Reduction of Soluble Leptin Receptor Levels in Women with Unexplained Infertility and the Effect of Leptin Receptor Gln223Arg Polymorphism on its Serum Level

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ABSTRACT

Background & Objective: Soluble leptin receptor (sOB-R) is the most important leptin-binding protein that can affect the level of active biological leptin. The Gln223Arg polymorphism in the leptin receptor (LEP-R) gene is associated with obesity, which can be a factor for infertility. The purpose of this study was to evaluate sOB-R levels in women with unexplained infertility and investigate the effect of LEP-R gene polymorphism on sOB-R serum levels.

Materials & Methods: One hundred and two women with unexplained infertility and 112 fertile women were studied in this case-control study. Subjects in both groups had a normal hormonal profile with age below 40 years. The levels of sOB-R were measured using the enzyme-linked immunosorbent assay (ELISA) method.

Results: There was a 2-fold decrease in sOB-R levels in the infertile group compared to the control group (P=0.001). Although sOB-R levels were lower in overweight and obese infertile subjects, this difference was not significant. However, this difference was significant compared to the control group. There was a direct correlation between body mass index (BMI), age, and infertility. Although sOB-R levels in Arg/Arg genotypes were higher than in Gln/Gln and Arg/Gln genotypes in the infertile group, they were not statistically significant. A significant decrease was observed in sOB-R levels of Gln/Gln and Arg/Gln genotypes in the infertile group compared to the control group.

Conclusion: There was a reverse correlation between sOB-R levels and unexplained infertility. It seems that, by a decrease in serum sOB-R, the serum leptin levels increase, which can enhance leptin inhibitory effects in infertility.

Keywords: Gln223Arg polymorphism, Leptin, sOB-R levels, Unexplained infertility

Introduction

Infertility refers to disability in fertility after a year of regular sexual intercourse without any prevention. Infertility as a life crisis is associated with a wide range of social, psychological, physical, and financial problems (1). Unexplained infertility is a type of infertility that no definite cause can be found for it using existing standard diagnostic methods (2).

Mild changes in hormonal conditions can lead to infertility. Leptin hormone is among the hormonal factors affecting ovulation, which affects the ovary in both paracrine and endocrine modes. It plays a key role in energy homeostasis and body weight (3).

Leptin with a 16 kDa weight from the family of cytokines consists of 167 amino acids, which is located on the human chromosome 7q31 (4).

Leptin is a hormone derived from adipocytes, which acts as an energy intake regulator and energy homeostasis through its specific receptor in the hypothalamus. Recent data suggest that leptin also influences a wide range of metabolic actions in peripheral tissues and controls reproductive axis processes (5). Leptin performs its effect through its receptors, which is from the group of cytokines’ receptors. Regarding the presence of leptin receptors (LEP-R) in all levels of the hypothalamic-pituitary gland axis, the regulatory effect of leptin is effective on reproduction and target organs such as the placenta and mammary glands. It has important physiological effects, including puberty, menstrual cycle, pregnancy, lactation, and early stages of fetal growth (6).
The diabetes (db) gene encodes the LEP-R (7). The LEP-R gene is located on the 1p31 chromosome with a length of 70 kb (8). The LEP-R belongs to the family of receptors of class 1 cytokines, which includes glycoproteins such as gp130, LIF receptor (LIF-R), and CNTF receptor (CNTF-R) (9).

The leptin receptor has three sections, which include the extracellular, intramembrane, and intracellular parts. Leptin receptor does not have kinase activity, but its intracellular portion is connected to the Just Another Kinase (JAK kinase) molecule, which has kinase activity (9).

Six leptin receptors (i.e., Ob-Ra, Ob-Rb, Ob-Re, Ob-Rd, Ob-Rf, and Ob-Re) have been found throughout the central nervous system and different tissues. The internal parts of different receptors have different lengths; in outer parts, they are the same. The extracellular domain has more than 800 amino acids, but the intracellular domains in each of these isoforms are different (10).

