# Effects of serum leptin level and combined pharmacological treatments on obese women having premenstrual tension syndrome: A randomized controlled trial

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**Abstract**

**Background:** Premenstrual tension syndrome (PTS) includes recurrent behavioural, psychological, and physical symptoms usually related to the luteal phase of the menstrual cycle. Leptin hormone might have an impact on its development.

**Objectives**: to investigate the effects of serum leptin level versus combined pharmacological treatments on obese women having premenstrual tension syndrome.

**Patients and methods:** This study enrolled 60 obese women having PTS, divided into a younger (18–39 years old) and an older (40–48 years old) age group versus an age-matched healthy control group. Each group contained 30 women. Ethical committee approval and participants' agreements were done. Leptin levels in the serum of all women were estimated. Nervousness was measured as a psychosomatic PTS symptom using a numerical rating scale.

**Results:** Obese women with PTS had significantly increased serum leptin compared to the control group ($p < 0.05$). A calorie-restricted diet, walking activities, metformin, amiloride/hydrochlorthiazide, and Vitazinc or Royal Vitamin G were among the combined treatments that significantly ($p < 0.01$) reduced the elevated serum leptin. The rating level of nervousness rose significantly ($p < 0.001$) in women with PTS. Using the combined therapies improved all of that much better. Such combined therapy significantly decreased serum leptin levels in conjunction with the decrease in nervousness ratings ($p < 0.001$).

**Conclusion:** PTS is more strongly associated with obesity and has been connected to elevated serum leptin levels, which were associated with elevated anxiety. Metformin, amiloride/hydrochlorthiazide, vitazinc, calorie-restriction diet, and 30 minutes of daily walking exercise were the combination of prescribed therapy that greatly normalized that to a satisfactory level.

**Keywords:** Premenstrual tension syndrome; Serum leptin; Nervousness.

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## Introduction

Premenstrual tension syndrome (PTS), (premenstrual syndrome) includes cyclic psychological, behavioural, and physical symptoms related to the phases of the menstrual cycle **(Delaram et al., 2011).** A far more severe type of PTS is called premenstrual dysphoric disorder. These symptoms include mood, sleep, appetite, and physical problems. Additional symptoms include bloating in the abdomen, weight gain, palpitations, hot and cold flashes, anxiety, breast tenderness, migraines, joint and muscle pain, and stomach bloating **(Chumpalova et al., 2020)**. During adolescence, menstrual symptoms may grow considerably and then plateau in later adolescence. Certain menstruation symptoms are linked to depression symptoms. Girls with higher levels of somatic complaints and depressive symptoms are more vulnerable than girls with lower baseline menstruation symptoms, in addition to experiencing more symptoms during adolescence **(Beal et al., 2014**).

Oestrogen is involved in mood regulation. Women who had their ovaries removed were given extracts from animals' ovaries, which helped with certain psychological issues **(Delaram et al., 2011; Badgujar et al., 2014)**. Furthermore, oestrogens stimulate osteoblast differentiation and regulate a number of anabolic bone-related proteins as procollagen type I, insulin-like growth factor-1, and bone morphogenetic proteins. Therefore, both bone resorption and bone production may be impacted by the postmenopausal decline in oestrogen **(Kelly et al., 2019)**.

Leptin, a metabolic regulator of the hypothalamic-pituitary-gonadal axis, is essential for human reproduction. It has neuroendocrine effects through its interactions with similar receptors in the hypothalamus, which also controls emotional drive **(Anim-Nyame et al., 2000)**. During the luteal phase, the BMI and leptin concentrations were greater in young women with premenstrual dysphoric syndrome **(Yen et al., 2020)**. Leptin levels increased dramatically during the luteal periods of the menstrual cycles compared with the follicular phase in an intriguing study involving both the control group and patients with PTS. Women with PTS showed higher levels of leptin than the controls. Additionally, during the follicular and luteal phases, PTS affected women's leptin levels were higher than those of the controls. It is imperative to conduct additional research on leptin as it may play a role in the pathogenesis of the disease **(Anim-Nyame et al., 2000)**. Leptin serum concentrations were nearly twice as high in PTS patients as they were during the postmenstrual and premenstrual periods; that is, these patients had higher levels of leptin serum concentrations across this entire period **(Unlu et al., 2014)**.

