








***The Predictive Role of Serum Leptin Levels in Pregnant Mothers
in Relation to their Delivery Type***

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Abstract

Background: It seems that in a vaginal delivery, serum leptin level increases as a cortisol-dependent factor due to the stress of the embryo. Studies have shown that if the level of serum leptin is low, the risk of chronic metabolic diseases, cardiovascular diseases, hypertension, and obesity in the mother and the baby will increase.

Objectives: This study aimed to determine the relationship between serum leptin levels in pregnancy and the type of delivery.

Methods: This study was a descriptive-analytic study, which adopted a longitudinal approach to examine 45 mothers in the first and second trimester of pregnancy in Tehran in 2015. The participants were selected using of cluster random sampling. After obtaining consent from the mothers, their blood samples were collected at 6-12 and 15-20 weeks of pregnancy and their serum leptin levels were determined. The mothers' examination continued after their delivery. Finally, the mothers were divided into two groups including the vaginal delivery group (24 participants) and the cesarean group (21 participants). Independent-Samples t-test, Pearson test, regression test, and Lambda test were used to analyze the data. SPSS was employed to carry out analyses at P value<0/05 level.

Results: The mean values of the serum leptin level in the first trimester and second trimester were higher in the normal delivery group in comparison with the cesarean group. Nonetheless, there was not a significant relationship between the serum leptin level and the type of delivery although there was a statistically significant relationship between the type of delivery and the changes in leptin levels during pregnancy and these changes were reported more frequently in the normal delivery group in comparison with in the cesarean group (P value=0.021).

Conclusion: Based on the results of this study, leptin level changes during pregnancy can have a predictive role in the mothers' type of delivery. However, further studies with larger samples are required to confirm the extent and type of this role.

Keywords: leptin, pregnancy, type of delivery

Introduction

Adipose tissue can create its own systemic effects by producing and secreting materials called

adipokines. As an adipokine, Leptin plays important roles in the regulation of insulin sensitivity, fat metabolism, and energy stability

[1-4]. Leptin, which is known as the “hunger hormone”, is a product of the ob gene and is a 16-kDa peptide which is largely produced by human adipose tissue and paired trophoblast and released in maternal and embryonic blood circulation [5-8]. The expression of the gene of protein leptin is associated with the secretion of essential hormones of pregnancy such as estrogen and the human chorionic gonadotropin hormone [1]. The half-life of plasma leptin is about 25 minutes [9, 10]. Leptin was originally discovered as a regulator of food intake and energy consumption. However, researchers now recognize it as a polytropic molecule which has a wide range of physiologic and pathologic functions [6]. The expression of Leptin gene in the endometrium and paired trophoblasts indicates the function of leptin in the implantation and reproduction of human in a way that unbalanced regulation of leptin leads to women’s infertility [2,11]. Serum leptin increases significantly during pregnancy. However, its precise mechanisms have not been completely characterized and categorized [5]. Leptin secretion of human placenta in pregnancy peaks in the second trimester, decreases in the third trimester in comparison with the first and the second trimesters, and falls after delivery [3,7,12]. Serum leptin is significantly higher in the obese mothers group in comparison with the in the normal group [13,14]. The ratio of leptin for cerebrospinal fluid to serum leptin is 1 to 100 [14]. Inflammatory and leptin factors in the blood circulation of obese, diabetic, and pre-eclampsic women and overweight placentas have increasing levels [2,15,18]. Recently, the tocolytic role of leptin has also been noted in studies [2,9,10,19]. Mean levels of leptin in term infants are about 6 times higher than premature infants. This issue may show the role of leptin in setting up an endocrine system near delivery [9]. Many factors such as body mass index, gestational age and tobacco can affect the leptin levels of the umbilical cord [9,17]. On the other hand, serum leptin can also affect weight gain during pregnancy [1,2,20]. In general, obese women, with higher levels of leptin, are more likely to experience post term deliveries. Moreover, laboratory studies have suggested that a myometers of obese women have low contraction abilities. High levels of leptin can be a probable mechanism of this issue [9]. In contrast to this

