

## **Leptin Resistance, Insulin and PCOS Infertility**

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<https://natural-fertility-prescription.com/leptin-resistance-pcos/>

In this article we'll explore the correlation between leptin resistance and insulin resistance in cases of PCOS.

Polycystic Ovarian Syndrome (PCOS) is one of the main causes of infertility in Western women, with an increasing prevalence among women of reproductive age.

According to the Androgen Excess and PCOS Society, *“PCOS typically involves the presence of irregular or absent menstrual periods, in combination with excess androgens and polycystic ovaries”*.

In PCOS there is an increased production of androgens resulting from dysfunction at all levels of the hypothalamic-pituitary-ovarian axis (HPO). Hyperandrogenaemia may originate from either the ovaries or the adrenals.

Is it possible that PCOS and its increasing prevalence in Western society is due to hormonal imbalance associated with environmental factors such as, weight gain and insulin resistance, which is further exacerbated by the little known hormone Leptin?

### **Hormonal Interactions and Imbalance in PCOS**

Before we explore the leptin, insulin relationship in PCOS we need to have an understanding of the hormonal interactions and imbalances that are relatively consistent in women with PCOS.

PCOS sees an imbalance in the gonadotropins follicle stimulating hormone (FSH) and luteinising hormone (LH).

In a normal menstrual cycle the hypothalamus in the brain signals the release of gonadotropin releasing hormone (GnRH) which, in turn stimulates the anterior pituitary gland to release FSH followed by LH. These hormones target the granulosa and theca cells respectively within the ovary. The dual action of these hormones causes the follicle to mature, and during its maturation oestrogen is increased. The endometrium is thickening and a surge in LH induces ovulation.

Once released the corpus luteum produces an abundance of oestrogen and progesterone. This increase in circulating hormones signals the hypothalamus to decrease GnRH, actioning a cessation of FSH and LH.

If fertilisation does not take place the corpus luteum breaks down, levels of oestrogen and progesterone fall and menstruation occurs.

In PCOS this intricate hormonal balance is dysfunctional. Infrequent or anovulation in PCOS leads to an increase of LH, whilst FSH either remains the same or is reduced. Reduced FSH prevents the granulosa

cells of the ovary from producing oestrogen through aromatisation, whilst at the same time LH is stimulating the ovary to produce androgens.

The end result is hyperandrogenism and reduced oestrogen due to failed follicular development.

It is at this point that the leptin, insulin relationship in PCOS becomes significant as it potentiates the vicious cycle of this hypothalamic-pituitary-ovarian disorder.

## **Link between Leptin Resistance, Insulin and BMI in PCOS**

Insulin is a hormone produced by the pancreas that promotes the uptake of glucose into your cells to be used as energy, or stored in the liver.

Insulin resistance occurs when the insulin receptors become less sensitive to insulin, causing glucose levels in the blood to rise. This rise in blood sugar signals the pancreas to release more insulin, resulting in high levels of circulating insulin.

Insulin resistance has proven to be a common metabolic disorder associated with PCOS. Often thought to be associated with obesity an article in the Journal of Clinical Endocrinology and Metabolism found that lean women with PCOS definitely had higher basal insulin levels (2.) than women with “normal” insulin levels.

Leptin or our “satiety” hormone is released by adipocytes (fat cells) to regulate energy balance. It is generally observed that when you have a higher percentage of body fat more leptin is released, your appetite is decreased and your metabolic rate increases.

However, leptin resistance appears to be another contributor to PCOS as the above scenario is not always the case. Elevated leptin levels have been shown in women with PCOS regardless of BMI (1.) (Body Mass Index).

Insulin resistance and leptin resistance are major players in PCOS and infertility.

Hyperinsulinaemia, or high circulating insulin acts together with LH to enhance androgen production in the ovary. Insulin also inhibits the production of sex hormone-binding globulin in the liver, which enables more free testosterone into circulation. Androgens are converted to oestrogen by aromatisation in the tissues, which stimulates the hypothalamus and pituitary gland to secrete more LH.

Leptin and its role in PCOS and infertility is still relatively new and it is the subject of much research and speculation. Insulin is an important factor in the stimulation of leptin secretion<sup>3</sup>, and so the insulin-leptin relationship in PCOS is gaining more attention.

Leptin plays a direct role in the production of steroid hormones by granulosa cells in the ovary. Whilst leptin is widely distributed throughout reproductive tissues, its relationship to reproductive hormones is still not fully known. Leptin is thought to inhibit the hypothalamic-pituitary axis, and stimulate the reproductive system, which may also contribute to ovarian overproduction of androgens and

hyperandrogenaemia.

Generally it is thought that leptin is a mediator of negative, rather than positive influential actions on ovarian function that may compromise fertility (3.).

With this in mind a study to assess the inter-regulatory phenomena between leptin and ovarian function in PCOS women showed the following:

- A positive correlation exists between leptin and BMI (1.)
- The major finding of this study is that irrespective of BMI or insulin resistance, the PCOS population had higher leptin levels (1.)
- This finding is quite valid, because leptin is mainly synthesised by adipocytes (fat cells), and a high BMI is distributed with high frequency in the PCOS group than the control women. The difference in leptin levels reached a greater level of significance when PCOS women were categorised under obese and non-obese sub groups (1.).
- The most noteworthy is the observation that even after normalisation of most of the known confounding factors, the PCOS women tended to have increased serum leptin levels (1.)
- Especially, a subset of PCOS population had significantly elevated leptin levels even after the adjustment of BMI.