Appetite is regulated by both insulin and leptin. Leptin is a hormone that may have an impact on mood and reproduction. Serum leptin levels were strongly associated with insulin levels and HOMA-IR between the time of the premenstrual dysphoric syndrome diagnosis and the menstrual phases. Throughout the luteal period, progesterone and insulin levels were substantially associated in individuals without premenstrual dysphoric syndrome **(Akturk et al., 2013)**. In premenstrual dysphoric syndrome affected women in terms of increased sweet cravings and compulsive eating, there is a connection between impulsivity and depression and the craving for sweets. Depression acts as a mediating factor in the relationship between premenstrual dysphoric syndrome and disordered eating. The

BMI of patients with premenstrual dysphoric syndrome was significantly correlated with changes in leptin **(Yen et al., 2020)**. Additionally, leptin levels were found to be adversely linked with calorie intake, with overweight premenstrual dysphoric syndrome sufferers having greater leptin levels than their normal-weight counterparts **(Ko et al., 2015)**.

## Patients and methods

### *Study design and settings*

Sixty obese women with PTS were randomly assigned (after exclusion of psychiatric illnesses) into two age groups: the younger age group (18–39 years old) and the older age group (40–48 years old) (non-obese women of the same age groups) where each group contained 30 women, versus the age-matched healthy control group. Investigating PTS in premenopausal versus postmenopausal women was done to investigate effect of menopause on PTS status. Control group participants were devoid of associated medical illnesses as chronic renal impairment, diabetes mellitus, metabolic syndrome and others. Parity, gravidity and marital status were not included in the inclusion or exclusion criteria. Women with met inclusion criteria were enrolled in the study.

**Ethical statement:** This study was performed over a 6-months period. The ethical committee approved this study as well as the informed permission of the patients, as our research team previously revealed in the first published paper **(Mariah et al., 2022)** with the code no. IRB00013006. This is a multicenter research study done in Tanta University, Egypt in 2019 as joined research between Tanta University & Sohag University in Egypt in collaboration with Taibah University in Saudi Arabia.

**Patients' inclusion and exclusion criteria:** It does not matter whether participating women were lactating or non-lactating. Inclusion criteria were: willing to participate, free of long-term hormonal imbalances, free of illnesses that might interfere with the study as rheumatoid arthritis, and prepared to continue utilizing the combination of medications. Exclusion criteria were: Women who met or exceeded the established age ranges (18–48 years), had ongoing hormone imbalances or other health issues, or expressed a willingness to withdraw from the study. Throughout the course of this trial, every participant maintained a low-calorie diet (less than 1000 calories/day) and engaged in regular exercise every day for 30 minutes while walking, and for six cycles in a row, took medication seven days before menstruation (amiloride hydrochloride/ hydrochlorthiazide 5/50 mg, metformin, and Vitazinc or Royal vitamin G capsules).

Sample size was calculated using Yamane's formula as previously reported **(Chaokromthong et al., 2021).** Participants were randomly assigned (using a shuffled deck of cards with odd numbers receiving Vitazinc-containing treatments and the even numbers receiving Vitamin G-containing treatments) to one of two groups for the distribution of combined treatments: the first group received combined therapies including Vitazinc, while the second group received combined therapies with Royal vitamin G. All of the subjects had their serum levels of leptin measured. Furthermore, nervousness was evaluated both before and after the prescribed therapies in the obese women with PTS. Normal, non-obese women were also included as a negative control.

***Leptin hormone assay in serum***

Human leptin assay kits (Cat. No. ab179884) provided by (Abcam, Cambridge, UK) in accordance with the manufacturer's recommendations. Based on sandwich quantitative immunoassay. The kit detection range of (15.63 - 1000 pg/mL) with 4.65 pg/mL sensitivity inter-intra-assay CV < 5%.

