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Full length Research paper

Maternal serum leptin levels in severe preeclamptic pregnant women in early postpartum stage

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The aim of this study is to determine early postpartum maternal serum leptin levels in severe preeclamptic pregnant women. This study was planned as a prospective controlled trial. The patient and control groups in the study were composed in the period between January 2003 and January 2004. The study, performed in the Department of Perinatology of SSK Bakirkoy Maternal Hospital and Women and Child Diseases Education Hospital, consists of forty-four singleton pregnant women giving birth after hospitalized with diagnosis of severe preeclampsia and forty-four normotensive singleton pregnant women who were found to have healthy pregnancy on examination and analysis before given birth. The venous blood of all pregnants was taken from the antecubital region in early postpartum period while they were all hungry. We studied the relation between demographic data, biochemical data, baby weight at birth and the serum leptin levels. Comparing the preeclamptic pregnant women with control group in terms of leptin, although leptin levels in severe preeclamptic pregnant women were found to be higher than control group, statistically, no significant difference was determined (p: 0.069). In severe preeclamptic group, baby weight at birth was found to be significantly lower (p: 0.000). Evaluating all pregnant women, it was determined that there has been a positive significant relation between serum leptin levels and diastolic tension (p: 0.044), urea (p: 0.019), creatinine (p:0.000), uric acid (p: 0.000); and a negative significant relation between serum leptin levels and baby weight at birth (p: 0.038). No relation was found between the leptin level and the gender of infants. No significant difference of early postpartum maternal serum leptin levels between severe preeclamptic group and normotensive group was determined.

Key words: Preeclampsia, early postpartum stage, serum leptin levels, severe preeclamptic pregnant women.

INTRODUCTION

Leptin, determined in human and rodents, is a protein hormone synthesized from fat tissue, coded by obesity (ob) gene (Zhang et al., 1994). Leptin is mainly produced from fat tissue, and additionally, it is produced in bone marrow fat cells, fundal epithelium of stomach, muscle, granulosa and cumulus cells in mature ovarian follicle, placenta, lactating mammalian epithelial cells (Lharrague et al., 1998; Cioffi et al., 1997). Leptin provides communication (transmission) between fat tissue and nervous system and plays a role in nutritional intake and energy consumption. Moreover, it plays a role in several physiologic events such as reproductive system, angiogenesis, hematopoiesis, immune system, lipid and bone metabolism, glucose metabolism under the control of insulin sensitivity, ovarian functions, sympathetic activation, gastrointestinal functions, cerebral development (Mantzoros, 1999). In pregnant women, leptin levels is determined

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high during pregnancy, espe-cially in second and third trimesters, in comparison to the women who are not pregnant and it decreases just before delivery (Masuzaki et al., 1997; Chien et al., 1997). As exogenous leptin is cleared from circulation rapidly, to maintain high leptin levels observed in pregnancy, conti-nuous stimulation of leptin secretion is likely required. Fluctuation of leptin levels in pregnancy correlates with estradiol and human chorionic gonadotropin (HCG) levels in maternal circulation. This situation suggests that there is a dynamic relation between fluctuating levels of repro-ductive hormones secreted (oscillated) in pregnancy and leptin (Hardie et al., 1997). Increased leptin levels in pregnancy have indicated that leptin could be a factor indicating food situation between mother and fetus. Leptin level is high in fetus at term as well (Jaquet et al., 1998). Leptin and receptor expression in fetal bone suggest that leptin can be important in bone and cartilage development and/or hematopoiesis in intrauterine life. Hypertensive diseases are the most frequent medical complications of pregnancy, and have the incidence ranging between 5 to 10%. Also, they are among the main causes of maternal and perinatal morbidity and morbidity worldwide (Williams, 2001).

Association between preeclampsia and maternal serum leptin levels has not been thoroughly understood yet. While in some studies, leptin level has been found to have increased in preeclamptic pregnant women (Mc Carthy et al., 1999). In other studies, no difference has been determined in hypertensive and normotensive pregnancies (Sattar et al., 1998). But, it has also been shown that leptin is produced by placenta and that the production is increased in preeclampsia (Mise et al., 1998).

The aim of this study is to compare postpartum early stage maternal serum leptin levels of normal and preeclamptic pregnant women.

