Obesity in PCOS - A Morbid Combination

Dr Alpesh Gandhi
President FOGSI

DR Anita Singh
Vice President
FOGSI

Dr Rakhi Singh
Chairperson
Endocrinology
Committee FOGSI
EDITOR

Editor :Dr Meenu Handa
Senior IVF specialist ,
Fortis Bloom IVF center
Gurugram.

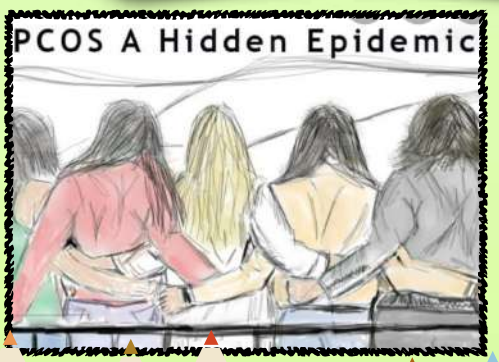
Author
Dr.Neelam Ohri
Senior IVF Specialist,
Director, NewLife Hospital
and Fertility Center,
Varanasi

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting 8–13% of women of reproductive age and is characterized by polycystic ovaries, hyperandrogenism and chronic oligo-anovulation. It is a heterogeneous disorder. Although the molecular mechanism underlying its pathogenesis remains largely uncertain, emerging evidence suggests that hyperandrogenism plays a vital role in PCOS1 by interacting with several factors such as insulin resistance, hyperinsulinemia and obesity to exacerbate its development and complications.2

Obesity and PCOS

In the present era we are facing an epidemic of both obesity and PCOS. Although, obesity is not a diagnostic criterion for PCOS, it is strongly associated with PCOS.3 This association dates back to history when in 1935 Stein and Leventhal described this syndrome with amenorrhoea, hirsutism, obesity and polycystic appearance of ovaries. Obesity is a moderator of hyperandrogenism and it adds to the risk of PCOS causing adverse metabolic effects on the PCOS phenotypes. Obesity is most common among PCOS patients who are both androgenic and anovulatory.4



Mechanisms by which Obesity effects risks and severity of symptoms in PCOS
Obesity affects androgen levels through many pathways as follows:

A) Adipose Tissue Dysfunction

Excessive visceral adipose tissue (VAT) is a peculiar feature of PCOS. Both obese and non-obese PCOS patients have more VAT than that of women without PCOS.(Figure1). VAT positively correlates with total androgen levels. Androgens cause adipose tissue dysfunction, including increased lipid accumulation and insulin resistance. Androgens may alter insulin-mediated glucose metabolism in adipose tissue by impairing phosphorylation of protein kinase C zeta in obese women.

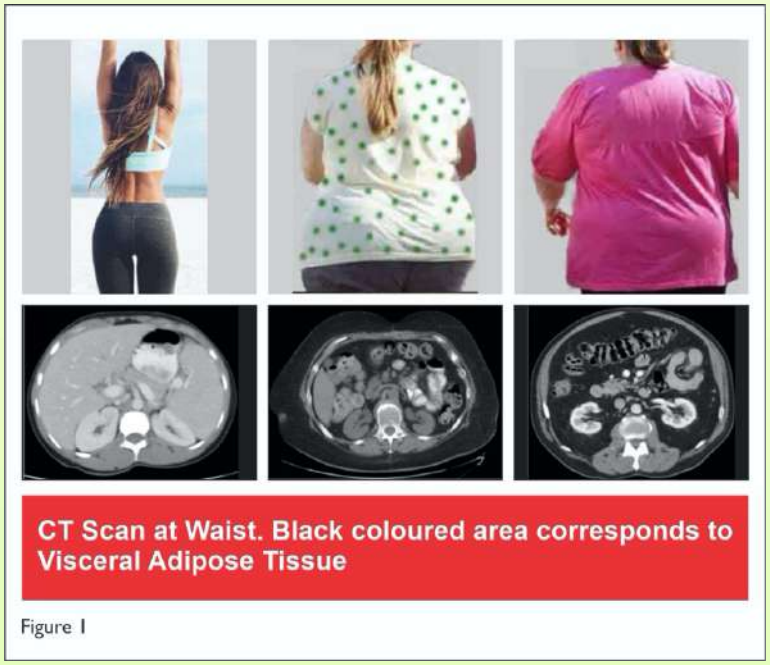


Figure 1

B) Excess Androgen Synthesis

Abdominal obesity is a condition of relative hyperandrogenism. Abdominal obesity and insulin resistance synergistically stimulate androgen synthesis in the ovaries and adrenal glands and subsequently further increase abdominal obesity and inflammation, thus creating a cycle.