The expression of leptin and its receptor isoforms in pre-ovulation follicles and the presence of leptin in adult oocytes indicate the role of this factor in the reproductive process in the ovaries (11).

There are two main forms of circulating leptin: protein-linked form and free form, which is the biologically active form. The soluble leptin receptor (sOB-R) is the main leptin-binding protein in human blood circulation. Further, sOB-R is derived from the ectodomain shedding of the long isoform LEP-R and acts as a carrier and transfers leptin to its membrane receptors in human circulation. The levels of sOB-R are also considered as serum LEP-R levels, which have been measured in several studies (12, 13).

The recombinant forms of sOB-R have a high tendency to bind to leptin and the formation of homodimers. They exhibit a significant degree of glycosylation (14).

Leptin has been shown to positively correlate with body mass index (BMI) and body fat percentage. However, there is an inverse association between LEP-R and BMI. The regulatory mechanism by which leptin may modify the levels of sOB-R is not yet proven (15). However, there are some clues to some of the studies in animal models and humans. Reduction of sOB-R was shown a few hours after recombinant leptin administration in mice. Also, LEP-R reduction was observed in patients with elevated leptin levels. These results suggest that regulation may occur at post-translational levels (16). In another study, a significant decrease in the serum level of sOB-R was reported in women with polycystic ovary syndrome (PCOS) compared with healthy females (17). A defect in the leptin gene or LEP-R not only causes overeating and obesity but also makes a set of problems, such as inappropriate reproduction, hormonal imbalance, infertility, decreased gonadotropin secretion, immune and circulatory deficits, diabetes, and resistance to insulin (18, 19).

To find gene variants that have potential relevance to the pathophysiology of obesity. Type 2 diabetes mellitus (T2DM), and its related consequences, the LEP-R gene was studied. For example, an important single nucleotide polymorphism (SNP) in the LEP-R gene located in locus 1p31.3, which involves the transfer of Q to R in exon 6 in nucleotide 668 of the initiation codon (Gln223Arg, rs1137101), is associated with higher levels of leptin and some types of cancers (15).

A significant association has been reported between Gln223Arg polymorphism and the risk of PCOS (20). In another study, the GG genotype in Gln223Arg polymorphism was introduced as a risk factor for patients with PCOS (21).

The exact role of leptin in the ovaries and the physiology and pathophysiology of human requires further studies. Studies on the amount of leptin and the serum level of LEP-R in different types of infertility are limited. No reports have been published so far regarding LEP-R serum levels in infertile women with unknown cause, Gln223Arg polymorphism, and its association with unexplained infertility. In our previous study, the association between Gln223Arg polymorphism and the risk of unexplained infertility was investigated (22). In the current study as the continuation of the previous one, we investigated the comparison of sOB-R serum levels in patients with unexplained infertility and fertile individuals, serum level association of sOB-R with the hormonal profile and demographic information of individuals, and association between Gln223Arg polymorphism and sOB-R serum levels.

Materials and Methods

Sample Collection

This study was performed as a case-control study. A total of 102 patients with unexplained infertility and 112 control subjects (fertile female candidates for oocyte donation to infertile patients) referred to the Infertility Clinics of Imam Khomeini and Day Hospitals (Tehran, Iran) were selected. After obtaining informed consent, the eligible individuals, according to the previous study (22, 23), were enrolled in this study. In short, patients with unexplained infertility were the women who had experienced infertility for at least one year and had regular menstrual cycles. In hysterosalpingography, the tubes were open, and the cervical cavity was normal. Also, their spouses had normal spermograms. The control group consisted of 112 normal women with at least one healthy child. Both groups were under 40 years old. Transvaginal ultrasound was performed on the third day of the menstrual period in the follicular phase in both groups. If at least five antral follicle counts (AFCs) were
presented in each ovary, blood sampling was carried out between 8 and 9 AM in the laboratory.