theory, Kuminairk et al. studied the role of leptin in early delivery. However, they did not report a significant difference between the two groups of the study [17]. In addition to receiving food and regulating endocrine, the immune system also plays an important role in the secretion of leptin. The results of experimental studies on animals have shown a correlation between leptin levels and inflammatory factors such as tumor necrosis factor-alpha in a way that, in the case of oxidative stress, leptin was introduced as a cytokine balance regulator [6]. According to a theory, Leptin levels increase in the process of delivery due to the inflammatory pathways of delivery and the mother's need for energy. This issue is probably related to the stimulation of the sympathetic system [10]. Studies have shown that, in vaginal delivery, the embryo is exposed to stress and stress hormones such as Cortisol. Increase in leptin levels occurs in a dose-dependent manner with cortisol. This is the most obvious difference between vaginal delivery and cesarean delivery, which can lead to a difference in maternal serum leptin levels in two types of delivery [21].

On a few studies have been conducted on leptin and type of delivery. These studies have produced conflicting results [10,12,22-24]. Investigations have shown that despite the increase in leptin during pregnancy, the concentration of leptin during delivery is associated with the type of delivery in a way that in cesarean delivery, it decreases significantly and noticeably and reaches about the half of the concentration level of normal delivery. Wilson conducted a study on the leptin in the cerebrospinal fluid. Based on the results, there was not a significant difference between the fasting leptin in non-pregnant women and women before cesarean delivery [10,12]. On the other hand, the study by Hajji Mirzaei et al. reported that the serum leptin in normal delivery was twice the amount of the serum leptin in cesarean delivery [10].

The theory in regard to the low level of leptin in cesarean delivery can put mothers and fetuses at risk of chronic metabolic diseases, cardiovascular diseases, hypertension, and obesity. Moreover, the tripled increase in the cesarean rate in Iran in comparison with the global standard of cesarean rate and its mortality and economic consequences in the country necessitate studies like the present study [2,6-8,10,16]. Given that limited studies

have been carried out with some contradictory results regarding maternal leptin plasma levels and type of delivery in Iran, we decided to study the predictive role of serum leptin levels in pregnant mothers in relation to their delivery type.

Methods

A longitudinal approach was adopted to conduct this descriptive-analytical study on women who visited crowded health centers which were supported by Shahid Beheshti University of Medical Sciences within the time period of September 2014 to January 2016. Cluster random sampling was employed to select the health centers. That is, which Tehran city (Iran) was randomly divided into four geographic regions including north, south, east and west. Next, 11 health centers were selected from the aforementioned regions based on the proportion of the population of each region. Lastly, convenient sampling was utilized to select 110 pregnant mothers from among all of the mothers who visited the centers in the first trimester. The final participants consisted of 45 mothers due in large to participant mortality which stemmed from various reasons such as the undesirable pregnancy outcomes like abortion and mothers' reluctance to continue their participation in the study. The participant mothers were Iranian and were in the first trimester. They ranged in age from 18 to 40. In addition, they had certain characteristics including: singleton pregnancy, lack of systemic diseases such as lupus, lack of diabetes mellitus and thyroid, lack of heart, kidney, and coagulation diseases, lack of epilepsy, asthma, and hepatitis, lack of high blood pressure, lack of psychological problems, lack of the experience of the death of the loved ones, lack of a history of the use of neuropsychiatric medications, and lack of the use of tobacco (cigarettes), drugs, and alcohol. The participant mortality criteria involved: suffering diverse pregnancy complications such as abortion, IUFD, preeclampsia, molar pregnancy, ectopic pregnancy, diabetes mellitus, placenta previa and placental abruption, using the medications other than pregnancy supplements, following special diets such as purely vegetable-based or a protein-based diets, and being reluctant to continue the participation in the study.