MATERIALS AND METHODS

This study was planned as a controlled prospective trial. The patient and control groups in the study were composed in the period between January 2003 and January 2004. The study consists of forty-four singleton pregnant women giving birth after hospitalized with diagnosis of severe preeclampsia and forty-four normotensive singleton pregnant women who were found to have healthy pregnancy on examination and analysis. The women gave birth in the Department of Perinatology of SSK Bakirkoy Maternal Hospital and Women and Child Diseases Education Hospital. The study was started by the decision taken from local ethics committee. The patients were informed about their diseases and the therapy and treatment authorization forms and the approval of all the patients were assured

Severe preeclamptic patients were chosen according to the severe preeclampsia criteria of American College of Obstetricians and Gynecologists (ACOG) Committee (American College of Obstetricians, 1986). All the patients were selected among the patients hospitalized in Perinatology Department and diagnosed with severe preeclampsia based on laboratory analysis. All the patients included in the study were singleton and in third trimester. From all the hypertensive pregnant women, demographic data and history were recorded, and the blood and urine samples were collected for complete blood count, complete urine analysis, urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and protein in 24-h urine (Esbach). All the cases were selected from the non-smoker patients who had no diseases and no drug use that could affect energy metabolism. Gestational age of all patients was determined by performing ultrasound (US) biometry and evaluating USg data belonging to the first trimester. Control group was paired with severe preeclamptic group in terms of pre-pregnancy BMI, education level, duration of marriage, age, number of delivery, gestational age and form of delivery. This group was consisted of the singleton non-smoker pregnant women who had no medical problem and drug use. All the analysis performed for severe preeclamptic pregnant women except Esbach were performed in control group. In postpartum early stage, blood samples of all the pregnant women were taken from antecubital region. Because of the nutritional prohibition before delivery for the patients in the period of delivery with normal spontaneous delivery (NSD) and because of the request of 6-8-h period of fasting for the patients undergoing cesarean section in our clinic, blood sampling was performed when all the patients were hungry. The blood sample for leptin test was centrifuged at +4ºC; the serum obtained was frozen immediately and stored at -20ºC until assay. Serum leptin level was determined by using solid phase Enzyme Amplified Sensitivity Immunoassay (EASIA) microtitre plate kit (Biosource Europe S.A., Nivelles, Belgium). Identifiable minimum leptin concentration was 0.1 ng/ml; interassay variation coefficient was 5.2%; and intraassay variation coefficient was 3.6%. Amongst the biochemical parameters, urea and uric acid was determined with UV test; creatinine was measured with Jaffe method; AST, ALT and LDH was measured by kinetics method; 24 h urinary protein was determined with Esbach's precipitation method. Measurements were performed with Hitachi modular H+ISE 900 auto analyser.

Statistical tests

For statistical analysis, Statistical Package for Social Sciences (SPSS) for Windows 10.0 program was used. For evaluating the data of the study, along with the complementary statistical methods (median, standard deviation), independent student's t test for comparing of parametric data, chi-square tests for comparing of non parametric data, pearson's correlation analysis for determining the association of leptin with other clinical and biochemical parameters were used. The statistical significance limit was accepted as $p<0.05$.

RESULTS

No significant difference was determined between severe preeclamptic pregnant women and the pregnant women in control group in terms of age, duration of marriage, number of delivery, BMI, gestational age at delivery ($p>0.05$). Between the two groups, a statistically significant difference was determined in terms of systolic and diastolic pressure and baby weight at birth (despite matching as gestational age) (p: 0.000; p: 0.000; p: 0.000, respectively) (Table 1).

When the severe preeclamptic pregnant women were compared with the pregnant women in control group in terms of leptin, although leptin levels in severe preeclamptic pregnant women were higher compared to control group, statistically no significant difference was determined (p:0.069). When the two groups were compared in

Table 1. Demographic data of severe preeclamptic and normotensive pregnant groups..

	Severe Preeclamptic Pregnant Women (n:44)	Normotensive Pregnant Women (n: 44)	P
Age (year)	27,34±5,9	28,3±6,0	NS
Duration of marriage (year)	5,88±5,3	6,5±5,5	NS
Number of delivery	0,84±0,9	0,88±0,9	NS
Systolic Pressure (mmHg)	174,3±15,7	111,8±8,9	P:0,000
Diastolic Pressure (mmHg)	115,9±10,6	71,13±6,8	P:0,000
Gestational Age at Birth (week)	34,6±3,3	34,7±2,8	NS
Weight at Birth (gr)	1938±706,7	2670±838,7	P:0,000
Body mass index	25,41±5,11	25,18±2,27	NS

NS**:** Not significant. All of the values are indicated as median± SD.