Hormone profiles of follicle-stimulating hormone (FSH), lutein hormone (LH), thyroid-stimulating hormone (TSH), prolactin (PrL), and anti-Mullerian hormone (AMH) were performed at the same day conducting the enzyme-linked immunosorbent assay (ELISA) method (Monobind Kit, USA). Patients with normal hormonal profiles (FSH<10, AMH>1, TSH<4, and PrL<19) were included in the study.

The Level of sOB-R Serum
The serum level of sOB-R was measured according to the protocol of the SLR ELISA kit (manufactured by EAST BIOPHARM Company) using an ELISA reader (DANA 3200, USA).

Detection of Genetic Polymorphism
The gene polymorphism was performed according to the method presented in the previous study (22).

Statistical Analysis
The statistical analysis of data was performed using POPGENE 1.32 and SPSS 20 (SPSS Inc., Chicago, Ill., USA). The analysis of descriptive data was as mean ± SD. The mean, frequency and association between LEP-R and infertility incidence, BMI, and hormonal profiles (i.e., FSH, LH, TSH, PrL, and AMH) were conducted using descriptive statistics, including t test/χ² and regression test. To test the association between genotypes in both control and patient groups, Fisher's exact test and chi-square test were done. The comparison of demographic and biochemical parameters in unexplained infertility and fertile groups was analyzed by the unpaired t test with Welch's correction. The comparison of sOB-R levels according to BMI in case and control groups was made by one-way analysis of variance (ANOVA) with Tukey's test. Correlation between unexplained infertility and other variables in the case group was analyzed by Spearman correlation between sOB-R, BMI, age, LH, FSH, AMH, TSH, PrL, and risk of unexplained infertility. Pearson correlation was used between sOB-R and other variables in the patient group. Logistic regression analysis (when unexplained infertility was used as a dependent variable, and sOB-R, BMI, age, LH, FSH, AMH, TSH, PrL were taken as independent variables) was used for correlation analysis between unexplained infertility and other variables in the case group. One-way ANOVA with Tukey's test was used for comparison between sOB-R levels of genotypes in case and control groups separately. The unpaired t test with Welch's correction was used for comparison of sOB-R levels between genotypes of case and control groups.

Results
In this study, 102 women with unexplained infertility (32.42±4.58 years) and 112 healthy fertile women (30.56±4.27 years) were studied. Patients were categorized based on BMI (lean<25, overweight=25-29.9, obese≥30-40). A number of 43 (42.15%), 25 (24.5%), and 34 (33.35%) individuals had BMI levels lower than 25, between 25-29, and higher than 30, respectively. The healthy fertile women had a BMI<25.

To ensure the homogeneity of the two groups, hormonal profiles (i.e., FSH, LH, AMH, PrL, and TSH) and the number of AFC were compared between the two infertile and control groups. No significant difference was observed (P>0.05) (Table 1).

The serum level of sOB-R in the control group was 11.49±12.39 and in the infertile group was 6.08±7.66. A 2-fold decrease in sOB-R serum level was observed in the patient group compared to the control group (P=0.001) (Table 1).

Lean infertile individuals had lower sOB-R than overweight and obese ones, but not statistically significant. This difference was significant when compared to the control group (P=0.009) (Table 2).

There was a reverse correlation between sOB-R levels and the risk of unexplained infertility (P=0.0008). However, a direct correlation was observed between BMI, age, and increased unexplained infertility (P=0.0001, P=0.002) (Table 3).

No significant correlation was observed between unexplained infertility and other variables, such as FSH, LH, AMH, TSH, and PrL (P>0.05) (Table 3).

There was no correlation between sOB-R and other factors, including BMI, age, FSH, LH, AMH, TSH, and PrL in the patient group (P>0.05) (Table 4).