C) Adipose Tissue Acts like an Endocrine Gland

Adipose cells release factors such as leptin and adiponectin via paracrine and autocrine secretion to regulate androgen levels. Leptin is a protein encoded by the obesity gene on human chromosome 7. Serum leptin is increased in some PCOS patients, and high leptin concentrations inhibit the expression of aromatase mRNA in granulosa cells, thus preventing the conversion of androgens to oestrogens, promoting follicular atresia.

Adiponectin is one of the most important adipose factors which can improve insulin sensitivity to reduce free fatty acids (FFA) intake and gluconeogenesis. Studies have found that adiponectin levels are lower in PCOS patients.

D) Adipose Tissue as an Endocrine Modulator

In addition to hormone synthesis, adipose tissue is an active site of two major hormone conversions, the conversion of androgens to oestrogens and the interconversion of cortisol and cortisone. These bring about various presentations of PCOS.

E) Obesity Leads to Hyperinsulinemia

The insulin resistance of PCOS typically has a prominent intrinsic element, although in some cases, it may simply be acquired because of exogenous obesity.
Upper body and visceral fat are associated with decreased insulin sensitivity. Release of FFA from adipocytes interferes with insulin action on hepatocytes. This results in decreased production of sex hormone binding globulin (SHBG) and insulin like growth factor binding protein 1(IGFBP-1). This leads to increased free androgens in the body. (Figure 2)

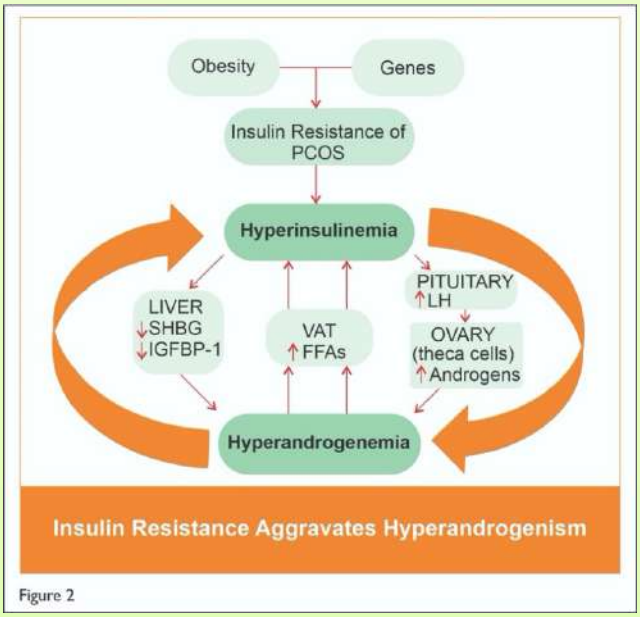


Figure 2

F) Obesity and Impaired Reproductive Functions in PCOS

Due to obesity and insulin resistance reproductive function takes a hit.[5] Hyperinsulinemia with hyperandrogenism stimulate theca cells. Elevated androgens from theca cells in turn stimulate pituitary and cause LH excess, which worsens hyperandrogenism and causes luteinisation of granulosa cells prematurely, leading to anovulation.

G) Obesity-induced chronic inflammation and oxidative stress

Obesity is a state of chronic inflammation and oxidative stress which are induced through multiple biochemical mechanisms. Apart from causing metabolic changes in body these factors may lead to decreased oocyte quality due to oxidative damage.

H) Obesity and Adverse pregnancy outcomes

Studies have suggested that obesity is the strongest predictor of gestational diabetes mellitus status and pregnancy related hypertension in PCOS women.

Managing Obesity Bring About Positive Changes

Evidence suggests that even a modest weight loss (around 5%) often results in clinically meaningful improvements in the reproductive, hyperandrogenic and metabolic features of PCOS.