In order to measure leptin in pregnancy, the total sample size was estimated to be 45 on the basis of the studies by Kim in South Korea and Castecano Filho in Brazil [25,26]. It was calculated by means of the following sample size formula with a confidence level of 95% and a test power of 0.8.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

Mothers were assigned to two groups including: the normal delivery group (24 mothers) and the cesarean group (21 mothers). The homogeneity of the groups in terms of the demographic and extraneous factors was examined by statistical tests due to the select of the sample from different regions of Tehran (Table 1).

The participants were provided with sufficient information on the study and were made aware of the benefits of the experiment and its free services. Next, their written consent was obtained and they were assured that their personal information would be kept confidential. Finally, their blood sample was taken. The researcher's personal contact number, name, and position were given to the mothers for any probable midwifery telephone consultations. In order to determine the gestational age, the first day of the last menstruation was used. The date of the first ultrasound imaging in the first trimester of pregnancy was used when the aforementioned data was uncertain. During the first visit, the researcher utilized the standard form of prenatal care of the Ministry of Health and face-to-face interview to determine the participant mothers' demographic characteristics, pregnancy history, and maternal medical histories. Next, this information was coded and recorded without mentioning the mothers' name in the questionnaire which was developed based on the prenatal questionnaire. Mothers' weights were by a single person by means of a single analog weight scale of the health center. Moreover, their blood pressure and the heart beats of fetus were measured by a single person through the use of a single digital blood pressure monitor and a single Doppler fetal monitor. The instruments were calibrated before each measurement. Mothers' specialized examinations, including thyroid examination and dental health examination were performed by a specialist physician and recorded

in the case. BMI was calculated by dividing the weight (kg) by height (2m). The participants' usual nutrition program was examined and at the end of the visit they were provided with appropriate nutritional education during pregnancy. Pregnant mothers' nutrition program was recorded by means of the recommended dietary protocol for pregnant women which was developed by the Ministry of Health. The usual method was utilized to provide the mothers with nutritional education in regard to prenatal care. In each prenatal visit, all of the factors in the prenatal care form including: weight, height, BMI, and weight gain, blood pressure, fetal heart beats and so on were examined to confirm the mothers' health. At the end of each visit, the mothers' gestational age was used to remind them of their following visit time. In order to develop a more emotional relationship with the mothers and to encourage them to continue their participation in the study, the researcher contacted them by means of telephone and obtained information on their health issues.

Mothers' venous blood samples were taken from the antecubital vein of the left hand in two sessions preferably in a sitting position. The hand veins and the midwifery veins were rarely utilized to measure the serum leptin at 6-12 weeks and 20-15 weeks of pregnancy between 9 a.m. and 11 a.m. The taken samples were examined up to and after the mothers' delivery to determine the existence of participant mortality criteria or miscarriages. Samples were sent to the Endocrinology laboratory within 48 hours. In the laboratory of the center, the samples were spun by means of a centrifuge for 10 minutes and their plasma was separated. The prepared serums were frozen at low temperature (20-70°C) until the test. After completing the required sample size of the study, the samples were measured at once by ELISA method through the use of leptin-specific kit. In the present study, a specific Mercodia, Uppsala (Intraassay CV%: 1.7 with sensitivity of 0.24 ng/ml) Sweden-made human leptin kit which

utilizes the ELISA method was purchased from the Padgin Teb exclusive company. According to the instructions of the kit, the samples were diluted 11 times and the results were multiplied by 11.

Finally, the researcher obtained information on the mothers' delivery by means of telephone and divided them into two groups including: vaginal delivery group and cesarean delivery group. The cesarean indications involved previous cesarean, dystocia, and meconium. Moreover, they were optional. The homogeneity of the groups was confirmed through the examination of the background and demographic variables such as age, education, occupation, number of households and sex, fertility status, income and body mass index by means of statistical tests. SPSS 21 was utilized to analyze the data. The quantitative data were reported in the form of mean values and standard deviations and the qualitative data were reported by means of percentages. The relationship between the variables of the present study and the correlation between them in each group were examined separately by independent samples t-test, Pearson and regression tests. In order to compare the correlation coefficients between the two groups (RA vs. RB), which were obtained from previous tests, the Lambda test was used at the $p < 0.05$ significance level.

