

Role of Metformin in Management of PCOS

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Introduction

Polycystic Ovarian Syndrome (PCOS) is a common, clinico-pathological and heterogeneous disorder of women of reproductive age, characterized by chronic anovulation or infrequent ovulation, obesity, hirsutism, hyperandrogenism and numerous follicular cysts in enlarged ovaries. Polycystic ovary syndrome (PCOS) is the commonest cause of anovulatory infertility. As there are no well-accepted criteria for diagnosis, the incidence of PCOS is not really known. However, it is postulated to be about 20-30% in the general population. Based on symptomatology incidence varies between 4-5% to 21% (menstrual abnormalities) and 3.5 to 9% (hyperandrogenism). It is important to remember that, 40% of women with oligomenorrhoea, 84% of women with hirsutism and 100% of women presenting with severe acne, have PCOS as their etiology (1-5).

Hyperinsulinaemia has proved to be a key link in the enigmatic generation of the symptoms of PCOS. Women with polycystic ovaries are profoundly insulin resistant, and the resultant hyperinsulinaemia exacerbates the reproductive abnormalities. Regression of these symptoms may be achieved by reducing the hyperinsulinaemia. As obesity exaggerates the expression of the symptoms induced by hyperinsulinaemia, a low calorie diet and lifestyle modifications resulting in loss of weight for obese women with PCOS is capable of reversing these symptoms. Drugs that ameliorate insulin resistance and reduce circulating insulin levels could provide a new therapeutic modality for PCOS. Hence, it is necessary to identify this subset of women who will respond to this therapy. Insulin-sensitizing agents, predominately metformin, have been examined for their

ability, in all patients with PCOS, to achieve similar beneficial changes to those induced by loss of weight in the obese.

This review focuses on the clues we have for an underlying pathogenesis and the potential approaches to therapy those might imply. At present, these emerging therapies focus on ovarianpituitary-hypothalamic axis abnormalities and steroidogenesis as well as insulin resistance. The aim of this review is to address the issue of hyperinsulinaemia and use of insulin sensitizing agent in the management of PCOS.

Pathophysiology

Although the fundamental pathphysiologic defect is not known, women with PCOS can be divided into two groups. One group is with evidence hypersecretion of LH and the other group of patients who are uniquely insulin resistant.

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Besides, PCOS is a multi-organ disorder and can give rise to long-term potential health risks. Endometrial cancer remains one of the more serious potential complications for women with polycystic ovarian syndrome. Obesity, hypertension (probably athero-sclerosis), and alterations

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in carbohydrate metabolism are all key features of the risk pattern for women with evidence of polycystic ovarian syndrome (3-9).

Management with Insulin Sensitizing Drugs

The discovery that insulin resistance has a key role in the pathophysiology of PCOS has led to a novel and promising form of therapy in the form of the insulin-sensitizing drugs, which will be discussed in-depth. The best method of treatment for these patients begins with weight reductions and life style modifications. In a group of patients, there will be need to add drugs which ameliorate insulin resistance (1, 2, 6, 7, 9-12).

The decision about the use of the therapy will depend on a number of factors

1. Age of the patient
2. Body Mass Index (BMI)
3. Menstrual history
4. Evidence of hirsutism
5. Interested in childbearing or not

Strategies to lower serum insulin concentrations include, possibly, oral insulin sensitizing agents such as metformin. The gold standard for improving insulin sensitivity in obese PCOS should be weight loss, by diet and exercise. Weight loss (of as little as 5%) alone can improve the fundamental aspects of the endocrine system of PCOS and result in low circulating androgen levels and spontaneous resumption of menses. Women with PCOS are like desert survivors, who fare better with less than their optimum weight. Many women will show spontaneous resumption of their menstrual cycle with weight loss alone. The mechanism of action of insulin sensitizers is by lowering the circulating insulin levels, which results in increased levels of SHBG and hence lowers androgens. This results in improved follicular growth, maturation and eventually ovulation and resumption of cyclical menstruation (7, 9, 11-13).