According to the previous study, in the patient group, the frequencies of Gln and Arg alleles were 61.76% and 38.24%, respectively. Also, the frequencies of Gln and Arg alleles in the control group were 65.62% and 34.38%, respectively. There was no significant difference in allelic frequencies (P=0.41). No association was obtained between Gln223Arg polymorphism of the LEP-R gene and the risk of infertility (95% CI, OR: 1.62 (0.69-3.8); P=0.26). By calculating the Hardy-Weinberg equilibrium, it was found that the two groups were in equilibrium with the Gln223Arg gene position (P=0.44) (Table 5).

An increase in sOB-R in the Arg/Arg genotype compared to the Gln/Arg and Gln/Gln genotypes in the infertile group was not statistically significant (P=0.32) (Table 6). There was no significant difference in serum levels of sOB-R among Gln/Gln, Gln/Arg, and Arg/Arg in the control group (P=0.92) (Table 6). However, there was a significant reduction in sOB-R serum levels in Gln/Gln and Gln/Arg genotypes in the infertile group compared to the normal (P=0.020, P=0.015, respectively) (Table 6).

The serum levels of sOB-R in the Arg/Arg genotype were also significantly lower in the patient group than in the control group (P=0.60) (Table 6).
There was a significant difference in mean BMI between Arg/Gln and Arg/Arg genotypes versus Gln/Gln in the patient group ($P=0.02$) (Table 6), but no significant difference was observed in mean BMI between Arg/Gln, Arg/Arg, and Gln/Gln genotypes in the healthy group ($P=0.31$) (Table 6).

A significant increase was shown in mean BMI in all three Arg/Arg, Arg/Gln, and Gln/Gln genotypes in the patient group compared to the control group ($P=0.001$, $P=0.0001$, $P=0.0005$, respectively) (Table 6).

No significant difference was obtained among the levels of FSH, LH, AMH, TSH, and PrL between Gln/Gln, Arg/Gln, and Arg/Arg genotypes either in the patient group ($P>0.05$) or between the two groups of patient and control ($P>0.05$).

### Table 1. The Comparison of the demographic and biochemical parameters in the unexplained infertility group (case) and fertile groups (control)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n = 102) Mean ± SD</th>
<th>Control (n = 112) Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>32.42 ± 4.58</td>
<td>30.56 ± 4.27</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI (m/kg²)</td>
<td>27.14 ± 6.53</td>
<td>21.88 ± 4.27</td>
<td>0.0001</td>
</tr>
<tr>
<td>AMH (MIU/I)</td>
<td>2.38 ± 1.08</td>
<td>2.44 ± 0.79</td>
<td>0.607</td>
</tr>
<tr>
<td>TSH (MIU/I)</td>
<td>2.65 ± 1.42</td>
<td>2.71 ± 1.28</td>
<td>0.724</td>
</tr>
<tr>
<td>Prolactin (MIU/I)</td>
<td>11.12 ± 4.82</td>
<td>11.08 ± 4.57</td>
<td>0.952</td>
</tr>
<tr>
<td>LH (MIU/I)</td>
<td>4.34 ± 1.52</td>
<td>3.96 ± 1.63</td>
<td>0.081</td>
</tr>
<tr>
<td>FSH (MIU/I)</td>
<td>5.18 ± 1.64</td>
<td>4.77 ± 1.63</td>
<td>0.071</td>
</tr>
<tr>
<td>sOB-R (ng/ml)</td>
<td>6.08 ± 3.83</td>
<td>11.49 ± 6.19</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Unpaired t test with Welch's correction

### Table 2. Comparison of sOB-R levels according to BMI in case and control groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>BMI (Mean ± SD)</th>
<th>sOB-R (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td>21.51 ± 2.72 a</td>
<td>5.28 ± 3.08 a</td>
</tr>
<tr>
<td>Over Weight</td>
<td>26.36 ± 1.63 b</td>
<td>6.74 ± 5.45 ab</td>
</tr>
<tr>
<td>obese</td>
<td>34.82 ± 4.09 c</td>
<td>6.51 ± 3.32 ab</td>
</tr>
<tr>
<td>Control</td>
<td>21.88 ± 2.91 a</td>
<td>11.49 ± 6.19 b</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*One Way Analysis of variance with Tukey's test