Table 2. Biochemical and leptin data of severe preeclamptic and normotensive pregnant groups.

	Severe Preeclamptic Pregnant Women (n:44)	Normotensive Pregnant Women (n:44)	P
Urea (mg/dl)	32,4±20,68	19,4±6,8	P:0,000
Creatinine (mg/dl)	0,99±1,03	0,55±0,13	P:0,007
Uric acid (mg/dl)	5,57±1,8	2,87±0,76	P:0,000
AST (U/l)	43,11±43,32	27,45±11,46	P:0,023
ALT (U/l)	43,47±42,09	11,09±4,11	P:0,000
LDH (U/l)	656,84±307,39	477,86±141,55	P:0,001
Hematocrit	32,36±4,24	30,55±3,06	P:0,025
Thrombocyte	162663±88325	201250±88325	P:0,011
Esbach (gr/24 saat)	3,39±2,3		
Leptin (ng/mL)	13,80±17,52	8,5±6,9	NSP:0,069

All of the values are indicated as median± SD.

terms of urea (p:0.000), creatinine (p:0.007),uric acid (p: 0.000), AST (p:0.023), ALT (p:0.000), LDH (p:0.001), hematocrit (p:0.025), thrombocyte (p:0.011), a statistically significant difference was determined (Table 2). As for neonatal morbidity, it was higher in severe preeclamptic patient group and it was statistically significant (p: 0.01) (Table 3). In terms of the form of delivery, no difference was determined (p: 1.000) between severe preeclamptic group and control group, but a significant difference was found between the two groups in comparing cesarean section indication (Table 4) (p: 0.001).

When all the pregnant women included in the study were evaluated together, no statistically significant association was determined between leptin and diastolic pressure, gestational age at birth, AST, ALT, LDH, hematocrit, thrombocyte, and BMI. There were a negative weak association between leptin levels and baby weight at birth (p: 0.038); a positive weak association between leptin levels and diastolic pressure (p:0.044); a positive weak association between leptin levels and urea (p:0.019); a positive moderate association between leptin levels and creatinine (p:0.000); a positive weak association between leptin levels and uric acid (p:0.000); a positive moderate association between leptin levels and Esbach.

Comment

High leptin levels in women may play a role to determine the presence of sufficient and long term energy reserves required for a successful reproduction (Chebab, 1997). In pregnant women, throughout pregnancy, especially in the second and third trimester, leptin levels are found higher than those of the women not pregnant, and just before the delivery leptin levels are decreased (Masuzaki et al., 1997; Chien et al., 1997). Hyperleptinemia in second and third trimester can be compared with that in obese animal and human. While exogenous leptin can be cleared from circulation rapidly, to maintain elevated leptin levels in pregnancy, probably leptin secretion should be stimulated continuously. Fluctuations in leptin levels in pregnancy show a correlation with estradiol and HCG levels in maternal circulation (Mc Carthy et al., 1999). This situation suggests that there is a dynamic relation between fluctuating levels of reproductive hormones secreted in pregnancy and leptin.

In a study of Misse et al. (1998), leptin level, for the first

Table 3. Comparison of delivery form and section indication of severe preeclamptic and normotensive pregnant groups.

		Severe Preeclamptic Pregnant Women (n: 44)	Normotensive Pregnant Women (n:44)	Total
NSD		11	11	22
Section indications	Fetal distress	20	3	23
	Prolapsed umbilical cord		1	1
	Abnormal presentation		1	1
	Section history	5	13	18
	Breech presentation	2	6	8
	Abruptio placentae	4		4
	Unpregressive labor	2	3	5
	Primigravid age		1	1
	Placenta previa		1	1
	Early membrane rupture		3	3
	Assisted pregnancy		1	1

Pearson chi-square p:0.001 (section indications).

Table 4. Comparison of neonatal morbidity of severe preeclamptic and normotensive pregnant groups.

