The influence of obesity on hyperandrogenism and infertility in the female

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Highlights / Hoogtepunte

- How to diagnose policystic ovary syndrome (PCOS) in patients with hyperandrogenaemia and oligo-anovulation (infertility).
- How does the presence of obesity influence the management of PCOS patients?
- Which special investigations should be done in PCOS patients, and who should be referred?

- Hoe om die diagnose van polikiesteuse ovariële sindroom (PKOS) te maak in pasiënte met hiperandrogenemie en oligo-anovulasie (infertiliteit).
- Hoe beïnvloed die aanwesigheid van vetsug die hantering van PKOS pasiënte?
- Watter spesiale ondersoeke moet gedoen word in pasiënte met PKOS, en wie moet verwys word?

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INTRODUCTION

"Fatness and flabbiness are to blame. The womb is unable to receive the semen and they menstruate infrequently" Essay to Scynthians: By Hippocrates 4th Century B.C.

The polycystic ovary syndrome (PCOS), one of the most common causes of ovulatory infertility, affects 5-10% of women[1]. Over the years, after the initial description by Stein and Leventhal in 1935, this syndrome has been defined in different ways. Finally, in 1990, the NIH established new diagnostic criteria for this disorder which are based on the presence of hyperandrogenaemia and chronic oligo-anovulation, with the exclusion of other possible causes such as adult onset congenital adrenal hyperplasia and hyperprolactenaemia. Approximately 60% of PCOS women are overweight or obese, and most of them have the abdominal phenotype[2]. The observation of an increased prevalence of PCOS among family members as compared to the general population favoured the hypothesis that, at the basis of this syndrome, a genetic component may exist. To date, more than 50 possible candidate genes have been identified[3]. The heterogenous characteristics of this syndrome indicate a more complex interaction between the genetic and environmental factors.

PATHOGENIC MECHANISMS

The timing of the main events during the normal menstrual cycle have been outlined in **(Fig 1)**. Although a critical mass of adipose tissue is essential for the normal development of the female reproductive function, obesity has been shown to produce menstrual disturbances and sub-fertility. The severity of obesity and the distribution of fat tissue are important factors that will influence the female reproductive system. Adipose tissue is a hormonal target as well as an endocrine organ, demonstrating an active role in sex steroid metabolism[1].

Among the hormonal abnormalities which have been described to be associated with obesity and anovulatory disturbances, hyperandrogenaemia appears to be the common one[4]. In addition, hyperinsulinaemia and insulin resistance **(IR)** associated with obesity will play a very important role in the syndrome in susceptible individuals **(Fig 2).** Insulin possesses true gonadotrophic functions, and increased insulin availability at the level of ovarian tissue may favour excess androgen synthesis. Interestingly, the IR paradox in PCOS may be associated with profound down-regulation of the insulin receptor at peripheral tissue with increased phosphorylation of the serine residue, whilst the ovary would have preserved expression of the insulin receptor function even in the face of severe IR **(Table 1).** Obese women will also display increased peripheral aromatization of androgens to estrogens **(Table 2),** altered gonadotrophin secretion, decreased sex hormone binding globulin, decreased growth hormone and diminished insulin-like growth

