

# Status of serum leptin levels in females with infertility

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## ABSTRACT

**الأهداف:** تقييم مستويات مصل اللبتين لدى النساء العقيمات بناءً على الحالات المحولة لمستشفى الرعاية الثلاثي في باكستان.

**الطريقة:** أجريت هذه الدراسة في كلية طب الشفاء - مستشفى الشفاء الدولي - إسلام آباد - باكستان، خلال الفترة ما بين يناير 2005م وحتى أغسطس 2005م. تمت مقارنة مستويات مصل اللبتين لدى 44 سيدة عقيمة مع 44 سيدة غير عقيمة مع تطابق العمر (مجموعة التحكم).

**النتائج:** كشفت النتائج ارتفاع مستويات مصل اللبتين بشكل ملحوظ لدى السيدات العقيمات (69.7±40.2ng/ml) بالمقارنة مع مجموعة السيدات الغير العقيمات (41.1±27.3ng/ml) ( $p<0.000$ )، كما تبين أن مدخلات كتلة الجسم BMI كانت أعلى بشكل ملحوظ لدى السيدات العقيمات (27.2±6.8kg/m<sup>2</sup>)، بالمقارنة مع غير العقيمات (24.1±5.2kg/m<sup>2</sup>)، إضافة إلى ذلك، تبين وجود صلة إيجابية قوية مع زيادة كتلة الجسم 0.019. كانت مستويات اللبتين الفعلية لدى النساء ذوات الوزن الزائد أعلى بشكل ملحوظ (81.4±32.4ng/ml) بالمقارنة مع النساء ذوات الوزن الطبيعي ( $p=0.000$ ) (30.6±20.6ng/ml).

**خاتمة:** إشارة هذه الدراسة أن الوزن الزائد المصحوب بفرط اللبتين في الدم مرتبط مع العقم لدى النساء، علماً أن المزيد من الدراسة مطلوبة لتحديد الآلية التي من خلالها تُسبب زيادة الوزن ومستويات اللبتين في الدم العقم لدى النساء.

**Objective:** To assess serum leptin levels in infertile females referred to a tertiary care hospital in Pakistan.

**Methods:** A case control study was carried out at Shifa College of Medicine/Shifa International Hospital Islamabad, Pakistan from January 2005 to August 2005. Serum leptin levels of 44 infertile females were compared with 44 age matched fertile female controls.

**Results:** The results revealed that serum leptin levels were significantly raised in infertile women (69.7±40.2ng/ml) as compared to fertile controls (41.1±27.3ng/ml) with  $p=0.000$ . Mean body mass index (BMI) was also found to be significantly higher in infertile women (27.2±6.8kg/m<sup>2</sup>) as compared to fertile females (24.1±5.2kg/m<sup>2</sup>) with  $p$ -value of 0.019. Moreover, a strong positive correlation was found between BMI and leptin levels as leptin levels increased with increase in BMI. Mean leptin levels in overweight women were significantly higher (81.4±32.4ng/ml) as compared to normal weight women (30.6±20.6ng/ml) with  $p=0.000$ .

**Conclusion:** The present study has indicated that overweight accompanied by hyperleptinemia is associated with infertility in females. However, further studies are required to determine the exact mechanism by which enhanced body mass and serum leptin levels lead to female infertility.

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Fat stores in the body are modulated by numerous hormones through their effects on energy balance.<sup>1</sup> Adipose tissues synthesize and express a hormonal substance called leptin into the circulation in proportion to their metabolic activity. The primary physiologic function of leptin is to provide a signal to suppress body fat by decreasing food intake or increasing energy expenditure.<sup>2</sup> Apart from its role in energy balance<sup>3</sup> and the pathophysiology of body weight regulation, the role of leptin in neonatal physiology, puberty, and reproduction has been addressed in recent years. The rise in leptin levels at the onset of puberty and fall in

