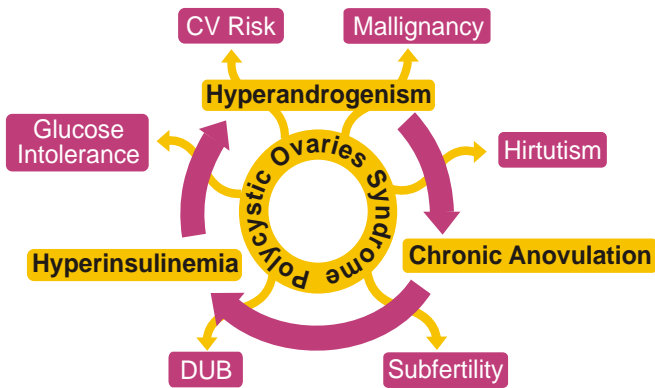


## Polycystic Ovarian Syndrome



PCOS is a condition that effects about 5 - 10% of Caucasian women of reproductive age and about 20 - 30% of infertility patients.

This diagram highlights how the various clinical components that make up PCOS interact with each other and produce the health problems associated with the condition.

All these clinical aspects to PCOS raise the question "What are we treating?"

Two definitions of PCOS are useful to clarify this:

1) A European (the European Society of Human Reproduction and Endocrinology) and American (the American Society of Reproductive Medicine) definition: A disease of ovarian dysfunction whose main features are raised male sex hormone levels and a polycystic ovarian appearance based on an ultrasound assessment.

This definition has been very useful to make a clear diagnostic basis for research, but it doesn't focus on the patient's complaints and is misleading in that it suggests a single underlying cause and disease process, which hasn't been proven.

*For practical reasons it is therefore more helpful to think of PCOS as:*

2) A clinical syndrome characterized by an unexplained, long term abnormality of ovulation associated with a spectrum of associated clinical conditions.

This definition highlights 2 key points, firstly it excludes other recognized hormonal causes of the same clinical presentation (such as other hormonal or glandular problems) and secondly, it highlights the syndromic nature of PCOS as shown in the diagram above.

### Hyperinsulinaemia

Hyperinsulinemia, or high blood insulin levels is caused by "insulin resistance" (IR). This is a term that describes the inability of insulin to exert its biological effects at a cellular level. This is caused in turn by an insensitivity of cells to insulin that is believed to be caused by a problem with the insulin receptors on cells. In PCOS patients the resulting elevated insulin levels are aggravated by reduced insulin clearance from the blood by the liver and increased sensitivity of the pancreas to glucose, causing increased insulin production.

Of note is the fact that obesity is not regarded as a cause of IR. It worsens rather than causes it, as evidenced by the fact that IR is found in thin PCOS women.

**The clinical effects of the hyperinsulinemia are:**

1. Increased cardiovascular risk related to: lipid changes (raised triglyceride and reduces HDL cholesterol), increased markers for intravascular inflammatory response which is associated with the development of atherosclerosis and hypertension.
2. The stimulation of fat deposition and its accumulation and the inhibition of stored fat mobilization and usage.

3. Raised blood pressure an effect that is proportional to insulin levels.
4. Potentially increased endometrial cancer risk mediated via a direct effect on the lining of the womb, but as yet unproven.
5. Hyperandrogenism (raised male sex hormone levels), primarily by acting on ovarian insulin receptors increasing ovarian androgen (male sex hormone) production in response to pituitary hormone stimulation. It is possible for a patient to have hyperandrogenism with insulin resistance and hyperinsulinemia. These effects are exaggerated by obesity but not all hyperinsulinemic, hyperandrogenic women are obese.

### Obesity

Obesity exacerbates the problems associated with PCOS by:

1. Raising androgens (by conversion of ASD (a weak androgen) to oestrone (a weak oestrogen))
2. Raising IR (as discussed above), and
3. Reducing Sex Hormone Binding Globulin (a carrier protein found in the blood stream that binds and inactivates sex hormones) and so raising free testosterone (a strong androgen) and oestradiol (a strong oestrogen). Central abdominal fat is more metabolically active than other fat stores. As a result a waist measurement of >90cm is predictive of abnormal endocrine and metabolic function and increase cardiovascular risk.

Weight loss of as little as 5% of starting weight has been shown to reduce hyperinsulinemia and hyperandrogenism and may cause a resumption of ovulation.

### Diet and PCOS

For some reason the combination of diet and PCOS is not well studied. There are very few published clinical trials into the effect of different diets on PCOS and those studies that are reported are on small numbers of patients.

Published studies have looked at the effects of:

- varying protein content,
- varying polyunsaturated fatty acid content,
- a low carbohydrate diet vs a monounsaturated fat rich diet and,
- a high protein vs high carbohydrate diet.

The only significant findings were that low carbohydrate diets reduced fasting insulin and free testosterone levels (after 16 days), and a diet high in protein reduced glucose levels after meals which could be expected to reduce circulating insulin.

Pending further evidence it seems that recommending a calorie restricted, low carbohydrate, high protein diet is appropriate.

Goals Of PCOS Treatment

- Normalise body weight
- Reduce androgens
- Lower cardiovascular risk
- Reduce hyperinsulinemia
- Ovulation induction

The good news is that whilst PCOS represents the vicious cycle shown above, with one component of the clinical syndrome acting to reinforce the others, breaking that cycle at one point will tend to have beneficial effect all around. The bad news is that the treatment will have to be maintained long term as the opposite is also true. Allowing the cycle to reform will bring a return of the full clinical manifestations of the condition.