Figure 1: The timing of the main events during the menstrual cycle

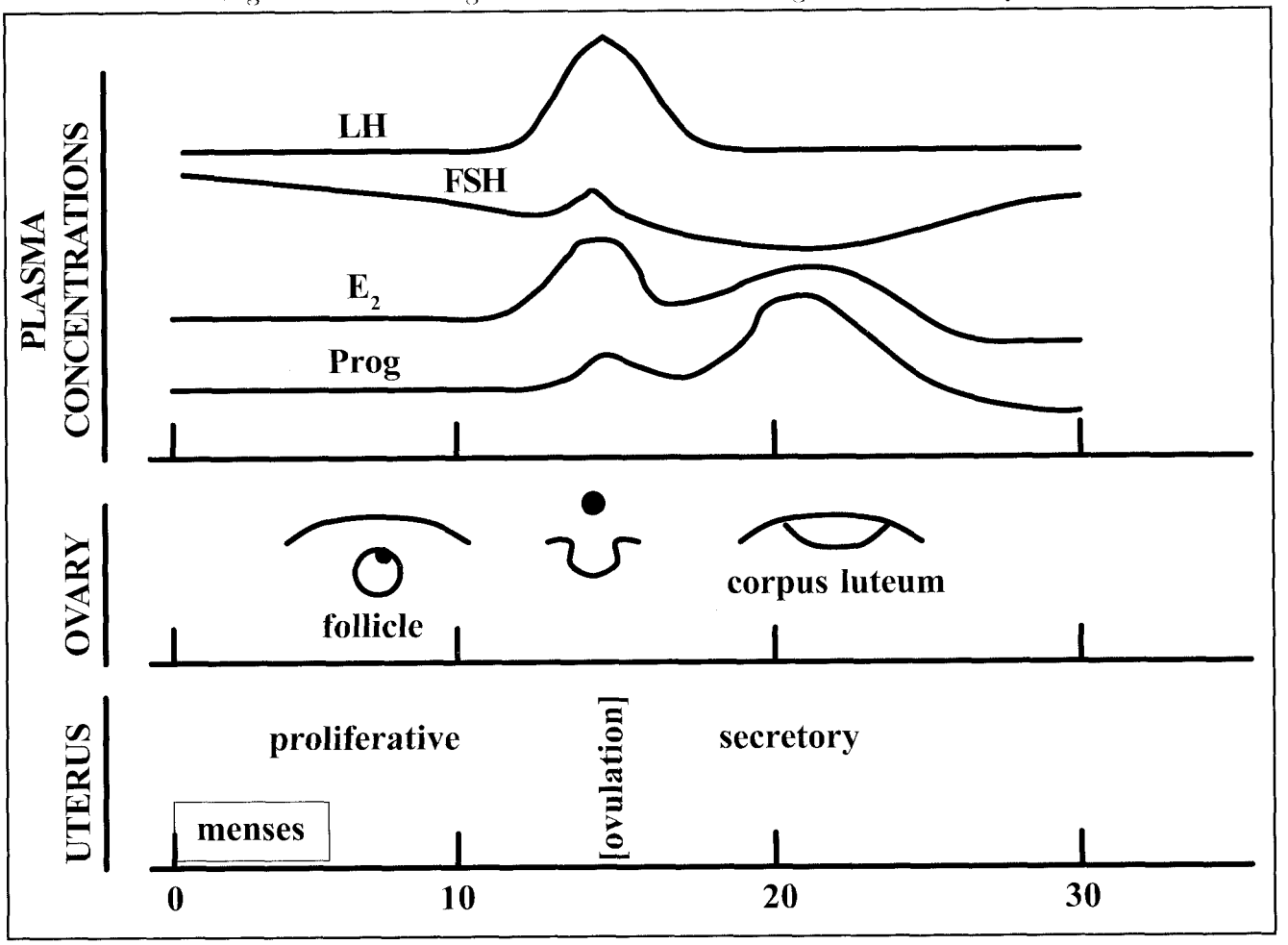


Figure 2: Proposed mechanisms by which obesity links with hyperandrogenism

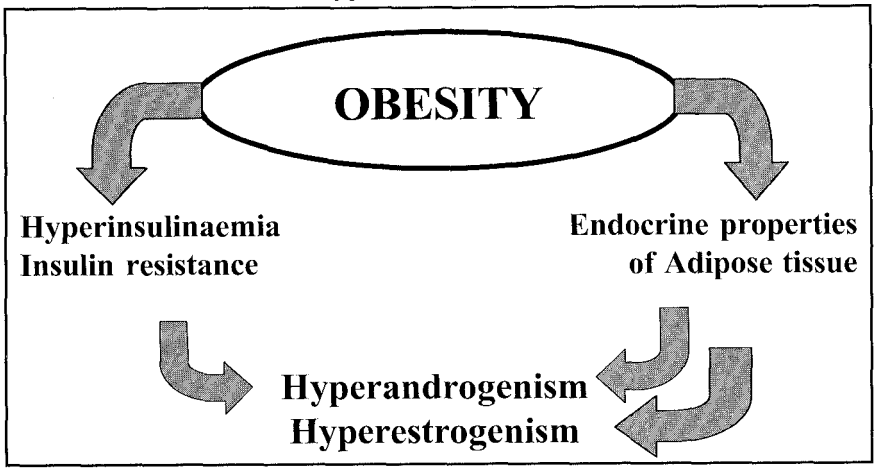


Table 1: Insulin resistance paradox in PCOD	
Peripheral tissue	**Ovary**
Down-regulation of insulin receptor	Preserved expression of insulin receptor even in the face of severe IR
50% of cases: ↑ phosphorylation of serine residue	

factor binding proteins[5].

In the presence of hyperinsulinaemia, the action of LH on granulose cells in women with PCOS will be amplified, and the putative effect of the frequency of gonadotropin releasing hormone neuronal discharge on the secretion of luteinizing hormone and follicle-stimulating hormone has been illustrated in **fig.4**[6,7]. Anovulatory follicles are thus likely to arrest prematurely in a more hyperestrogenic milieu resulting from

Table 2: Endocrine properties of adipose tissue
• Increased aromatase activity
• Increased E_1
• Decreased SHBG
• Increased 17βOH-dehydrogenase
↑ **Progesterone/Testosterone/ DHEA**
• Increased 11β dehydrogenase
↓ **Aldosterone / Cortisol**

obesity, where the role of androgens as substrate cannot be neglected **(Fig. 3)**. Androgens will play a synergistic role, together with elevated levels of LH and insulin in premature luteinization and follicular arrest.