### Table 3. Correlation between unexplained infertility and the others variables in the case group

<table>
<thead>
<tr>
<th>Variables</th>
<th>r Value a</th>
<th>P-value</th>
<th>$\beta$ b</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sOB-R (ng/ml)</td>
<td>-0.26</td>
<td>0.0008</td>
<td>-0.054</td>
<td>0.002</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI (m/kg²)</td>
<td>0.47</td>
<td>0.0001</td>
<td>0.273</td>
<td>0.0001</td>
<td>1.31</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.21</td>
<td>0.002</td>
<td>0.096</td>
<td>0.003</td>
<td>1.10</td>
</tr>
<tr>
<td>LH (MIU/I)</td>
<td>0.12</td>
<td>0.082</td>
<td>0.152</td>
<td>0.083</td>
<td>1.16</td>
</tr>
<tr>
<td>FSH (MIU/I)</td>
<td>0.12</td>
<td>0.071</td>
<td>0.153</td>
<td>0.072</td>
<td>1.16</td>
</tr>
<tr>
<td>AMH (MIU/I)</td>
<td>-0.03</td>
<td>0.607</td>
<td>-0.076</td>
<td>0.605</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Table 4. Correlation between sOB-R and the others variables in the patient group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sOB-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.119</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI (m/kg²)</td>
<td>-0.148</td>
<td>0.059</td>
</tr>
<tr>
<td>LH (MIU/I)</td>
<td>0.031</td>
<td>0.69</td>
</tr>
<tr>
<td>FSH (MIU/I)</td>
<td>-0.039</td>
<td>0.62</td>
</tr>
<tr>
<td>AMH (MIU/I)</td>
<td>-0.084</td>
<td>0.28</td>
</tr>
<tr>
<td>TSH (MIU/I)</td>
<td>0.092</td>
<td>0.24</td>
</tr>
<tr>
<td>Prolactin (MIU/I)</td>
<td>-0.017</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Pearson's Correlation between quantitative traits.

Table 5. Genotypic and genetic frequency and Hardy-Weinberg equilibrium

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Case n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gln/Gln</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>Gln/Arg</td>
<td>44</td>
<td>53</td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>17</td>
<td>12</td>
</tr>
</tbody>
</table>

HWE of Case P-value: 0.35 (χ² = 0.86), HWE of Control P-value: 0.638 (χ² = 0.22), Genotypic P-value: 0.44

Abbreviation: HWE Hardy-Weinberg equilibrium, Significant level: * = p < 0.05.

Table 6. The comparison of sOB-R levels and BMI in genotypes of patient and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Genotype</th>
<th>Categorical</th>
<th>Genotype</th>
<th>Categorical</th>
<th>Genotype</th>
<th>* P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sOB-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* P-value</td>
</tr>
<tr>
<td>Case</td>
<td>Gln/Gln</td>
<td>Mean ± SD</td>
<td>Arg/Gln</td>
<td>Mean ± SD</td>
<td>Arg/Arg</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>5.61 ± 3.90</td>
<td></td>
<td>5.41 ± 3.63</td>
<td></td>
<td>8.60 ± 4.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.23 ± 6.41</td>
<td></td>
<td>10.95 ± 5.75</td>
<td></td>
<td>11.40 ± 7.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* P-value</td>
<td>0.02</td>
<td>0.015</td>
<td></td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Gln/Gln</td>
<td>Mean ± SD</td>
<td>Arg/Gln</td>
<td>Mean ± SD</td>
<td>Arg/Arg</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>24.98 ± 4.9</td>
<td></td>
<td>28.39 ± 6.8</td>
<td></td>
<td>29.12 ± 7.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.98 ± 3.07</td>
<td></td>
<td>22.06 ± 2.72</td>
<td></td>
<td>20.67 ± 3.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* P-value</td>
<td>0.001</td>
<td>0.0001</td>
<td></td>
<td>0.0005</td>
<td></td>
</tr>
</tbody>
</table>

* One-Way Analysis of variance with Tukey’s test has been used for comparison between genotypes in case and control group separately.

