
Leptin level at 6 months after birth	$P=.65$ $r=-.05$.71 .04	.89 .02	.42 .09	.24 -.14	.004* -.33	.001* -.38	.001* -.39	.39 -.12	0.8 -.03	.49 -.08	.398 -.10

* indicates significant correlation and the related *P*-value in each case

years of age. Additionally, stress induces preterm labor which also causes low weight and inappropriate growth of offspring. The infants of stressed mothers are more prone to experience physical and cognitive disorders such as cerebral palsy and learning deficits (Kammerer et al., 2002; Robertson et al., 2004). Although we observed no significant association between maternal PSS and child development at 4 and 6 months of age, our findings support the results of the mentioned studies. This discrepancy may be resulted from using ASQ which is filled out according to parents' expressions and any inaccurate answers

from parents could affect the results.

The findings of the current study suggested significant negative correlations between cortisol level at 6 months and height at 2 months of age and also between leptin level at 6 months and height at 2, 4 and 6 months of age. Leptin is considered as an anti-obesity hormone which reduces food intake through its receptors in hypothalamus. It also regulates bone growth and functioning of the immune system. According to studies, leptin level in fetus correlates with birth weight which shows the significance of leptin in fetal growth and development (Briffa et al.,

Table 4: Correlation of infant development with maternal perceived stress score (PSS), infant cortisol and leptin levels in cord blood (at birth) and saliva (at 6 months after birth)

		Maternal perceived stress score	Cortisol level at birth	Cortisol level 6 months after birth	Leptin level at birth	Leptin level 6 months after birth
Infant development criteria (p and r)	2 months after birth	<i>P</i> < 0.001* <i>r</i> = -0.26	0.242 0.132	0.385 0.104	0.054 0.216	0.286 -0.28
	4 months after birth	<i>P</i> = 0.509 <i>r</i> = 0.075	0.115 0.178	0.217 -0.147	0.306 -0.116	0.623 -0.059
	6 months after birth	<i>P</i> = 0.747 <i>r</i> = -0.037	0.419 0.092	0.152 0.138	0.964 0.005	0.105 0.183

* indicates significant correlation and the related *P*-value

2015). In a study, negative correlation between leptin and growth hormone has been reported. The growth hormone treatment was accompanied by decreased serum levels of leptin by a mean of -24% (Eden Engstrom et al., 2003). Also, leptin levels in patients with acromegaly are significantly lower than those in normal subjects (Isozaki et al., 1999). However, it has been reported that leptin pretreatment of pituitary cells in culture or rats does not change growth hormone secretion (Isozaki et al., 1999). Conversely, leptin stimulates linear growth by stimulating the production and secretion of growth hormone from the hypothalamus; simultaneously, it has a direct effect on the chondrocytes in epiphyseal plate and involved with bone remodeling (Gat-Yablonski and Phillip, 2008). In the context of these discrepancies, we assume that, in the current study, higher levels of leptin might accompany by lower levels of growth hormone or other growth factors such as IGF1, which led to shorter height in these infants, or simply it might be an experimental mistake of unknown origin and future studies may confirm the result.

In the current study, we observed a significant relationship between leptin and cortisol levels at 6 months of age which might be due to the effects of glucocorticoids on leptin synthesis and secretion. Leptin is also able to affect adrenal gland functions; specifically, the HPA axis, in harmony with the leptin, establishes a basic brain-body feedback loop, which empowers the central nervous system to sense and regulate peripheral fat stores, energy homeostasis and feeding behaviors, but the exact mechanism is almost unknown (Aschbacher et al., 2014). There is controversy over the effects of HPA axis on leptin secretion (Nishii et al., 2006). Studies suggested that

due to decreased glucocorticoid receptors in hypothalamus, particularly in periventricular nucleus, the negative feedback for corticotropin-releasing hormone was weakened and a plasma level of cortisol (human) and corticosterone (rats and mice) was elevated in subjects experiencing PS (Gholipour et al., 2017). Thus, these subjects might face problems in adaptation to the environment (Weinstock, 2015). Edward et al. (2002) also carried out a study to assess the effects of stress during pregnancy on changes of behavioral and hormonal responses which are involved in regulation of body weight such as increased appetite and combination of metabolic syndromes including insulin resistance and increased serum levels of cortisol and leptin. They concluded that fat tissues played a role in response to stress by secreting leptin. Thus, it can be inferred that due to significant correlation between cortisol and leptin levels, increased cortisol level as a stress hormone stimulates leptin secretion and has adverse effects on offspring growth.

In the current study, the effect of PS was evaluated on offspring growth and development from 24 weeks of pregnancy up to 6 months after birth. As this was the first longitudinal study examining these effects in the Iranian society, we recommend further longitudinal studies in this field with higher sample sizes in various statistical populations with checking mother's body mass index (BMI) which was not checked in the current study.

Conclusion

In conclusion, we observed that PSS significantly correlated with offspring growth and development. Leptin appears to play a key role in growth and

development, which may adversely affect the risk of developing a number of diseases in adulthood. Although further studies are required in this field, we conclude that due to changes in cortisol and leptin levels at birth and 6 months after birth and their correlation with offspring growth and development, these hormones can probably be appropriate biomarkers for prediction and diagnosis of offspring growth and developmental disorders in context of stress. Thus, better understanding of the role of leptin during development can assist in the prevention and treatment of a number of disease states that occur later in life.

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Conflict of interest

Authors declare no conflict of interest regarding this paper.

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