Other factors **(fig.5)**, such as increased activity of the opioid system and upregulation of the hypothalamic-pituitary-adrenal axis, have also been implicated[8]. In addition, leptin appears to be a link in the circle of communication between adipose tissue and the reproductive system in a direct and indirect manner. Leptin can affect ovulation independently of insulin or androgen level[9]. Neuropeptide Y (NPY) has also been implicated in control of food intake, oestrus behaviour and the mechanisms controlling ovulation. This can, via direct effects on GnRH neurons or by amplifying the pituitary responsiveness to GnRH[10]. Chronic administration of NPY leads to hyperinsulinaemia and IR[11]. It is known that tumor necrosis factor is increased in obesity. It participates in the control of fertility, influencing negatively folliculogenesis and ovarian maturation[12]. It will stimulate apoptosis of early antral follicles by inhibiting aromatase activity induced by follicle stimulating hormone (FSH). Inhibins are heterodimeric gonadal peptides that suppress FSH release. They are involved both in the anovulatory component of PCOS and in the excess of intraovarian androgens[13]. A negative correlation exits between body mass index and Inhibin A and B. The activation process of inhibins is impaired in the theca-interstitial cells of PCOS, and this deficit is worsened by obesity. Decreased levels appear to act as a marker of diminished levels of ovulation taking place. Finally, it appears that a diet high in fat and low in fibre intake will be associated with PCOS[14].