Results

In this study, 24 of the mothers had normal deliveries and 21 mothers had cesarean deliveries. The mothers' age average ($n=45$) in the present study was 27.47 ± 5.55 years and the minimum and maximum participant ages were 19 and 37 respectively. Some of the mothers' demographic information and the results of the examination of the homogeneity of the groups in regard to the background and demographic variables including age, education, occupation, number of households and sex, fertility status, income and body mass index are provided in Table 1.

Table 1: Distribution of the Mean Frequency of Homogeneous Variables in Two Groups of Study

Variable	Normal Delivery Group	Cesarean Group	P value*
(Year)Age Average	24.5±5.718	29±5.198	0.603
Mother's Education (Percentage)	Primary	21.7	0.549
	Diploma	26.1	
	Higher	52.2	
Mother's Occupation (Percentage)	Employed	91.3	0.157
	Unemployed	8.7	
Number of Households (Percentage)	2	21.7	0.255
	3	69.6	
	4 and more	8.7	
Average Monthly Income (Percentage)	Less than 600000	8.7	0.087
	600000-1000000	87	
	More than 1000000	21.7	
The Frequency of the Newborns' Sex (Percentage)	male	52.2	0.291
	female	47.8	
Fertility Status (Number)	Gravida	2	0.961
	Para	1	0.851
	Abortion	0	1
	Live child	1	0.731

The results of this study showed that, in the first and the second trimesters, leptin was higher in the natural delivery group in comparison with the cesarean group. However, there was not a significant relationship between leptin and the type of delivery. The investigation of the

relationship between the type of delivery and the changes in leptin levels during pregnancy showed that these changes were significantly higher in the normal delivery group in comparison with the cesarean group (Table 2).

Table 2: Comparison of Serum Leptin Levels (ng/ml) in Normal and Cesarean Delivery Groups

Leptin \ Group	Normal Delivery	Cesarean Delivery	P value
Leptin in the First Trimester	36.25±0.7	35.15±0.6	0.33
Leptin in the Second Trimester	40.58±0.8	38.09±0.6	0.72
Leptin Changes	4.33±0.3	2.93±0.2	0.021

Discussion

The results of this study indicated that there was a significant difference between the changes in serum leptin levels during pregnancy in the mothers who had normal deliveries and the mothers who had cesarean deliveries. These results are in line with the results of a large number of studies which have been conducted on this issue in the other countries. Most of the research studies in Iran have examined the

relationships between leptin and obesity, diabetes, and mothers' preeclampsia.

Logan et al. conducted a study in 2016 in order to investigate leptin and adiponectin of the umbilical cord blood in selected cesarean, emergency cesarean, spontaneous labor, and instrumental labor groups. According to the results, leptin levels were significantly higher in the active delivery group in comparison with the other groups and the lowest serum concentration was observed in the selected cesarean group.

