Comparing serum leptin levels between pregnant women with preeclampsia and normal pregnant women

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ABSTRACT

Objective: Serum leptin, the product of the obesity gene, correlates with adiposity and increases fat utilization. Maternal serum leptin, triglyceride and free fatty acids are elevated in healthy pregnancy, and are increased further in preeclampsia. This study has compared serum leptin levels in pregnant women with preeclampsia and normal pregnant women. Materials and Method: This case-control study was done in 2018 on eighty pregnant women of a hospital in Zahedan city, Iran. Forty of the chosen women had preeclampsia (case group) and the rest were normal (control group). Serum leptin level was measured by enzyme-linked immunosorbent assay test and analyzed using the t-test. Results: The leptin levels were 1985 pg/mL and 2595 pg/mL in case and control groups which was significantly different (P = 0.016). Leptin level had no significant correlation with age, preeclampsia history or blood pressure (P > 0.05). Also, leptin levels increased with increase of body mass index in pregnant women with preeclampsia (P = 0.029). Conclusion: We found that the blood leptin levels were significantly lower in the preeclampsia group compared with the normal pregnant women. Measuring blood leptin levels, BMI and Systolic blood pressure in pregnancy may be helpful as early tests in the early detection of high risk individuals.

Keywords: preeclampsia; pregnancy; leptin; Maternal: healthy pregnancy.

1. INTRODUCTION

Maternal obesity increases the risk of diabetes, preeclampsia, and hypersensitivity to chronic diseases such as diabetes and hypertension in children (Beneventi et al. 2019). Approximately, 50,000 women worldwide die due to hypertension or preeclampsia during pregnancy annually. The same figures die of its complications, including cerebral hemorrhage and kidney failure. Still, the number of patients who have severe morbidities because of this disease is much higher than the mortality rate. (Danforth 2008) Preeclampsia is a pregnancy-specific disorder that affects 2–8% of all pregnancies and remains a leading cause of maternal and perinatal morbidity and mortality worldwide. Diagnosis is based on new onset of hypertension and proteinuria. (Jeyabalan 2013; Eissa, Sayyed, and El-Bagoury 2019) Preeclampsia can progress rapidly and cause high blood pressure, edema, and proteinuria. If the disease is not detected, it is possible to Preeclampsia turn into eclampsia, which is one of the leading causes of maternal and fetal mortality and accounts for 13% of maternal deaths worldwide (Yusrawati, Habibah, and Machmud 2015).

Leptin is a 16 kDa protein hormone that was discovered in 1994. It has a key role in regulating energy intake and expenditure. It is also involved in numerous physiological processes including regulating endocrine function, inflammation, immune response, reproduction and angiogenesis. So leptin increases the insulin sensitivity by affecting insulin secretion, consumed glucose, glycogen synthesis and fatty acid metabolism. It regulates gonadotropin release from hypothalamus and activates the sympathetic nervous system. Leptin is mainly produced by fat cells. Serum leptin level is correlated with fat mass. It passes through the blood-brain pathway by a specific neural receptor that regulates appetite in the nucleus arc. In addition, leptin induces human chorionic gonadotropin (hCG) production in trophoblasts, regulates placental growth, helps mitogenesis and stimulates amino acids’ uptake. (Miehle, Stepan, and Fasshauer 2012) Leptin concentrations increase in pregnant women from the earliest stages of pregnancy, implying that this increase does not only originate from maternal weight gain. Circulating leptin levels are two- to three-fold higher in pregnancy compared to non-pregnancy conditions. Its peak occurs around 28 weeks of gestation and decrease immediately after delivery (Song et al. 2016).

Also, insulin resistance, subclinical inflammation and obesity are common in preeclampsia. Insulin resistance has been suggested as a pathophysiology of preeclampsia and obesity (Miehle, Stepan, and Fasshauer 2012). Increased leptin level in pregnant women can mobilize body fat to increase access and support placental transfer of lipid precursors. Strong evidence suggests that placenta is more involved in increasing leptin concentration during pregnancy than fat tissue (Miehle, Stepan, and Fasshauer 2012). Some studies have reported that women with preeclampsia have higher leptin levels than normal pregnant women (Laivuori et al. 2006; Mumtaz et al. 2008; Baksu et al. 2005; Salimi et al. 2014). In 2005, Hendler and colleagues found that women with severe preeclampsia who have a body mass index more than 25 kg/m² have higher leptin levels than normal weight women with preeclampsia (Hendler et al. 2005). Also, Mendieta and colleagues found that women with body mass index more than 40 kg/m² have a significantly higher serum leptin levels than those with body mass index less than 40 kg/m² (Zeron et al. 2012).