		Severe Preeclamptic Pregnant Women (n: 44)	Normotensive Pregnant Women (n:44)	Total
Neonatalmorbidity	Stillbirth or death within 12 h	3	0	3
	Morbidity present	24	14	38
	Morbidity absent	17	30	47
Total		44	44	88

Pearson chi-square p:0.001

time, was found to be significantly high in preeclamptic pregnant women, especially in cases with severe preeclampsia (Mise et al., 1998). In these patients, it has been shown that placental leptin mRNA expression was increased proportionally with serum leptin levels and that serum leptin level was decreased following expelling of placenta after delivery. That indicates that leptin increase in preeclamptic woman is related to placental production. Increase of placental leptin production reflects placental hypo perfusion and/or hypoxia. Hypoxia increases placental leptin production inducing a group of placental genes in trophoblastic cells. Thus, it is deduced that elevated leptin level is a general response of trophoblastic cells to hypoxia. Leptin is an indication of severe preeclampsia, reflecting placental hypoxia (Chebab, 1997). The importance of increased placental leptin production is not known. It is known that leptin increases production and degradation of noradrenalin in brain fat tissue (Takaya et al., 1996). And it shows that leptin can augment sympathetic activity. Moreover, considering increased sympathetic activity in preeclamptic pregnant women, it can be thought that leptin can contribute to increased sympathetic activity in preeclampsia. That intra-cerebroventricular leptin infusion increases arterial pressure has made us to think that in preeclampsia, leptin may play a role in development of hypertension (Dunbar et al., 1997). Some other studies have not observed any difference in terms of leptin between normal and preeclamptic pregnant women (Sattar et al., 1998; Martinez-Abundis et al., 2000). In another study, while leptin levels were determined high in normal weight preeclamptic pregnant women at second trimester, leptin levels were determined low in overweight preeclamptic pregnant women (Williams et al., 1999). It can be thought that in preeclamptic pregnant women, maternal serum leptin levels can be varied due to the severity of disease. But Martinez-Abundis et al. (2000) has determined similar serum leptin levels in insignificant preeclamptic, severe preeclamptic and normotensive pregnant women [(Martinez-Abundis et al., 2000).

Despite the leptin levels in the blood samples of pregnant women in control group, and the fact that severe preeclamptic pregnant women were determined higher in severe preeclamptic pregnant women in our study, no statistically significant difference was determined (p: 0.069). That can make one to think that although leptin level is high in severe preeclamptic pregnant women, postpartum sudden decrease of leptin level (Hardie et al., 1997; Lage et al., 1999) results in not detecting a statistically significant difference.

Many studies, investigating the relation of baby weight

at birth with maternal serum leptin and umbilical blood leptin levels, have been performed. In these studies, while a correlation has been determined between umbilical blood leptin level and baby weight at birth (Hassink et al., 1997; Tamura et al., 1998; Schubring et al., 1997), no correlation has been determined between maternal serum leptin levels and baby weight at birth (Tamura et al., 1998; Schubring et al., 1997; Butte et al., 1997; Tamas et al., 1998; Kolusarı et al., 2008; Kolusari et al., 2009). In our study, we determined a weak correlation between maternal serum leptin levels at early postpartum period and baby weight at birth. This result, contrary to the literature, can be originated from prepartum or postpartum blood sampling.

In our study, when maternal serum leptin level was compared to the other parameters tested, a positive correlation was determined with leptin level and diastolic pressure, urea, creatinine, uric acid, Esbach. No relation was found between liver function tests (AST, ALT, LDH) and leptin levels. Decreased renal clearance due to impaired renal function, one of the pathophysiologic findings in preeclamptic pregnant women, can cause this result. It should be considered that, not an increased production of leptin, but decreased renal clearance can be the cause of increased serum leptin level determined in preeclamptic pregnant women in most of the studies. Decreased plasma volume that can be a subject in preeclampsia may have a responsibility for increased leptin level leading to hemoconcentration. But in our study, although a significant difference was determined between hematocrit values of two groups, no difference was determined between leptin levels.

As a conclusion, no significant difference was deter-mined between severe preeclamptic pregnant women and normotensive pregnant women in terms of early postpartum maternal serum leptin levels. A positive significant correlation was determined between leptin levels and diastolic pressure, urea, creatinine, uric acid and Esbach. A negative significant correlation between leptin levels and baby weight at birth was determined. There is a correlation between leptin and several physiologic functions and situations. But the role of leptin in pregnancy has not been explained yet. It is getting even more and more difficult because of the differences between animal models and human in leptin physiology. But the studies to explain the exact role of leptin in fertility, pregnancy and lactation have been performed continually. The recent studies have shown that leptin can be very important in mammalian reproductive and gestational tissues, especially placenta which can be the main source of leptin production in pregnancy. Varying leptin levels in normal pregnancy and in gestational trophoblastic diseases have been shown that leptin can play a physiologic or pathophysiologic role in human pregnancy. Further studies are required to understand its importance, and it is essential to perform more and more studies to verify and clarify the relationship between leptin and parameters of biochemistri in preeclampsia.

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