Figure 3: Mechanisms by which obesity links with anovulation and infertility

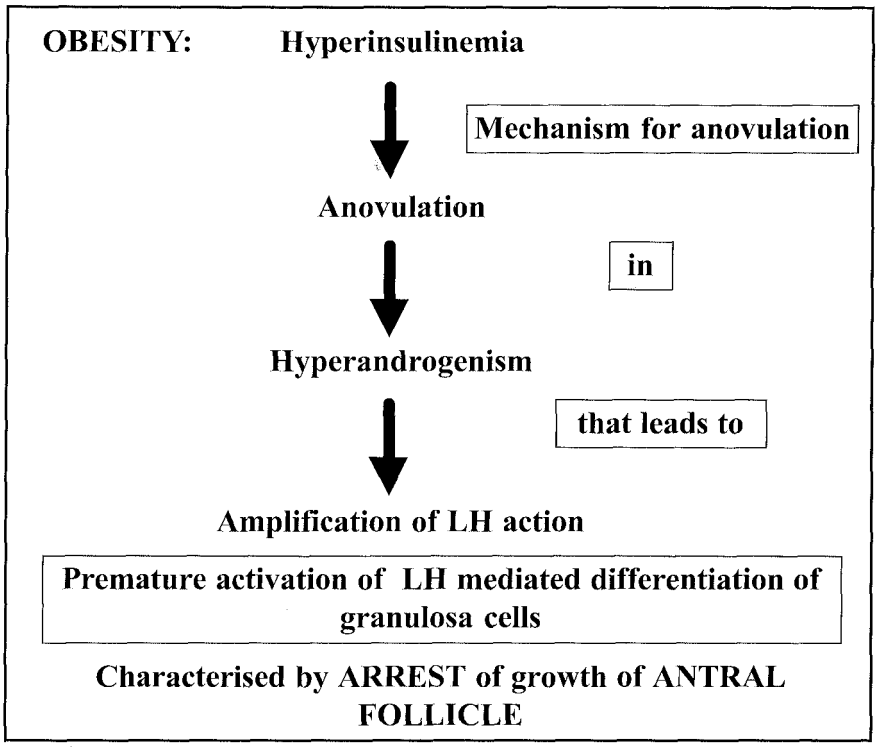


Figure 4: Putative effect of frequency of gonadotropin-releasing hormone neuronal discharge on the secretion of luteinizing hormone and follicle-stimulating hormone