Table 1. Criteria taken into account when evaluating any therapy for PCOS

| Clinical Outcomes |
|---|
| <input type="checkbox"/> Body weight Index (BMI) & Waist-hip ratio (WHR) <input type="checkbox"/> Menstrual cyclicity <input type="checkbox"/> Spontaneous ovulation <input type="checkbox"/> Pregnancy <input type="checkbox"/> Acne-severity <input type="checkbox"/> Hirsutism <input type="checkbox"/> Side-effects experienced by patient |
| Biochemical Outcomes |
| <input type="checkbox"/> Fasting Blood glucose & GTT <input type="checkbox"/> Insulin levels <input type="checkbox"/> LDL & HDL Cholesterol <input type="checkbox"/> Triglyceride levels <input type="checkbox"/> Testosterone & the androgen levels <input type="checkbox"/> Plasminogen Activator Inhibitor levels (PAI-1) <input type="checkbox"/> FSH & LH levels <input type="checkbox"/> LH: FSH ratio |

Infertile PCOS

The first line of treatment is still clomiphene citrate (CC) in patients with PCOS and infertility. However, about 20-30% of patients will be resistant to CC therapy. Strategies to induce ovulation include weight loss, oral anti-estrogens, parenteral gonadotrophin therapy and laparoscopic ovarian surgery. There have been no adequately powered randomized studies to determine which of these therapies provides the best overall chance of an ongoing pregnancy. Women with PCOS are at risk of ovarian hyperstimulation syndrome (OHSS). Hence, insulin sensitizers today form an important part in the armamentarium for the management of PCOS.

Insulin Lowering Drugs

Many trials have specifically examined the effects of these drugs on ovulation, hyperandrogenemia, and metabolic features in PCOS, and some of these are discussed here (14-29). Women previously resistant to CC have shown evidence of ovulation and improved outcome after metformin therapy. Metformin has also been used with improved outcome in patients on gonadotrophin therapy with decreased incidence of OHSS in this group. Metformin has also been used in patient undergoing IVF cycles and shown a better clinical pregnancy rate and take home baby rate. There is also a decrease in the incidence of OHSS in these patients.

There are many studies now which suggest the beneficial effects of continuing metformin therapy in early pregnancy to reduce early pregnancy losses. In some patients who do not show adequate response with metformin, rosiglitazone has been tried with successful results. However, rosiglitazone cannot be continued in pregnancy and hence, therapy should be stopped once induction of ovulation is started.

Table 2. Insulin sensitizers in current practice

| |
|--|
| □ Metformin |
| □ Rosiglitazone |
| □ Pioglitazone |
| □ Troglitazone (withdrawn due to reports of hepatic infarcts and fatal liver failure.) |

More recently, insulin resistance has been found to be common in PCOS, along with an increased prevalence of other features of the "metabolic syndrome", namely glucose intolerance, type 2 diabetes mellitus, and hyperlipidaemia. Hyperinsulinaemia is likely to contribute to the disordered ovarian function and androgen excess of PCOS. Reducing insulin resistance by lifestyle modifications such as diet and exercise improves endocrine and menstrual function in PCOS. These lifestyle modifications are the best initial means of improving insulin resistance. The mainstay of managing insulin resistant PCOS is with insulin sensitizers (14-29). The commonest drug used is metformin in the dose of 1500-1700 mg/day in divided doses. Metformin is a biguanide which acts in PCOS by lowering the blood insulin levels and increasing insulin sensitivity. It has been shown to reduce serum concentrations of insulin and androgens, to reduce hirsutism, and to improve ovulation rates. It does not decrease blood glucose in non diabetic individuals.

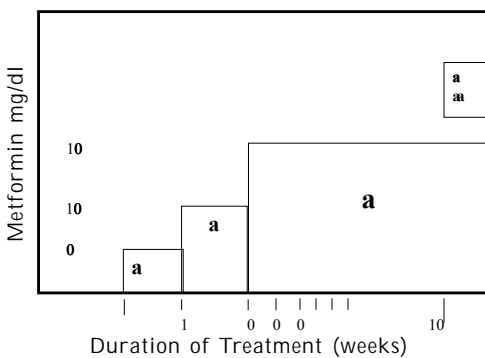


Fig. 1. Incremental Dosage with Metformin Therapy

Studies have shown that in amenorrhic women with PCOS and hyperinsulinemia, metformin therapy resulted in normal resumption of menses in most of patients. Kowalska et al (15) have suggested that, insulin-sensitizing therapy could be considered as an additional therapeutic option in obese women with PCOS.

In a randomized control trial by Batukan et al (16), at the end of the CC cycles 4.2% of patients got pregnant and 65.2% of the remaining group got pregnant with metformin plus CC cycles (p=0.0001). Heard et al (17), reported that, metformin alone in patients with PCOS results in a substantial number of pregnancies, with 69% (20/29) of those who ovulated conceiving in less than 6 months.

In a randomized, double blind study by Vandermolen et al (18), they concluded that "metformin therapy significantly improved ovulatory rates and pregnancy rates as compared to placebo therapy in ovulatory PCOS women who are resistant to CC".