The finding of high leptin levels appears to be a masking effect of high insulin levels after the adjustment of data to take into consideration the distribution of insulin resistance between the PCOS and the control groups. Leptin levels were statistically similar between the two groups having a similar value of BMI and IR.

Within the PCOS group, normalisation of data in regard to obesity and IR, however showed positive influence of insulin and obesity individually on fasting leptin levels, independent of body fat and IR respectively (1.).

Taking into consideration the above information both insulin and obesity play a role in elevated leptin levels.

In obesity there can be an element of leptin-resistance where the hormone receptors become less sensitive and the message of satiety is not relayed to the brain, despite high energy stores. More leptin is secreted from fat cells in an attempt to regulate appetite resulting in hyperleptinaemia.

As stated previously insulin plays a role in leptin secretion. Insulin increases leptin mRNA in fat cells, confirming its role in leptin secretion. It is possible that elevated leptin in hyperinsulinaemia PCOS women is a secondary consequence of insulin-stimulated synthesis of leptin (1.).

This relationship between leptin and insulin in PCOS may also explain the high leptin levels seen in lean women in PCOS.

As both leptin and insulin can influence ovarian overproduction of androgens and lead to hyperandrogenism we can prove a positive relationship between leptin, insulin and BMI in PCOS.

## **What can you do naturally to address the leptin insulin relationship in PCOS?**

Addressing the underlying issues of obesity and insulin resistance (for both overweight and lean women) in PCOS should be a priority when treating PCOS naturally.

Reducing weight by even a small amount can improve metabolic and reproductive outcomes in women with PCOS. Weight loss can see an improvement in both ovulation and insulin resistance. Weight reduction can have a direct effect on hyperandrogenism and the resultant hirsutism by increasing the function of SHBG concentration which binds testosterone.

Long-term weight loss is the goal and needs to focus on a change of lifestyle rather than a restrictive diet plan.

- Increase quality protein in your diet. High protein diets have shown good results in both insulin-resistant and PCOS women. Protein can improve satiety and have a regulating effect on blood sugar levels. Good sources of protein included: fish and seafood, turkey and chicken
- Increase vegetables, whole grains, nuts and seeds
- Increase good fats (avocados, coconut oil, olive oil)
- Consume plenty of water (8 glasses per day)
- Limit foods high in sugar (e.g. cakes, pastries, soft drinks) and processed foods
- Limit high fructose foods as these have been shown to increase leptin levels.

Exercise is a must in the treatment of PCOS whether it is associated with obesity or not. Dietary counselling and exercise may result in a normalisation of hormone levels as observed by LH:FSH ratio in PCOS women, even in the absence of weight loss (4.). Exercise has also been shown to have positive effects on menstrual regularity.

The positive influence of physical activity on glucose control cannot be overlooked as dysfunction of glucose control is a major contributor to high leptin levels and PCOS. Physical activity aids the uptake of glucose into the cells having a beneficial effect on insulin-resistance.

Reducing stress will also help directly with PCOS and fertility. Stress stimulates the release of cortisol from the hypothalamic-pituitary axis. The “stress” hormone cortisol promotes central obesity and insulin resistance, and these are the two main concerns for increases in leptin levels.

Stress exacerbates the vicious cycle of PCOS by promoting both androgen overproduction in the ovaries and also increasing cravings for carbohydrates which can contribute to obesity.

Try taking a yoga class, practicing mindfulness meditation for just 10 minutes a day or taking a walk on the beach. Stress reduction will not only have a positive influence on the leptin, insulin and PCOS relationship, but is also great for general health and wellbeing.

Get plenty of restful sleep 7 - 8 hours per night. Chronic sleep deprivation has been associated with weight gain. Poor sleep can have an adverse effect on the hormones that regulate appetite, leptin and

ghrelin.

Whilst the above lifestyle factors should be the first line of defence in the treatment of PCOS and fertility, and in addressing the leptin, insulin relationship in PCOS there are also many nutrients and herbs that may assist with PCOS.

Some research has found whey protein supplements to improve biomarkers in PCOS patients due to the positive effect protein can have on blood sugar control and satiety in weight loss.

Inositol is an amino acid that may improve ovarian function in women with oligomenorrhoea and polycystic ovaries<sup>5</sup>. Weight loss and leptin reduction was also noted in those taking inositol (5). Inositol has also shown a positive effect on non-obese women with PCOS and improved insulin resistance.

Alpha Lipoic Acid has been shown to enhance the uptake and utilisation of glucose into the cells so may improve insulin resistance in the PCOS women whether overweight or lean.

Chromium may assist with carbohydrate cravings and improve insulin-resistance.

Galega officinalis (Goat's rue or Galega as it is more commonly known) has been used traditionally in the treatment of insulin resistance. Galega contains chromium salts and guanidines, The allopathic drug of choice in the treatment of PCOS is Metformin which is a synthetic derivative of guanidine.

Gymnema sylvestre is an Ayurvedic herb that may also play a role in the treatment of glucose regulation and insulin resistance. Gymnema also has the unique ability of anaesthetising the taste buds which may reduce sweet cravings and have a positive influence on weight loss

Do you suffer from PCOS? Do you think Leptin may be an issue for you? We would love to hear your thoughts and feedback on what natural treatments have helped and assist other PCOS sufferers.

1. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728861/>
2. <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2003-031378>
3. <https://www.ncbi.nlm.nih.gov/pubmed/19794290>
4. <https://www.ncbi.nlm.nih.gov/pubmed/16900227>
5. <https://www.ncbi.nlm.nih.gov/pubmed/15206484>