However, in further explanations the researchers argued that the duration of labor had a more influential role in the increase in leptin levels in comparison with the type of delivery. As they stated, the probable mechanism was the pre-inflammatory role of leptin in signaling labor [24]. In the study by Nomah et al. in Japan, it was argued that, plasma leptin concentration significantly increased during labor in comparison with the period before labor and reached non-pregnancy levels 3 to 6 days after delivery. Moreover, they stated that leptin levels in the normal pregnancy group were higher than these levels in the cesarean group 1 hour and 24 hours after delivery. Finally, they concluded that, inflammatory cytokines can probably stimulate the secretion of leptin from the placenta, which can cause an increase in plasma leptin of labor [5]. Yoshimitsu et al. conducted a study on 30 mothers in the selected cesarean group and 34 mothers in the normal delivery group. The results of their study showed that, the venous and arterial umbilical cord leptin was higher in the natural delivery group in comparison with the cesarean group immediately after delivery [29]. In the study by Hermonson et al. in 2014, umbilical cord adiponectin in infants was measured after delivery. The researchers confirmed the homogeneity of the newborns in regard to their sex and weight and found that leptin was significantly lower in the selected cesarean group. They concluded that, this issue can be a risk factor of obesity and its metabolic effects in the future [28]. The role of leptin in energy metabolism and hypoxic conditions constitutes one of the discussed mechanisms for higher levels of leptin in normal delivery. This issue stems from the fact that, active labor is accompanied by uterine and fetal hypoxia and the mother's increased need for energy.

The results of the study by Ortega Sanovila in 2013 showed that serum cortisol level was higher in the natural delivery group in comparison with the cesarean group. Moreover, the serum leptin level was higher in the cesarean group than the natural delivery group. However, these differences were not statistically significant. The researchers argued that, the lack of significant differences between these groups stemmed from the similarity of the infants' fat masses [22]. Kohort Rietalsky et al. conducted a study on 40

women with gestational hypertension and 40 women with no pregnancy complications. The results of their study showed that, there was a significant increase in the interferon gamma concentration and maternal serum leptin of the gestational hypertension group in a way that in this group 1.4 times the risk of cesarean delivery was reported in the case of an increase of 0.1 picograms in interferon gamma and a three-fold increase in leptin [6]. The results of the study by Prang et al. indicated that there was a positive correlation between factor 5 and leptin 12 hours after delivery. Furthermore, the amount of factor 5 in the cesarean group was significantly higher than the vaginal delivery group [30]. The results of these studies highlight the fact that an increase in inflammatory and corticosteroid factors during normal delivery caused an increase in the levels of leptin. These physiological conditions do not occur before cesarean delivery.

Farid et al. conducted a study in Tabriz in order to examine SGA infants' resistin concentration. Based on the results, resistin concentration in the spontaneous normal delivery group was significantly higher than the cesarean group. Moreover, the results showed that there was a positive correlation between resistin and leptin [23]. Another study reported that, in the group of mothers with SGA infants, there was a significant decrease in leptin in the process of converting cholesterol milk to whole milk [27]. These studies highlight the protective role of leptin in maintaining healthy pregnancy and term and improving the health of the infants' homeostasis.

The results of this study showed that the changes in leptin levels from the first trimester to the second trimester had a significant relationship with the type of delivery in a way that the changes in leptin in women who had normal delivery were higher than the women who had cesarean delivery. The amount of leptin in the first and the second trimesters were separately higher in women who had normal delivery in comparison with the ones who had cesarean delivery. However, there was not a significant relationship between leptin and the type of delivery. During pregnancy, the amount of leptin in the mother's serum increases progressively and reaches its maximum level in the second trimester and remains constant at this level (which is about 2-3 times more than that of non-pregnant women)

until delivery [31]. Several studies have shown the role of leptin changes in the outcome of pregnancy and infancy. Nonetheless, the comparison between the results of this study and the results of other studies due to the lack of studies on the role of leptin changes in mothers' delivery. The leptin hormone plays a role in the physiology and pathophysiology of pregnancy and maternal and neonatal outcomes. It may be possible to use this hormone to predict the pathophysiology of pregnancy. In this study, the weight of placenta was not measured and matched after delivery. This issue constitutes one of the limitations of the present study. The other limitation of the study was the lack of grouping of the mothers who had cesarean delivery. It is suggested that, the following studies should examine two groups of mothers including the group of mothers who had cesarean delivery before the onset of pains and the group of mothers who had cesarean delivery due to dystocia. Therefore, there is a need for more similar studies with larger samples to reach a firm conclusion in regard to the role of leptin in the prediction of mothers' delivery type.

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