postmenopausal women suggested that leptin may be associated with normal reproductive events.<sup>4</sup> Low leptin levels may also disrupt the reproductive system, as ovulation stops in starving women and testosterone levels fall in men.<sup>5,6</sup> One early indication that leptin might have an impact on reproduction came from the observation that ob/ob mice (which lack functional leptin) or db/db mice (which lack leptin receptors) are infertile, and fail to undergo normal sexual maturation.<sup>7</sup> Administration of recombinant leptin to these animals reduced body weight and restored fertility to ob/ob mouse.<sup>8,9</sup> Similar findings have also been reported in humans.<sup>10-12</sup> Infertility is defined as one year of unprotected coitus without conception,<sup>13</sup> and it is a common problem among Pakistani women of reproductive age.<sup>14,15</sup> According to 2 studies conducted in Pakistan, among all the patients attending a Gynecology clinic, 11% complained of infertility. After investigative workup, 64-65% of these patients were diagnosed with primary infertility and 35-36% had secondary infertility,<sup>14,15</sup> but to-date no study has been carried out in the Pakistani population to explore the status of serum leptin in patients of infertility. As leptin plays a critical role in normal reproductive functions in particularly, ovulation, a change in the circulating leptin may prove to be an important link between body fat stores and status of fertility among women of child-bearing age. Establishment of such a link may provide new insight into causes of infertility and may lead to better treatment modalities in young women. The present study has therefore been designed to establish a correlation between serum leptin levels, body fat stores, and infertility among young Pakistani women of childbearing age.

**Methods.** This study was carried out at Shifa College of Medicine, Islamabad, Pakistan, from January 2005 to August 2005. The study was formally approved by the Institutional Review Board and Ethics Committee of Shifa College of Medicine/Shifa International Hospital, Islamabad, Pakistan. The non-probability convenience sampling technique was used. It was a case control study, in which a group of infertile females was compared with a control group of fertile females to find out the contribution of serum leptin levels in causation of infertility. Written consent was obtained from all the subjects included in this study. All females who failed to conceive after one year of unprotected coitus were included in the study,

irrespective of the cause of infertility. Those females in whom semen analysis of the husband gave abnormal results were excluded from this study. Serum was obtained randomly from blood samples of 88 infertile females (17-38 years of age), and age matched fertile controls presenting to the Department of Gynecology & Obstetrics at Shifa College of Medicine and Shifa International Hospital, Islamabad. Leptin levels were measured by DSL-10-23100 ACTIVE Human Leptin ELISA kit by Diagnostic Systems Laboratories, Inc., (Webster, Texas, USA), and body mass index (BMI) was calculated as weight in kg/height (m<sup>2</sup>). Patients with BMI 25 kg/m<sup>2</sup> and above were considered overweight.<sup>13,16</sup>

Data was analyzed on computer software SPSS version 10. Mean leptin levels and BMI between the infertile cases and the fertile controls, and between cases of primary and secondary infertility were compared by t-test. *P* values less than 0.05 were taken as statistically significant.

**Results.** Out of all the infertile cases included in this study, 57% were found to have primary infertility and 43% had secondary infertility. Overweight/obesity is considered to play a role in cases of infertility. For this purpose, BMI was calculated in both groups and was found to be significantly increased in infertile (n=44) patients (27.2±6.8) as compared to fertile (n=44) controls (24.1±5.2) (*p*=0.019). The primary objective of the study was to find out the levels of serum leptin in infertile females in comparison with fertile females. Leptin levels were found to be significantly increased in infertile females (69.7±40.2 ng/ml) as compared to fertile controls (41.1±27.3 ng/ml) with *p*=0.000. To evaluate the relationship of body fat and leptin levels, all subjects (infertile females and controls) were divided into 2 groups, normal weight with BMI of less than 25 kg/m<sup>2</sup>, and overweight with BMI more than 25 kg/m<sup>2</sup>. Leptin levels in overweight females were 81.4 ±32.4 ng/ml as compared to normal weight women (30.6±20.6 ng/ml), and the difference between the 2 groups was highly significant with *p*=0.000. To find the relationship of weight with leptin levels, data were further analyzed, and it showed that mean leptin levels in patients with infertility were also significantly higher (92.36±29.8 ng/ml) in the overweight group as compared to controls (62.9±28.5 ng/ml), but in normal weight infertile females, leptin levels were higher than controls, but not significantly (*p*=0.423). Data were further analyzed to find the relationship of leptin with type of fertility (primary/secondary), and it showed that in normal weight patients with primary infertility, leptin levels were 38.7±29.3 ng/ml whereas in cases of secondary infertility they were 22.05±6.1 ng/ml, but