Some studies have shown that increased leptin level in preeclampsia has prognostic significance in determining preeclampsia development even before the onset of symptoms and suggest the pathophysiological role of leptin in preeclampsia (Samolis et al.
However, Dalmaga and colleagues did not find a significant association between leptin level and preeclampsia. (Dalamaga et al. 2011) Also, Dostery and colleagues showed that there is no significant difference in leptin levels of patients with mild and severe preeclampsia and there is no relationship between leptin level and gestational age (Aghoozi 2019).

Thus, there is no consistency regarding the role of leptin in preeclampsia. Hence, this study compared the leptin levels of pregnant women with preeclampsia and normal pregnant women.

2. MATERIALS AND METHODS
A number of 80 pregnant women who had referred to Ali-ibn-Abitaleb hospital, which is a tertiary center in Zahedan, Iran, in 2018 entered this case-control study. Forty women had preeclampsia (case group) and the rest were normal (control group). Preeclampsia was diagnosed based on clinical and laboratory criteria, that is: blood pressure ≥ 140/90 in two separate measurements in two separate sessions with at least 4 hours and proteinuria more than 300 mg in collected urine 24 hours or more than +1 by dipstick sample, which is diagnosed by urine dipstick after 20 weeks of pregnancy.

Inclusion and exclusion criteria
The inclusion criteria were: 1) pregnant women at 28 to 40 weeks of gestation, 2) having preeclampsia for case group and being normal in control group, and 3) being 18-35 years old.

The exclusion criteria were having diabetes, chronic hypertension, chronic kidney disease and appearance of preeclampsia in any participant in the control group. Also Patients with lupus, rheumatoid disease, endocrine glands (thyroid and adrenal), systemic infections, previous vascular diseases, pregnancies over one and Clinical signs based on symptoms of Chorioamnionitis were excluded from the study.

Study protocol and Biologic samples
The study protocol was explained to all participants and they signed an informed consent before entering the study. The participants were chosen by non-random consecutive sampling. Blood pressure was measured in a sitting position after resting for at least 10 minutes and participants did not smoke or caffeine for 30 minutes before the measurement and blood samples were taken after six hours of fasting after hospitalization. Data were gathered by physical examination, filling a check list and measuring serum leptin levels in third trimester pregnancy (Table 1). After filling out the questionnaire 2 mL of blood was taken from the participants and centrifuged for approximately 15 minutes at 1000 round per minute (rpm) to measure their leptin level. The blood serum was separated and stored at −70°C. All participants were followed-up two weeks after delivery and any new evidence were included in the questionnaires.

Data collection
Venous blood samples were collected in test tubes containing clot activator, immediately stored on ice, and—one hour after collection—centrifuged at 3800 rpm for 12 minutes. Plasma were separated and stored at −70°C through the hour to be analyzed. Also, the definition of preeclampsia in this study is based on blood pressure ≥140/90 mm Hg and proteinuria ≥+2 in a dipstick test or ≥0.3 g in 24-hour urine collection. Demographic data of patients and laboratory results were recorded in a pre-designed information form and finally entered for statistical analysis.

Biochemical analyses
Leptin level was measured by enzyme-linked immunosorbent assay (ELISA, Diaplus, Tina Pajoohan Arvin co., Canada) using a leptin kit (pg/mL). Other related metabolites levels were measured with electrochemiluminescence using kits from Roche Company, Germany.

Statistical analysis
Data were analyzed using descriptive statistics (mean), independent t-test and chi-square. SPSS V.25 (Chicago, IL, USA) was used applied for statistical analysis. Statistical significance was assessed at the 5% level.

Ethical committee approval number & details
This research was approved by ethical committee of Zahedan University of Medical Sciences with code IR.ZAUMS.REC.1393.6975.
3. RESULTS

The two groups were not significantly different regarding age, but they were significantly different in body mass index and systolic blood pressure (Table 1). Leptin levels were 1985 ± 1470 and 2595 ± 1040 in the case and control groups. The serum leptin levels were significantly lower in the case group (P = 0.016), but there was no significant difference between women younger and older than 30 years old regarding serum leptin levels. Leptin level was not significantly different in women with a history of preeclampsia (P = 0.543, Table 2) compared to those without it (P = 0.156). There was significant association between body mass index and serum leptin levels in the investigation group (P = 0.029) so that serum leptin levels increased with increasing body mass index. But there was no change in the control group (P = 0.575, Table 3).