Unpaired t test with Welch's correction has been used for comparison between genotypes of case and control group.
Discussion

To identify unexplained infertility, the following criteria are necessary: the naturalness of seminal fluid analysis, the presence of ovulation, the natural nature of the uterus cavity, and two-way openness of fallopian tubes (24). Various reasons are involved in the development of unexplained infertility, such as mild bugs in the spermogram, mild changes in hormonal conditions, and underlying pathophysiological mechanisms (25).

Smith et al. suggested that leptin can play a dual role in reproductive regulation. They showed that when leptin levels are less than normal, it may have a negative effect on neuroendocrine regulation, while elevated levels of leptin may have a negative effect on normal ovarian function and embryo development and viability (26).

Gogacz et al. showed that serum leptin levels were similar in patients with unexplained infertility, PCOS, and endometriosis. The similarity of BMI in the three groups was the main reason for the similar serum leptin levels (27).

Further, sOB-R is inversely associated with the total serum leptin level and BMI in women of reproductive age (28).

As mentioned above, sOB-R is the major leptin-binding protein in human circulation. In lean individuals, leptin mostly attached to the receptor in the bloodstream, while, in obese individuals (due to the low concentrations of sOB-R), it is predominantly in free form (29).

Another study showed that there is a negative correlation between sOB-R levels, BMI, insulin resistance, cholesterol, and leptin (30).

Also, weight loss following stomach surgery led to a decrease in circulating leptin and an increase in sOB-R (31). It has been shown in a study that the reduction of sOB-R can act as a compensatory mechanism to overcome leptin resistance (32, 33).

Leptin is often affected by body composition, but sOB-R levels are influenced by genetic background (34).

Previous studies have shown that sOB-R levels are dependent on leptin, gender, endocrine system, and adiposity (35-37).

Regarding the role and function of sOB-R, it is possible to maintain the serum leptin concentration, its degradation prevention, and leptin function inhibition by preventing its binding to membrane receptors, which is dependent on the lesser leptin transfer via a blood-brain barrier (15).

To the best of our knowledge, no similar study was conducted on the level of sOB-R in patients with unexplained infertility and the effect of Gln223Arg polymorphism on serum levels of sOB-R. Several studies have been conducted on the changes in leptin and sOB-R levels in PCOS patients. Therefore, there are some limitations in comparing the results. In this study, a 2-fold decrease was observed in sOB-R serum level in the infertile group compared with the control group (P=0.001).

It seems that the reduced level of sOB-R in women with unexplained infertility is a temporary mechanism to overcome leptin resistance. Incomplete leptin function or genetic differences may be factors for the low level of serum LEP-R in the infertile women with unknown cause. It seems that, with an increase in serum sOB-R, serum leptin levels are decreased, which can inhibit leptin inhibitory effects in infertility. Excessive sOB-R can delay the clearance of leptin by its binding to the membrane-bound protein, and thus increase the leptin levels, its bioavailability, and consequently its effects (12, 38).

To determine the association between the level of sOB-R and BMI, patients were divided into three groups based on BMI, and results showed that the mean level of sOB-R in infertile lean patients was significantly lower than the control group. Also, the mean serum level in overweight and obese subjects was lower than in control subjects, but this difference was not significant.

Regarding similar results from other studies, BMI may be one of the determinants of the balance between the sOB-R system and leptin. It seems that overall elevation in BMI increases the levels of leptin, and possibly sOB-R is not available sufficiently to connect to leptin, which is ultimately evident as an increase in serum leptin and decrease in sOB-R.