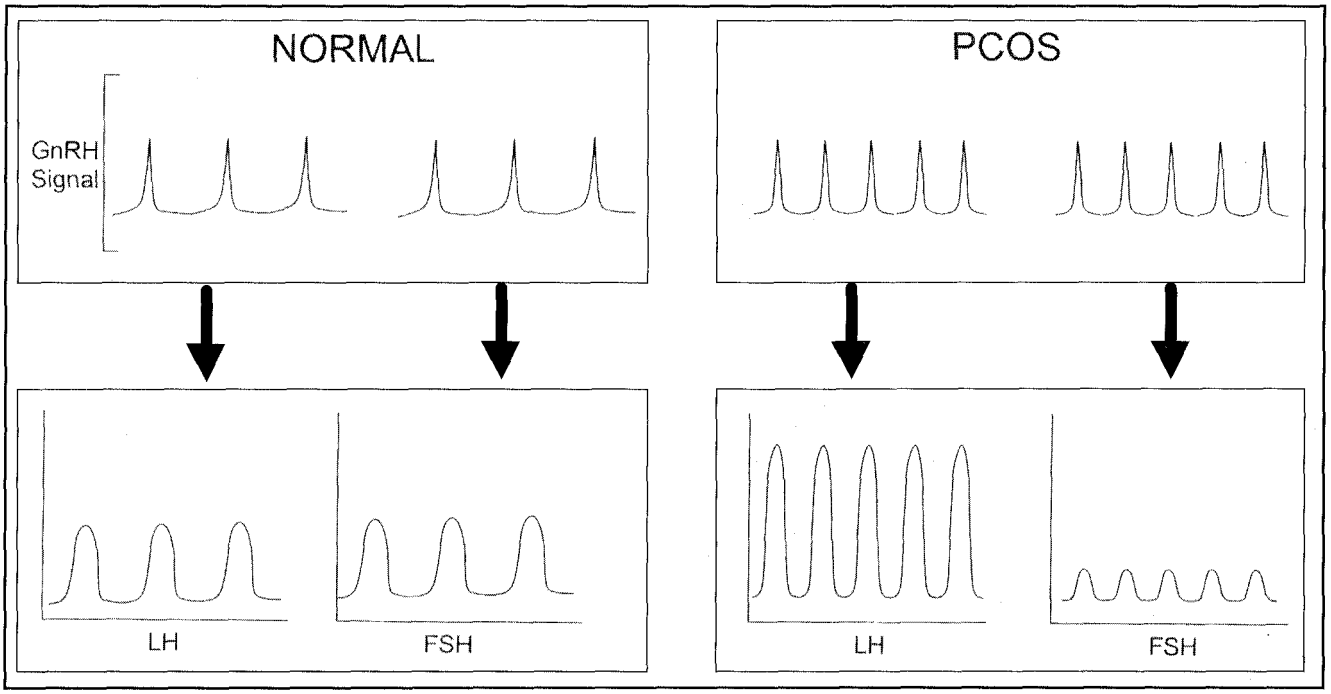
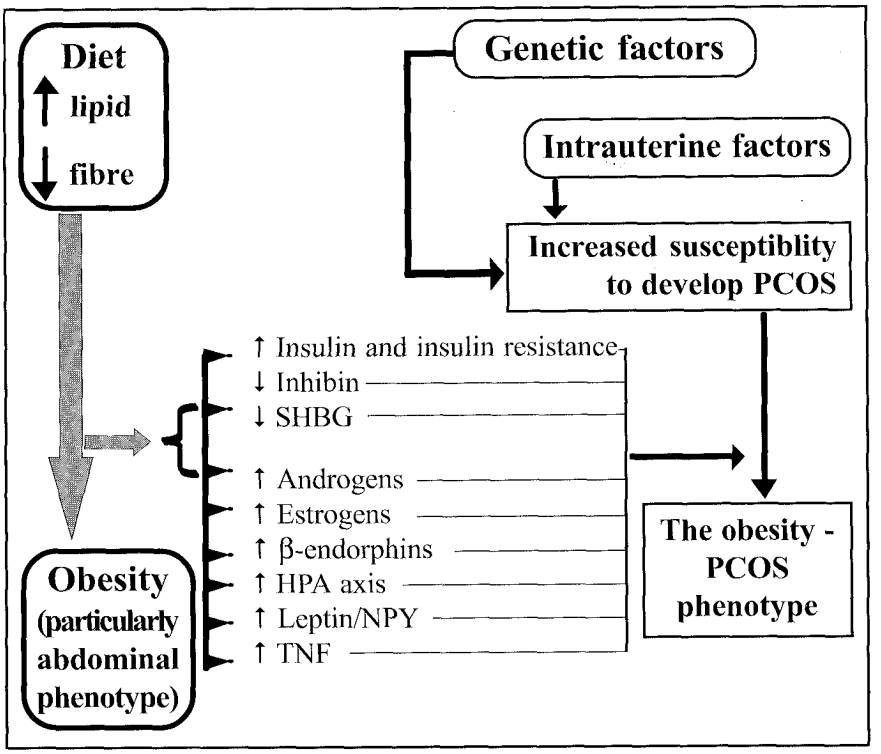