1. Measuring Obesity

- WHO defines overweight as a BMI of 25.0 to 29.9 kg/m2 and obesity as a BMI of ≥30 kg/m2
- However, as a defining parameter, BMI has certain limitations as it does not distinguish the difference between lean mass and fat nor does it identify fat distribution.
- Consequently, measures of central fat such as waist circumference (WC) or waist/hip ratio correlate more closely with obesity risk than BMI.
- PCOS women have a raised waist/hip ratio. WC > 88cm is a criterion for metabolic syndrome. (Figure 3)

Figure 3

2. Therapy for Obesity

- Insulin sensitizers and anti-obesity drugs and bariatric surgery are very effective and have shown to produce positive metabolic changes, but for sustained benefit disciplined and permanent life style changes are needed.
- Any medical or surgical management of obesity without regular exercise and a rational dietary plan is of no use in the long run.
- Lifestyle improvement leads to positive change in body composition, bringing about improvements in insulin sensitivity and improvement of hyperandrogenism.

3. Exercise Component

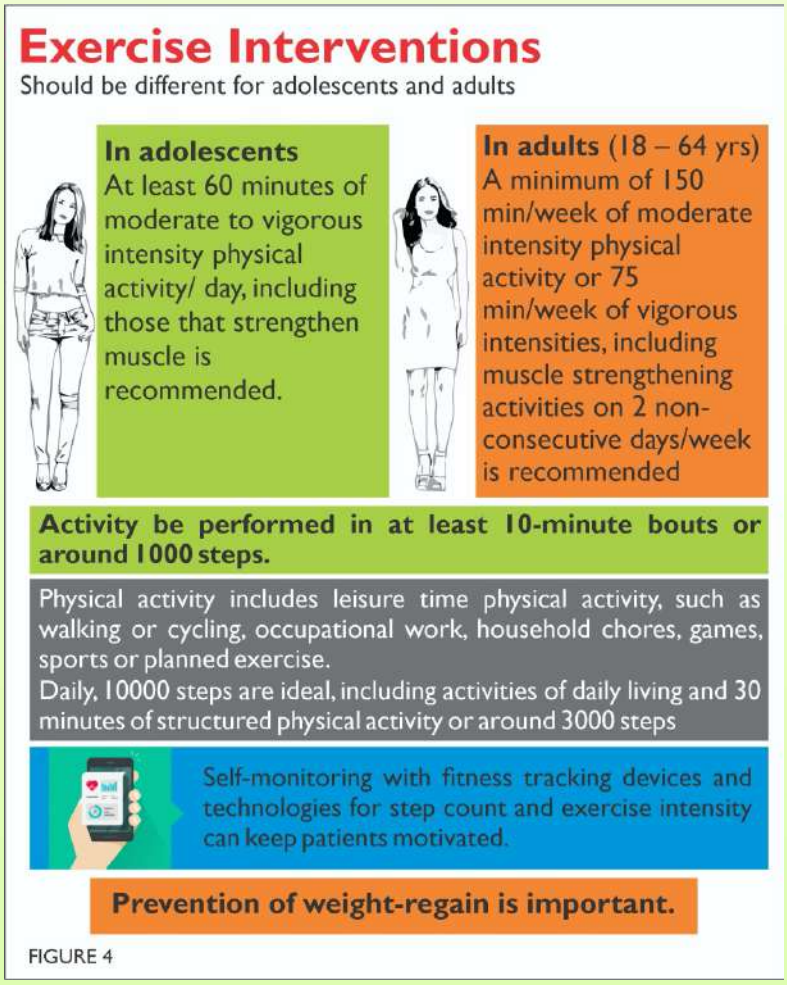


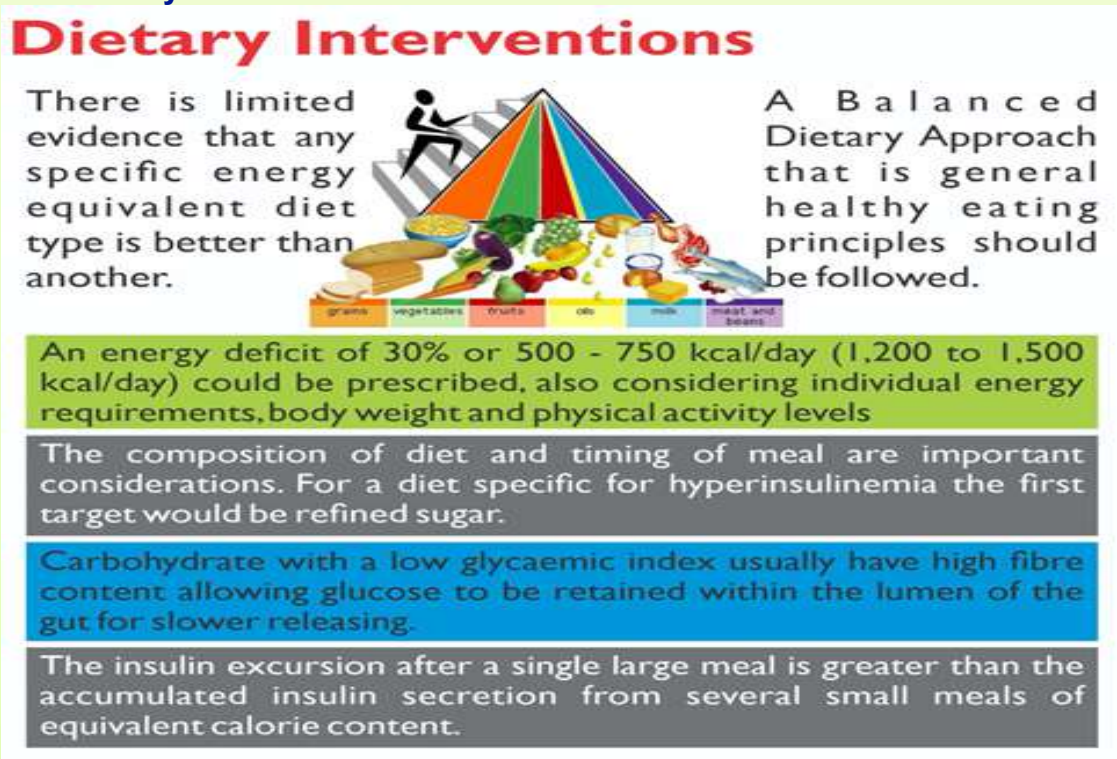
FIGURE 4

Achievable goals are

- 5% to 10% weight loss should be set within six months.
- Goals should be SMART i.e. specific, measurable, achievable, realistic and timely. They should be inclusive of individual requirements

- There can be major orthopaedic limitations to weight bearing exercise in morbidly obese women with joint problems and arthritis, so exercise must be tailored to their abilities.
- A recent study has found that exercise can improve pregnancy rates in patients with PCOS.
- Kogure et al used progressive resistance training in both PCOS and non-PCOS patients, and found that the testosterone levels decreased in both groups after the patients lost weight and increased their lean body mass and muscle strength.[6]

4. **Dietary interventions:**



5. **Psychological factors:** anxiety and depressive symptoms, body image concerns and disordered eating need consideration.