On the other hand, in the present study, a reduction in sOB-R levels was seen in lean infertile patients compared to the healthy fertile individuals with similar BMI. These results were consistent with Hahn et al. (33) and Chavarria-Avila et al.’s (15) studies. Such findings can highlight the direct role of leptin in the pathogenesis of unexplained infertility independent of obesity/BMI.

Hahn et al. (2006) reviewed the serum levels of leptin and sOB-R in 122 women with PCOS and 81 healthy women. They reported that there is a direct association between leptin levels and reversal of sOB-R serum levels with BMI. They also reported that lean PCOS patients with lower levels of sOB-R and higher free leptin in comparison with control subjects had similar BMI. They suggested that a reduced level of sOB-R in women with PCOS can be considered as a possible compensatory mechanism for resistance to leptin (33).

In 2015, Rizk et al. compared serum leptin and sOB-R levels in PCOS women (divided into three groups based on BMI) and healthy fertile ones with BMI=25. They also confirmed that leptin levels directly and serum levels of sOB-R were inversely related to BMI. It was also reported that lean patients with PCOS had lower...
levels of sOB-R and higher free leptin indices compared with those in the control group with similar BMI (17).

Chavarria-Avila et al. (2015) showed that overweight and obese women had higher levels of leptin and lower levels of SOB-R compared with subjects with normal weight (15). In the present study, for the first time, a comparison was performed on the mean serum levels of sOB-R between the three Gln/Gln, Gln/Arg, and Arg/Arg genotypes in women with unexplained infertility and fertile women. A significant decrease in LEP-R serum concentration was found between Gln/Gln and Gln/Arg genotypes in the infertile group compared to the control group in the Gln/Gln genotype. In the Arg/Arg genotype, a decrease in sOB-R was observed in the infertile group compared to the control group, but it was not significant. However, no significant difference was observed in the levels of sOB-R between genotypes in the control and patient groups. It seems that a decrease in the serum level of sOB-R in Gln/Gln and Gln/Arg individuals increased the risk of unexplained infertility in Gln233Arg polymorphism.

Similarly, no significant difference was obtained in the levels of sOB-R and leptin between genotypes in both PCOS and control groups (39).

In other studies, similar to our study, no association was observed between genotypes and LEP-R serum level (40-42).

The study of Chavarria-Avila et al. showed that obese individuals had higher levels of serum leptin and lower levels of sOB-R compared with normal subjects. Obese Arg/Arg subjects had higher sOB-R and less leptin compared with Gln/Gln subjects. They showed that allele-2548G or polymorphism in the leptin gene affects the LEP transcription and eventually serum leptin levels by increasing them. The 223Arg allele from the LEP-R encodes a protein with altered signaling capacity, which increases the level of sOB-R and delays leptin resistance. If cells express LEP-R, leptin signaling is decreased. Therefore, the accumulation of body fat mass will be less, and the orexigenic signaling will stay active (15).

It has been suggested that glutamine amino acid (Gln or Q) changed by arginine (Arg or R) in the receptor extracellular part causes a change in the electrical charge from neutral to positive, which leads to changes in the binding of leptin to the receptor, and hence receptor dimerization and change in the capacity of LEP-R signaling. Gln223Arg polymorphism has been studied regarding its association with obesity in different populations, which itself can be a factor causative of infertility. Several studies have been published on SNPs associated with LEP-R and their associations with infertility in the past decade (8).

Conclusion
Considering the importance of unexplained infertility, this polymorphism and serum LEP-R should be studied in larger populations. Since other polymorphisms of the LEP-R gene were not considered in this study, more extensive studies are needed. Since women infertility is a multifactorial condition, evaluating the role of involved genetic and environmental factors is necessary. Investigating other genes and their mutual effects on each other seems to be necessary in studies on women infertility.

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Conflict of Interest
The authors declared that there is no conflict of interest.

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