Table 1: Comparing demographic information of the two study groups with t-test

<table>
<thead>
<tr>
<th></th>
<th>Pregnant women with preeclampsia (n=40)</th>
<th>Normal pregnant women (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>28.0 ± 5.2</td>
<td>27.4 ± 5.1</td>
<td>0.587</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 ± 5</td>
<td>25.4 ± 5.1</td>
<td>0.014</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>145.7 ± 8.4</td>
<td>107.7 ± 11.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2: Comparing age and leptin level based on Mann-Whitney U test and parity and leptin level based on t-test

<table>
<thead>
<tr>
<th>Index</th>
<th>Leptin level ± (sd)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 30 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older than 30 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women with preeclampsia (n=40)</td>
<td>1963 ± 1327</td>
<td>1951 ± 1228</td>
</tr>
<tr>
<td>Normal pregnant women (n=40)</td>
<td>2545 ± 1117</td>
<td>2680 ± 929.5</td>
</tr>
<tr>
<td>Parity condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women with preeclampsia (n=40)</td>
<td>1806 ± 1347</td>
<td>2009 ± 1263</td>
</tr>
<tr>
<td>Normal pregnant women (n=40)</td>
<td>2941.2 ± 789.7</td>
<td>2480 ± 1098</td>
</tr>
</tbody>
</table>

Figure 1: Relationship of BMI and leptin level in pregnant women with preeclampsia and normal pregnant women
Table 3: Relationship of body mass index and leptin level based on ANOVA

<table>
<thead>
<tr>
<th>BMI ± (sd)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5</td>
<td></td>
</tr>
<tr>
<td>18.5 – 24.9</td>
<td></td>
</tr>
<tr>
<td>19.9 - 25</td>
<td></td>
</tr>
<tr>
<td>25 - 30</td>
<td></td>
</tr>
</tbody>
</table>

Pregnant women with preeclampsia (n=40)

- 1305 ± 1171

Normal pregnant women (n=40)

- 1771 ± 1470

There was no significant relationship between systolic blood pressure and leptin levels in both groups. The case group had a blood pressure more than 140 mmgh and the control group had less than 140 mmgh blood pressure. There was no relationship between systolic blood pressure and serum leptin levels. \( r = -0.036 \) and \( P = 0.728 \). Only body mass index (BMI) and leptin level had a significant correlation (Table 4).

Table 4: Correlation between leptin level and the studied variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pregnant women with preeclampsia (n=40)</th>
<th>Normal pregnant women (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>( r = 0.168 )</td>
<td>( r = 0.202 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.300 )</td>
<td>( P = 0.211 )</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>( r = 0.418 )</td>
<td>( r = 0.201 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.007 )</td>
<td>( P = 0.213 )</td>
</tr>
<tr>
<td>Blood pressure (mmhg)</td>
<td>( r = 0.036 )</td>
<td>( r = 0.044 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.827 )</td>
<td>( P = 0.786 )</td>
</tr>
<tr>
<td>Parity</td>
<td>( r = 0.070 )</td>
<td>( r = 0.194 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.668 )</td>
<td>( P = 0.230 )</td>
</tr>
<tr>
<td>History of preeclampsia</td>
<td>( r = 0.099 )</td>
<td>( r = 0.229 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.543 )</td>
<td>( P = 0.156 )</td>
</tr>
</tbody>
</table>

4. DISCUSSION

In present study showed that serum leptin levels in pregnant women with preeclampsia are less than normal pregnant women. Also, there was a significant relationship between BMI and leptin level in women with preeclampsia. Higher BMI resulted in increased leptin level in the case group. In a similar study of 71 preeclamptic women and 71 age, parity, and BMI matched controls reported lower leptin levels at 18 weeks of gestation in women who developed subsequent preeclampsia (Clausen et al. 2002).