Figure 5: Mechanisms by which obesity may determine the obesity - PCOS phenotype



THE INFLUENCE OF BODY FAT DISTRIBUTION

Abdominal adipose tissue behaves like a special fat tissue with characteristic metabolic activity[15]. The abdominal-visceral (central) phenotype is associated with supranormal estrogen production, due to increased activity of the aromatase system[16]. Excess abdominal adipose tissue has a positive effect on the free testosterone level, through the well-known negative effect on sex hormone binding globulin[17]. In addition, obese women have insensitivity to endogenous insulin that is positively correlated with the presence of an abdominal fat distribution[18]. An abdominal waist circumference of more than 88cm shows a high correlation with insulin resistance. There appears to be a direct action of insulin to increase adrenal sensitivity to ACTH in hyperandrogenic women, especially with the abdominal phenotype of obesity[19]. High cortisol levels will favour further abdominal fat accumulation as a result of the high density of cortisol receptors on visceral adipocity. In addition, PCOS women with this phenotype present with a prevalence of menses abnormalities, acanthosis nigricans, a tendency towards worsened hirsutism, a more unfavourable lipid profile, increased FFA turnover and a worsened degree of glucose intolerance[20].

CLINICAL AND BIOCHEMICAL CHARACTERISTICS

Table 3 gives an outline of the differences in clinical appearance and biochemical profile between PCOS women with a lean or obese phenotype. For practical purposes, this classification is important as it will influence the decision-making process around treatment. Several features of the metabolic syndrome, particularly insulin resistance and hyperinsulinaemia, are consistently present in the majority of women with PCOD. This represents an important factor in the evolution of this syndrome throughout life, and implies that PCOD by itself may not be a hyperandrogenic disorder exclusively related to young and fertile women, but may have some profound health implications later in life[21].

Obesity is a very common manifestation in women affected with PCOS (> 50%), and the history of weight gain frequently precedes the onset of oligomenorrhea and hyperandrogenism. This suggests that a pathogenic role of obesity in the subsequent development of the syndrome. However, most obese women have normal menstrual cycles and remain fertile, suggesting that obesity *per se* is not the only factor involved in the genesis of hyperinsulinaemia and hyperandrogenism. Interesting, some recent data have introduced the idea that, in PCOS women, the disorder may originate during intrauterine life, depending on the mother and also on birth weight[22]. However, PCOS is characterized by a very high prevalence of several metabolic diseases, which are more strongly influenced by the presence of obesity. This will be of importance in phenotyping PCOS, and in the therapeutic strategy aimed at reducing both the hyperinsulinaemia and hyperandrogenaemia.

MANAGEMENT (TABLE 4 AND 5)

The GP should refer all patients with an increased LH/FSH ratio of more than 2.6, a strong family history, glucose intolerance or diabetes and clear clinical signs of hyperandrogenism and long-standing infertility to a specialist.

There is evidence that a reduced incidence of pregnancy and blunted responsiveness to pharmacological treatments to induce ovulation may be more common in obese PCOS[23]. Patients with obesity have higher gonadotrophin requirements during stimulation, fewer oocytes, a higher abortion rate and lower live-birth rate than their non-obese counterparts[24]. The presence of hyperinsulinaemia and hyperandogenaemia are probably the major factors responsible for this undesirable situation. Weight loss represents the first line treatment of obese PCOS women, since it improves hyperandrogenism and hyperinsulinism in most of them and, by itself, it may favour spontaneous ovulation and better fertility rate in approximately 25% of women. Whether hypocaloric dieting combined with longterm insulin sensitizers **(Table 4)** may be more effective than diet alone, is still under debate. However, there is mounting evidence that it may further improve the