6. **Insulin-Sensitizing agents** like Metformin can be prescribed in obesity with comorbidities and features of insulin resistance.

The use of metformin in many studies of women with PCOS as well as in the Diabetes Prevention Program has been associated with weight loss but remains an off-label indication.

7. Effect of Anti-Obesity Drugs in PCOS

- The FDA-approved drug for the treatment of obesity is orlistat.
- It inhibits intestinal lipase activity and thus inhibits fat absorption. Adverse effects include steatorrhea and flatulence that are reduced with adherence to a low-fat diet.
- Limited studies in women with PCOS show a relatively modest weight loss ~5 to 7 lbs (in combination with lifestyle change) and modest improvements in biochemical measures of insulin sensitivity and hyperandrogenism after a year of use.

8. Effect of Bariatric Surgery in PCOS

- Bariatric surgery can be a last choice when other modalities fail. Recommended in BMI> 40 or between 35-40 with co-morbidities.
- Bariatric surgery has been demonstrated to improve or even cure type 2 diabetes, hypertension, hyperlipidaemia, and obstructive sleep apnoea.
- More so, there are studies that reported complete resolution of all features of PCOS, even hirsutism, hyperandrogenism, anovulation, and menstrual irregularity.

Conclusions

In PCOS, Obesity aggravates hyperandrogenism through many pathways. Obesity causes adverse metabolic effects on the PCOS phenotypes, especially CV risk factors, mainly related to insulin resistance. It is also associated with a poor response to infertility treatment and likely an increased risk for pregnancy complications. We need to adopt a holistic approach to weight management in PCOS: one that addresses not just lifestyle change but any potential mental and emotional barriers to its effective implementation. The take-home message is: obesity with PCOS makes a morbid combination and should not be ignored.(7)

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