Many studies have shown that leptin levels are higher in pregnant women with preeclampsia compared to normal pregnant women (Laivuori et al. 2006; Mumtaz et al. 2008; Baksu et al. 2005; Salimi et al. 2014; Hendler et al. 2005; Zeron et al. 2012). In 2007, Sharma and colleagues found that serum leptin levels increase in women with preeclampsia. However, this was not significant in severe preeclampsia (Sharma, Satyam, and Sharma 2007). In 2016, Kharbs and colleagues reported that leptin levels increase in women with preeclampsia and hyperglycemic preeclampsia (Kharb et al. 2016). This mismatch can be a difference in our sample size, sampling method and serum leptin measurement. For example, in a study in 2005, Baksu and colleagues used radioimmunoassay to determine leptin levels (Baksu et al. 2005). But we used ELISA which might explain the differences in results. Also, we followed up all patients up to two weeks after delivery and if preeclampsia appeared in normal women of the control group, we excluded them.

Thagaard and colleagues reported that where BMI could not have a predictive effect and lack of connection between preeclampsia and adiponectin/leptin ratio, adiponectin could be considered an indicator for gestational Diabetes mellitus. It is suggested that adiponectin is an alternative process for insulin resistance in preeclampsia pregnancy. This role of adiponectin may be the result of its anti-inflammatory effects. In obese women, fat causes chronic inflammation. In addition, studies have shown that endothelial and vascular dysfunction cause pre-inflammatory factors from the placenta, leading to high blood pressure and eventually preeclampsia (Doster et al. 2016).

Rahman and colleagues concluded that strong correlation exists between serum leptin levels and blood pressure in normal pregnant women and those with preeclampsia. Hence, it may contribute to pathogenesis of preeclampsia (Rahman, Rehman, and Ahmed 2016). Taylor and colleagues showed that serum leptin levels in early pregnancy are significantly higher in women with preeclampsia compared with normotensive women after adjusting for known confounding factors, such as body mass index. They
found out that leptin may increase in women who will subsequently develop preeclampsia. Furthermore, they reported lower leptin levels at 18 weeks of gestation in women who had developed preeclampsia. Also, umbilical cord leptin levels were significantly higher in women with preeclampsia compared to normal women after adjustment for gestational age (Taylor et al. 2015).

Since some studies have reported no change in leptin levels of women with preeclampsia compared to normal women, the pathophysiological role of leptin in preeclampsia development should be considered with more caution. However, in 2011, Dalamaga and colleagues found no significant relationship between leptin level and preeclampsia in pregnant women (Dalamaga et al. 2011). Also in another study did not find any significant difference in leptin levels of women with mild and severe preeclampsia. They suggest that this might have been because of the younger ages of their studied pregnant women with severe preeclampsia (Miehle, Stepan, and Fasshauer 2012). They found out that body mass index is associated with leptin level in normal pregnancy but not in pregnancy with preeclampsia. These results are similar to Salimi and colleagues (a case control study that was done on 45 women with preeclampsia and 45 healthy pregnant women) and Molvarec and colleagues’ results (Salimi et al. 2014; Molvarec et al. 2011).

These conflicting results can be attributed to a variety of factors, including different criteria for diagnosing preeclampsia, medications that affect energy balance, gestational age, smoking, and ethnicity (Salimi et al. 2014).

In our study, leptin levels increased in women with higher body mass index in both groups. But it was significant in the case group. The relationship between body mass index and leptin level can highlight the role of obesity in the preeclampsia pathophysiology. Hendler and colleagues showed that women with severe preeclampsia and a body mass index more than 25 kg/m² have higher leptin levels than women with preeclampsia and normal weight (Hendler et al. 2005). This finding is consistent with our results. Many studies have reported inconsistency results. Most of these studies have been performed on serum samples since late pregnancy. Therefore, it is difficult to distinguish between pathogenic changes in the first trimester and possible epi-phenomena of preeclampsia when approaching term (Thagaard et al. 2019).

Limitations
A limitation of our study was that some participants did not cooperate easily. Although we assessed the relationship of leptin level and systolic blood pressure, we did not evaluate the relationship of leptin level with mild and severe preeclampsia.

5. CONCLUSION
There is a significant correlation between serum leptin level and preeclampsia. We found that the blood leptin levels were significantly lower in the preeclampsia group compared with the normal pregnant women. It is suggested that the relationship of leptin level and mild and severe preeclampsia be studied in further research. Measuring blood leptin levels, BMI and Systolic blood pressure in pregnancy may be helpful as early tests in the early detection of high risk individuals. Since there are controversies regarding the relationship of leptin level and preeclampsia in pregnancy, conducting a large-sampled clinical trial is recommended.

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Conflicts of Interest: The authors declare no conflict of interest.

REFERENCE