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the difference was not significant with  $p=0.084$ . In overweight patients, leptin levels in primary infertility were  $81.0 \pm 26.1$  ng/ml and in secondary infertility were  $102.8 \pm 30.1$  ng/ml, and the difference was not significant ( $p=0.056$ ).

**Discussion.** The present study has demonstrated that serum leptin levels are significantly raised in infertile women as compared to fertile controls, irrespective of primary or secondary infertility. Body weight and BMI were also found to be increased in infertile women as compared to fertile controls. Although many multiparous women are obese, most of them can conceive regularly. Indeed, a large study of fertile women did not show any relationship between rates of conception and body weight/BMI.<sup>17</sup> Obese and overweight women are over-represented in gynecological and reproductive medical clinics. Obesity in teenagers is more common among married girls who never became pregnant as compared to married women who did become pregnant.<sup>18</sup> Kusakari et al<sup>19</sup> in 1990 reported in Japan that obesity was related to anovulation or infertility, and Balen et al<sup>20</sup> found in 1995 that obesity was correlated with higher infertility rates. Indeed, obese or overweight subfertile or infertile women have a lower success rate of pregnancy during infertility treatment.<sup>21</sup> Reduction of obesity, particularly abdominal obesity is associated with improvements in reproductive functions.<sup>22</sup> Even a moderate weight loss of 5-10% of body weight can be sufficient to restore fertility and improve metabolic markers.<sup>23</sup> It has been established that leptin is essential for normal reproduction in animals and humans. Indeed, ob/ob mice lacking leptin due to a genetic mutation, are obese and infertile, and administration of recombinant leptin to these animals reduces body weight and restores fertility.<sup>24</sup> But, at the same time many studies confirmed the inhibitory effect of hyperleptinemia on reproduction. Thus, extremes of body mass associated with either low or high leptin levels can both disrupt normal reproductive function.

As leptin exerts a permissive effect upon reproduction, obesity associated with high leptin concentration and infertility may be due to leptin resistance. This was demonstrated in a study carried out by Tortoriello et al<sup>25</sup> in 2003, who suggested that obesity associated hyperleptinemia, gradually induces central leptin resistance, increases hypothalamic neuropeptide Y-ergic tone, and ultimately causes hypothalamic hypogonadism. Gungor et al<sup>26</sup> found higher levels of leptin in the peritoneal fluid in patients with endometriosis, which is a major cause of primary infertility. A recent study showed a significant increase in serum leptin levels in women with unexplained infertility.<sup>27</sup> Bouvattier et al<sup>28</sup> found in 1998 that BMI and circulating leptin were

statistically negative determinants of gonadotrophin secretion. Duggal et al<sup>29</sup> in 2000 demonstrated in in-vitro and in-vivo studies that high leptin levels in the ovary may interfere with the development of dominant follicles and oocyte maturation. This indicates that elevated leptin levels may be able to exert a direct inhibitory effect on ovarian function. A study conducted by Kikuchi et al<sup>30</sup> in 2001 indicated that leptin causes an inhibitory effect on the early follicular development of both immature and adult mice. In another study, it was concluded that a certain group of normally ovulating subfertile patients lack leptin receptors in human endometrium which may make them unable to develop a 'receptive' endometrium to accomplish embryo implantation.<sup>31</sup>

The present study has clearly demonstrated that overweight accompanied by hyperleptinemia is generally associated with infertility in females. Increased leptin levels as a result of overweight may deregulate the hypothalamic-pituitary-gonadal system, leading to reproductive dysfunction, including infertility. Financial and time limitations led us to conduct a random study with limited sample size. Further studies are needed to elaborate the relationship between hyperleptinemia and infertility.

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### Related topics

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