***Quantitating nervousness behavior***

For all obese and non-obese women of the young and old age groups, nervousness was assayed. Nervousness severity was also assayed in all control subjects and patients having PTS using a numerical scale as was reported previously (**Tsirgiotis et al., 2021**). Briefly, the following scores were given to measure nervousness:

+4: Aggressive blatantly violent, combative, direct threat to staff

+3: Extreme agitation aggressively pulls or removes catheter(s) or tubes

+2: Agitated Frequent purposeless movement interferes with the ventilator

+1: Restless tense yet neither violent or aggressive in their movements

0: Alert and relaxed

**Statistical analysis**

Data collection and statistical analysis were carried out using SPSS software version 2020 (version 20 SPSS Inc., Chicago, Illinois, USA). Normal distribution was tested analytically using Shapiro-Wilk test The SD and mean were compared between the obese non-treated groups (positive control) versus the healthy control groups (negative control) using student t test. The estimated significance p values where given asterisks (*p < 0.05, **p < 0.01, and ***p < 0.001) indicate statistically significant differences from the control group, respectively. Significant differences between the different treatment groups versus the obese non-treated groups were indicated by the symbols #, ##, and ### ($p < 0.05$, $p < 0.01$, and $p < 0.001$), respectively.

**Results**

***Obesity effects on increasing serum leptin were alleviated using combined therapies***

Obese females (of both age groups) experiencing PTS had significantly higher serum leptin levels compared to the control group ($p < 0.05$). Using a calorie restriction diet, Vitazinc, Metformin, Amiloride/ Hydrochlorothiazide, and half an hour of daily walking exercise in combination significantly decreased serum leptin concentrations ($p < 0.01$). Additionally, a calorie restriction diet, combined treatment with metformin, amiloride/hydrochlorthiazide, vitazinc or royal vitamin G, and half an hour of daily walking exercise) significantly lowered serum leptin levels ($p < 0.01$) (**Fig.1**). No significant differences existed between both groups as regard the decrease in serum leptin ($p > 0.05$) that was almost similar i.e. receiving either Vitazinc or Royal vitamin G got similar improvements.

***Effects of obesity and combined therapies on leptin-related nervousness***

PTS in obese participants of both age groups showed a substantial increase in nervousness severity ($p < 0.001$) (**Fig.2**). Combination therapies with either Vitazinc or royal vitamin G resulted in a marked reduction in the incidence of nervousness (**Fig.2**). Between Vitazinc-containing combined therapy and Royal Vitamin G-containing combined therapy, no discernible difference was found (**Fig.2**).

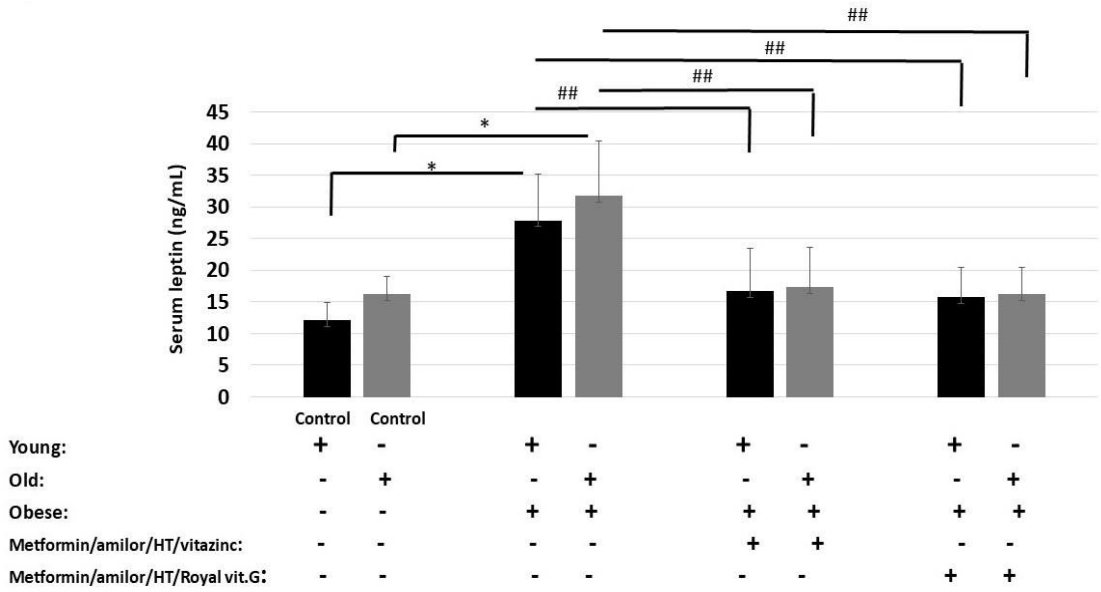


**Fig.1. Obesity and combination treatments' effects on blood leptin levels.** Serum leptin levels in obese females with PMTS in both age groups significantly increased when compared to the control group ($p < 0.05$). Vitazinc-based combination therapies effectively reduced blood leptin ($p<0.01$) in a manner comparable to that of Royal vitamin G-based combination therapies.

