Metformin: a newer intervening agent for PCO
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**Introduction**
Polycystic ovarian syndrome is the most common cause of anovulatory infertility.\(^1\) It affects 5-10% of women in the reproductive age group.\(^2\) The disease is characterized by ovarian dysfunction, androgen excess and multiple cysts in the ovary. Clinically patients may present with oligomenorrhea, amenorrhea, infertility, hirsuitism, acne & obesity. Women with this syndrome have at least seven times the risk of myocardial infarction and ischemic heart disease than other woman, and by the age of 40 years upto 40% will have type -II diabetes or impaired glucose tolerance.\(^3\), \(^4\)

**Aetiology of PCO**
The aetiology of the condition is unknown but more recently, insulin resistance leading to hyperinsulinaemia & excess ovarian androgenesis has been indentified as the the principal underlying disorder. Principal insulin resistance is most evident in overweight patients. Studies have shown that over 30% of lean & 75% of obese women with PCOs are hyperinsulinemic.\(^5\) It is still not clear wheather hyperinsulinemia in all these women is secondary to insulin resistance. Further research in molecular biology revealed that there are two underlying defects in the insulin receptors, leading to insulin resistance and hyperinsulinemia. Type A syndromes is due to a point mutation in the DNA sequence coding for alpha & beta subunit of insulin receptor.\(^6\) Type B syndrome is due to the presence of autoantibodies against the insulin receptor that is often associated with other autoimmune disorders. From a clinical point of view, it is evident that hirsutism is a marker of hyperandrogenism and Acanthosis nigricans is a cutaneous marker of insulin resistance. Despite insulin resistance in adipose & skeletal muscle, the there is relative excess of insulin that enhance ovarian stimulation. Along with this elevated leutinising hormone (LH) concentration brings about thecal hyperplasia, increased androgen secretion, arrests of follicular development and eventually anovulation along with menstrual disturbances. Insulin acts on liver & decrease the production of sex hormone binding globulin (SHBG) & insulin like growth factor-I binding protein. A reduction in SHBG leads to an increase in free androgen level. This high level of free androgen interfere with the normal physiological fuction of the hypothalamo - pituitary ovarian axis, leading to increase LH level, anovulation, amenorrhea & infertility. On the other hand inhibition of production of insulin like growth factors-I binding protein results in an increased concentration of circulating free insulin like growth factor-I, further stimulating ovarian androgen production.\(^8\)

Insulin resistance also lead to an out head lipophytic response to insulin. It empairs the suppression of release of free fatty acid from adipose tissue. An increased flow of free fatty acid from central sites enter the portal circulation, increasing the availability of substance to the liver for triglyceride production. Woman with the syndrome also exhibit increased activity of hepatic lipase, that is responsible for the convention of large lipoprotein particle to smaller, more atheongemic species.

**Diagnosis of PCO**
Diagnosis of the disease can be done on the basis of common clinical features, confirmed by biochemical evidence of endocrine abnormalities and by exclusion of other possible etiologies.

**Clinical features**
- Oligomenorrhea or amenorrhea
- Dysfunctional uterine bleeding
- Anovulatory infertility
• Hirsutism and/or acne
• Central obesity

Clinical criteria suggesting insulin resistance are
• BMI greater than 27 kg/m²
• Waist to hip ratio > 0.85 or
• The presence of acanthosis nigricans

Laboratory tests
• Increased testosterone activity.
• Elevated L.H concentration with normal F.S.H concentration.
• Presence of insulin resistance is evidenced by elevated fasting insulin concentration and elevated glucose-to-insulin ratio. A significant issue is that the laboratory measurement of insulin is technically difficult.

Treatment: Treatment of PCO should address the following zones.
• Normalization of menstrual cycle.
• Treatment of infertility &
• Treatment of acne & hirsuitism.

Conventional Treatment of PCO
(1) The combined oral contraceptive pill (OCP) is commonly used to regulate menses. By increasing levels of sex hormone binding globulin (SHBG) and decreasing androgen secretion, it reduces the circulating free testosterone level. But many patients are overweight and obesity is a relative contraindication of OCP. So, this treatment may be unsuitable for obese patients with PCO.

(2) Hirsuitism is addressed by the use of the antiandrogen cyproterone acetate or spironolactone. Their principal mode of action is inhibition of the binding of dihydrotestosterone to its receptor at the hair follicle. Beneficial effects can be seen after 3 months but excessive hair growth returns soon after cessation of treatment, cyproterone acetate may exacerbate irregularity of menstrual cycle are unsuitable for use in those trying to conceive.

(3) Ovulation inducing drug clomiphene citrate is used for the treatment of infertility.