Glueck et al (19), in patients of PCOS, suggest that the use of metformin is associated with a 10-fold reduction in gestational diabetes (31% to 3%). There are many more studies in literature, but it is outside the purview of this article to discuss them all in detail (20-29).

There are also some studies which do not seem to show any benefit from metformin and hence these seem to stress the need for larger and randomized studies for proving the efficacy of the use of metformin in patients with PCOS (26-28).

Sturrock et al (26), in their study failed to show any benefit from the use of metformin. Whereas the study by Yarali et al (27) seems to show that though Metformin may restore ovulation but, there was no improvement in insulin resistance in clomiphene citrate-resistant PCOS patients with normal glucose tolerance, and also has no significant effect on ovarian response during rFSH treatment. Homburg (28) in his review article suggest a note of caution in the over judicious use of metformin in PCOS. Insulin-sensitizing agents, predominately metformin, have been examined for their ability, in all patients with PCOS, to achieve similar beneficial changes to those induced by loss of weight in the obese.

Our Experience

At our clinic, we have used metformin therapy successfully in patients with CC resistant PCOS. We find that obese PCOS have a better response with metformin therapy than the lean PCOS. This may be as obesity itself causes insulin resistance, and compounds the metabolic changes of PCOS. The high pregnancy rate of our study population is consistent with the hypothesis that insulin resistance plays an important role in the pathogenesis of anovulation in patients with PCOS. Women with PCOS undergoing treatment with metformin alone, metformin combined with other methods of ovulation induction such as clomiphene citrate (CC) or gonadotropin injection were in this group. The total gonadotropin dose given to metformin-study group was significantly lower than the control group. In addition, duration of therapy, and plasma estradiol level on HCG-day in the study group was significantly lower than in the control group. This also decreased the incidence of moderate and severe OHSS in patients on metformin due to the lower E2 levels. Metformin is started in an incremental dose and the patient is asked to follow up after 7-10 weeks of therapy. Spontaneous resumption of regular cycles and/or evidence of ovulation is checked for. If not, in the next cycle CC therapy is started concomitantly in the dose of 50-100mg/day. If no evidence of ovulation with CC 100mg/day, then, the patients are put on gonadotropin therapy. We had 68 patients who were resistant to CC and were found to have insulin resistance and hence put on metformin therapy, in the year 2002-2003. I have not included those women who needed IVF in this group.

Table. Results from our centre for the year 2002-2003 for CC resistant PCOS

| Drugs used | N=68 | Pregnancy n=46 (67.6%) |
|------------------------------|---------------------|---------------------------|
| Metformin alone | 19 | 10 (14.7%) |
| Metformin with CC | 29 (26 ovulated) | 22 (32.3%) |
| Metformin with gonadotropins | 20 | 14 (20.5%) |

Conclusion

Polycystic ovary syndrome (PCOS) is a convergence of multi-system endocrine derangements. Impairment in insulin metabolism is a prominent feature of the syndrome

and appears to play a key pathogenetic role precipitating the cascade of other disorders associated with PCOS. The impairments in insulin metabolism appear central to the physiologic cascade of PCOS and in about 20-30% of patients CC fails. It is in this group that addition of insulin sensitizers like metformin has a definite therapeutic advantage. Insulin sensitizers and weight loss can be effective methods of inducing ovulation and pregnancy and may reduce the number of CC resistant PCOS who need gonadotropins, ovarian surgery or IVF with ET. Recent studies report that insulin-sensitizing agents, such as metformin, reduce hyperinsulinemia, reverse the endocrinopathy of PCOS and normalize endocrine, metabolic and reproductive functions, leading to the resumption of menstrual cyclicity and ovulation. Further properly planned, large, multi-centric, randomized double blind controlled trials with the primary end point of pregnancy or live-birth rate for an accurate assessment of insulin sensitizers in PCOS are required, to conclusively prove this hypothesis.

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| ED | NR | NR | □ 600-800 | NR | NR | NR | □ 10 |
| RA | NR | NR | □ 3000 | Variable | 2 | 2 | 30-35 |
| OA | □ 200 | 3-5 | □ 2000 | Standard | 4 | □ | 20-25 |
| SC | □ 100 | 3-5 | □ 1200 | Standard | 2 | □ | 10-15 |
| CR | < 50 | 3-5 | □ 600-800 | Standard | 1 | □ | □ 10 |
| DR | NR | NR | □ 1000 | NR | 1 | □ | □ 10 |

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