Table 3: Clinical and biochemical characteristics

NORMAL WEIGHT	OBESE
1. Minority	1. >50% of PCOD
2. Early onset oligomenorrhoea	2. Weight gain precedes oligomenorrhoea
3. IR independent factor	3. IR as a result of obesity
4. Normal FFA levels	4. Increased FFA levels
5. GH amplitude normal	5. Decreased 24h mean GH Increased GH clearance
6. IGFBP normal/low *Insulin-induced hepatic and ovarian suppression*	6. Decreased IGFBP-1
7. IGF bio-availability higher *Insulin-induced IGFBP-1* *GH-induced hepatic IGF stimulation*	7. IGF bio-availability lower
8. IFG/IGBP ratio higher	8. IGF/IGBP ratio lower
9. SHBG normal/decreased	9. SHBG greatly decreased (esp. abdominal phenotype)
10. Testosterone (T and F) increased	10. Testosterone greatly increased
11. Estrone / Free E_2 increased	11. Estrone / Free E_2 greatly increased
12. Little additional extra-glandular E-production	12. Extra-glandular E-production greatly increased 'Functional hyper-estrogenism'
13. GnRH-mediated increased LH (LH ↑↑↑) *Neg. correlation with BMI*	13. Estrogen-mediated increased LH (Mainly) *Can be normalised with Progesterone*
14. Normal opiate tone	14. Opiate driven increased LH in abdominal obesity *'β-endorphin resistance' of PCOD/ β-cell hypersensitivity*
15. Cortisol levels normal	15. Hyper-reactive HPA axis *especially abdominal typing*
16. IGT very unusual	16. IGT (20-50%)
17. Abnormal lipid profile unusual	17. ↑TG; ↑LDL; ↓HDL

Abbreviations
IR = insulin resistance
FFA = Free fatty acids
GH - growth hormone
IGFBP = Insulin-like Growth Factor Binding Proteins
IGF = Insuline-like Growth Factor
SHBG = Sex Hormone Binding Globulin
IGT = Impaired Glucose Tolerance

effects of diet on body weight, reduction of visceral adiposity, and amelioration of hyperinsulinaemia and hyperandrogenism[25]. Anti-androgens may significantly improve IR in both obese and non-obese women with PCOS. The most clinically efficacious approach, using oral contraceptives in PCOS women, can be obtained combining estrogen with cyproterone acetate, which has progestogen and anti-androgen properties and also induces hepatic metabolism and increases testosterone clearance. In combination with estrogen, cyproterone acetate is almost as effective as a GnRH agonist at suppressing serum LH and testosterone, and the clinical efficacy of the two treatments appear equivalent[26].

CONCLUSION

The pathogenic role of obesity in PCOS may involve different mechanisms, the major one being hyperinsulinaemia, since insulin is capable of stimulating ovarian androgen production, controlling androgen metabolism and influencing follicular development. Different therapeutic modalities such as diet, insulin sensitizers, anti-androgens and oral contraceptives can be used to improve fertility and metabolic profiling.❐

Please refer to the CPD questionnaire on page 53.

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Table 4: Management of PCOS

Normal weight	Obese
1. Often normal menses	1. Usually abnormal menses
2. No dietary induced changes on androgen profile	2. Even 5% LL: Marked improvement of E/androgen profiling
3. Role of insulin-sensitizers doubtful	3. Positive metabolic/hormonal response *More so in abdominal phenotype* • Metformin • Glitizones • Inositolglycons
4. High rate of ovulation with GnRH	4. Blunted treatment response with GnRH-high abortion rate with IVF
5. Anti-androgens *Spirolactone/flutamide/ finosteride/GnRH antagonist* - Decreased insulin resistance	5. Anti-androgens *Spirondactone/flutamide/finosteride GnRH antagonist* - Decreased insulin resistance - ? decreased visceral fat
6. Oral contraceptive *(with cyproterone acetate)* • *(Progestogen:↓ GnRH pulses ↓ + LH secretion ↓* • *Estrogen: Induces P receptors in hypothalamus and ↑SHBG* - Decreased Androgens / T - Decreased Hirsutism - Decreased LH	6. Oral contraceptive *(with cyproterone acetate)* - Also decrease in waist circumferences - Decreased IGT

Table 5: Prodecures by which plasma insulin levels were reduced in women with polycystic ovary syndrome

- Low-calorie diet
- Drugs inhibiting β-cell secretion
  - diazoxide
  - semoatostatin
- Insulin sensitizers
  - metformin
  - troglitazone
- Putative mediators of insulin action
  - D-chiro inositol

before and after weight loss. *J Clin Endocrinol Metab* 1989;68:173-179.

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