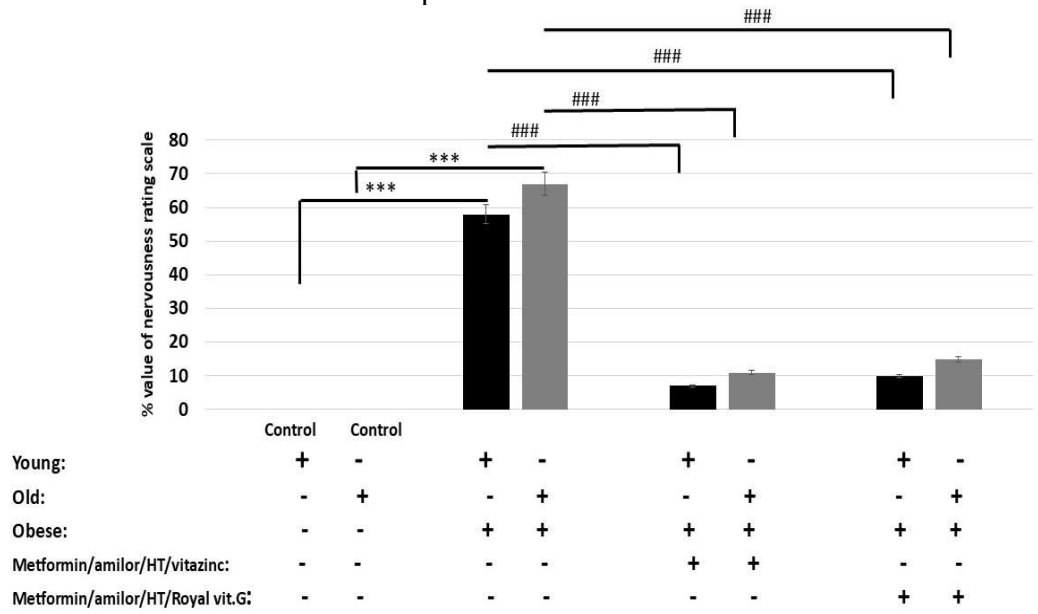


**Fig.2. Effects of obesity and combination treatments on premenstrual tension syndrome-induced nervousness.**

## Discussion

Age plays a part in the hormonal alterations that exacerbate PTS. This demonstrates the potential advantages of phytoestrogens-containing medicinal plants like fennel (as a suggestion owing to its rich phytoestrogens) in reducing a variety of hormonal alterations in women. **(Delaram et al., 2011; Badgujar et al., 2014)**.

Women with PTS had significantly higher serum leptin levels ($p < 0.05$) in this study compared to

non-PTS women. This is consistent with other earlier findings **(Anim-Nyame et al., 2000; Unlu et al., 2014; Yen et al., 2020).** Interestingly, combined pharmacological treatments significantly decreased serum leptin and nervousness in women having PTS in both age groups.

The results here are in line with the previous findings of our research group, which confirmed the influence of inflammatory markers associated with obesity on psychosomatic manifestations of PTS. In obese women with PTS, there was a correlation found between the levels of TNF-, HIF-1, and RANKL (receptor activator of nuclear factor-kappa-B ligand), which in turn caused edema, anxiety, and exhaustion. Combining medications such as multivitamins, diuretics, and lifestyle changes also produced several encouraging therapeutic results **(Mariah et al., 2022).**

According to the author's own opinions, women with PTS should undergo regular hormonal follow-up in order to improve the assessment of their overall clinical status. The authors advise treating women with PTS with a combination of therapies that include dietary changes, vitazinc, or royal vitamin G. One of the current study's shortcomings is that combining medicines and lifestyle modifications may be better ways to control PTS. Suggested medications might reduce PTS symptoms owing to their diuretic effects and their rich content in minerals and vitamins. Future studies should yield more helpful hints for treating PTS.\

## Conclusion

PTS is associated with elevated serum leptin levels and is more closely correlated with obesity. Psychosomatic symptoms such as anxiety linked to elevated blood leptin levels are ascribed to PTS. Combination therapy using Vitazinc or Royal Vitamin G significantly lowers serum leptin and anxiousness and has been associated with significant reductions in psychosomatic symptoms.

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