By inhibiting the estrogen mediated negative feedback loop of hypothalamus, it enhances secretion of F.S.H. But it carries an increased risk of multiple pregnancies. Also due to potential risk of ovarian cancer, it should not be continued more than 6 months. Those failing to conceive after clomiphene treatment usually respond to exogenous gonadotrophin, but this is expensive, not available, needs special care during therapy and is burdened with the risk of multiple pregnancy.

(4) Alternative to Medical treatment includes laser or electro cautery of the ovary.

Modern Concept of treatment of PCO
As there is good evidence to support the hypothesis that reduced peripheral insulin sensitivity & consequent hyperinsulimia are pivotal in the pathogenesis of the diseases, so the modern concept of treating PCO is to reduce the level of insulin.

It can be achieved by-
(1) Reducing body weight- weight reduction has multiple benifit for obese woman with PCO. The weight reduction decrease insulin resistance, corrects the hormonal imbalance, promotes ovulation & regular menses & improve the metabolic consequences of the disorder, but it seems to be hard to achieve.

(2) Insulin sensitizing agent, recent trials in different parts of the world has of the successfully process the efficacy of the drugs in treating PCO related problems.

Metformin: a biguanide, used in non-insulin dependent diabetes mellitus has been used most successfully. Troglitazone, a thiazolidinedione that improve muscle insulin sensitivity in muscle, has been studied, but has recently been removed from the market because of adverse effect on hepatic function. The key rational metformin for use of in women with PCO who are infertile is the presence of a positive correlation between the degree of insulin resistance & anovulatory infertility. It is thought that metformin by suppressing hepatic gluconeogenesis & improving insulin resistance, reduces ovarian
hyperandrogenemia & resistances normal ovarian steroidogenesis & PAI-1 levels, thus enhancing ovulation & improving fertility. It has also been shown to reduce systemic LH & PAI-1 levels, both of which increases the risk of miscarriage. It offers the real advantage over clomifen by avoiding the increased risk of multiple Pg (4-11%) and ovarian cancer (used >12 months) 14. First line use of metformin also avoid the cost associated with 2nd & 3rd line therapies for woman with PCO who are infertile, such as gonadotrophin used ovulation induction, laparoscopic ovarian drilling & in vitro fertilization (IVF). It acts by improving insulin sensitivity, lowered serum LH, total free testosterone concentration increased in serum FSH.

**Patient selection for metformin**

It is offered as a first line drug to all women with anovulatory infertility due to PCOs who have been trying to conceive for a year or more. Hypoglycaemia is extremely rare with if & patient are advised to look out for signs of hypoglycaemia & stop treatment this is suspected. General advise should be given to reduce weight (If BMI>30) stop smoking & alcohol. Pre & peri conceptional folic acid supplementation is given. Before prescribing metformin, renal & hepatic function should be checked as it may cause lactic acidosis, if there is mild renal impairment.

**Dose regimen**

The usual dose is 500mg TDS To minimise GIT upset women are advised to take the drug prior to meal & increase gradually from once daily. The optimal period of first line metformin monotherapy for fertility is debatable. It may be continued for 6 months if regular ovulation is documented. However if it has not been effective after 6 months of treatment, clomifene should be added for a further 6 month. Metformin should be stopped once Pg is confirmed. Where Pg has not occurred after 1 year at either metformin alone or metformin-clomifene combination therapy, then alternative treatment, namely laparoscopic ovarian drilling, gonadotrophin or in vitro fertilization, should be considered.

**Adverse effects & contraindication of metformin**

The main immediate adverse effects are gastrointestinal- anoroxia, nausea, vomiting & diarrhoea. Long term use may interfere with vitamin B12 absorption. It may provoke lactic acidosis specially in Patient with renal impairment. It is also contraincated in chemical conditions that predispose to lactic acidosis eg - severe dehydration, infection, shock, heart failure, recent MI, hepatic impairment & use of x-ray contrast media.

**Conclusion**

From many studies it can be concluded that, metformin can be offered to woman with PCOs who are anovulatory, whether obese or non-obese. It is suggested that first line metformin use is reasonable, particularly in the context of the hazards of 1st line clomifene use (ovarian cancer & multiple pg) with ovarian hyperstimulation. It has also been shown to reduce the risk of gestational diabetis in woman with PCOs. For the treatment of irregular menses caused by PCOs in women not attempting conception, it may restore ovulatory menses in the majority of the women. So, we can use metformin in the management of patients with anovulatory infertility in PCO before proceeding to ovulation induction with expensive & relatively risky drug like gonadotrophins as well as before in invasive and expensive treatment of ovarian drilling.

**References**

3. MJA: kidsom, polycystic ovary syndrome, a new direction in treatment (1-9) MJA 1998; 169; 537-540.
5. Kahn C R and Goldstein B J 1989, molecular defects in insulin action, science