### Treatment

Overall the advice has to be for a lifestyle modification and the recognition that this is a lifelong problem with women aiming at an ideal weight equating to a BMI of 27. This correlates well with reduced insulin and androgen levels as well as a return to normal menstrual function.

The Combined Oral Contraceptive Pill (OCP).

The OCP is the logical treatment for women not wanting to conceive. Acting centrally to reduce pituitary hormone release it reduces ovarian androgen production by reducing thecal (the ovarian source of androgens) stimulation. It also raises sex hormone binding globulin (SHBG) levels thereby binding both circulating androgens and oestradiol and reducing the amount of active (free or unbound) hormone. This improves both short and long term manifestations of PCOS. In terms of insulin resistance, the OCP does not improve it, but doesn't appear to worsen it either.

Which OCP? If hirsutism is a problem in the past, Dianne-35 for three cycles is effective for its immediate anti-androgen effect, and has long been the first choice. Yasmin however, is a newer OCP that has Drospirenone as its progestin component which is as effective in this capacity and also has useful diuretic and antihypertensive effects. It is also a 30mcg (ethinyl oestrodial) pill and therefore has fewer oestrogenic side effects. After three months a change to either Levlén ED or Marvelon is recommended because Dianne-35 has a 4 fold increased risk of venous thrombosis associated with it when compared to other OCPs due to its higher oestrogen content and Levlén ED is significantly cheaper and therefore more likely to be taken long term. If hirsutism treatment and contraception are not required, and lipid profiles are at normal female levels, either cyclic Provera 10mg from 1st to 14th of each month or a Mirena IUS are good options.

#### Metformin

Metformin acts to reduce insulin resistance and hence fasting insulin levels by:

- a. Decreasing hepatic glucose production (its main effect) and
- b. Increasing peripheral tissue sensitivity to insulin.

In PCOS women its effects are controversial and difficult to separate from weight loss. However on balance Metformin is thought to reduce basal LH levels and hyperandrogenism (free testosterone levels) and to reduce insulin induced cardiovascular risk giving an expected but as yet unproven benefit to longer term treatment.

Metformin is thought to be ineffective in producing weight loss, however, it may reduce abdominal fat. A recently published multi-center RCT looking at the effect of lifestyle modification and Metformin in obese PCOS patients found no improvement in weight loss. The trial took 10 years to complete and the lifestyle change involved a reduced calorie, (reduced by 500 Kcals/day) high carbohydrate, low fat diet (50% carbohydrates, 10% fat), which seems again to support low carbohydrate diets in these patients.

Due to the beneficial effects of Metformin it sounds like the ideal treatment however, it has the following disadvantages:

1. It requires a 3 times a day dose that is poor for compliance as are its abdominal side effects, which stop about 20% of women from taking it.
2. There is a risk of lactic acidosis, a potentially serious medical condition that requires the initial monitoring of renal and hepatic function.
3. It is contraindicated in pregnancy as it freely crossed the placenta, however this is slowly being challenged as it seems to be both safe and efficacious in pregnancies complicated by Gestational Diabetes Mellitus.

As Metformin may need to be taken long-term, these disadvantages pose a significant challenge for patient compliance.

#### Fertility Treatments

##### Metformin

Many trials have shown that Metformin alone can make PCOS patients ovulate. It will restore ovulation in about 40% of non-ovulatory PCOS women. It may also increase the sensitivity of women to other fertility drugs and so increase their effectiveness, however recent large trials suggest this is not the case.

A systematic review of clinical trials looking at the effectiveness of Metformin as a fertility treatment done in 2003 found it to be an effective fertility treatment recommending its use as an adjuvant to lifestyle changes. When compared to placebo, PCOS patients were four times more likely to ovulate and it was also found it to be effective in both obese and lean women. This recommendation was endorsed by the NICE guidelines for Fertility assessment and treatment for people with fertility problems. NICE being the National Institute for Clinical Excellence in the UK.

Therefore Metformin has a prominent place in treatment but remains a hard sell due to its side effects. Furthermore, because most women want immediate results and other fertility treatments have a greater likelihood of producing ovulation, other OI methods are preferred.

##### Clomid

Clomid (Clomiphene Citrate) is an anti-oestrogen, non-steroidal, diethylstilbestrol derivative like Tamoxifen, made in 1957 and licensed in the US for use in 1967. It acts by binding to receptors in the brain causing their depletion which increases pituitary hormone secretion. In essence it tricks the brain into thinking there is less oestrogen circulating than there actually is, causing increased pituitary FSH release stimulating ovulation.

Clomid produces ovulation rates in PCOS patients of up to 70%, is well tolerated and has few side effects. The more commonly reported adverse effects are hot flashes and breast tenderness. However, with unmonitored use the multiple pregnancy rates rises to about 5%.

Those NICE guidelines found a combination of Clomid and Metformin was better than Clomid alone for ovulation giving an approximately 4.5 fold increased chance of ovulation which is a similar chance as seen with injected fertility drugs, but it does not increase the overall pregnancy rate compared with Clomid alone. Even in this context the significant side effects associated with Metformin reduce its usefulness.

Therefore Clomid is first line therapy starting with one tablet for 5 days on the 2nd to the 5th day after the onset of a spontaneous or induced period.

#### Conclusion

Polycystic ovarian syndrome poses significant for both the patients who suffer from it and the doctors who treat it. However, by focusing on the aims of therapy with a combination of lifestyle modifications and medicinal therapeutic measures real improvements in both fertility and long term health outcomes can be achieved.



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