Metformin Induced Resumption of Menses, Ovulation and Subsequent Pregnancy in Hyperinsulaemic Polycystic Ovarian Disease

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The polycystic ovary syndrome is a common cause of anovulatory infertility, women with severe insulin resistance are a unique subset of PCOD. The syndrome of hyper androgenism , insulin resistance and acanthosis nigricans (HAIR-AN-Syndrome) in one presentation of the insulin resistance subset of PCOD. In women with insulin resistance and hyperandrogenism associated anovulatory infertility fail to result in pregnancy by clomiphene citrate treatment. For these women, weight loss and insulin sensitizers (like metformin) can be effective method of inducing ovulation and pregnancy.

Key words: Polycystic ovarian syndrome (PCOS) hyperandrogenism, insulin resistance hyper insulinaemia

The components of polycystic ovary syndrome are hyperandrogenism (elevated serum testosterone, androstendione and anovulation (irregular or absent menstrual periods) in the absence of other causes of hyperandrogenic disorders such as adrenal hyperplasia and androgen secreting tumours. Patient with this syndrome may complain of abnormal bleeding, infertility, excess hair growth and acne. Laboratory evidence of hyperandrogenism includes increased free circulating testosterone concentration, decreased Sex Hormone Binding Globins (SHBG), increases Dehydro Expiandosterone (DHEAS), increased Luteinizina Hormone (LH) and decrease in Follocular Stimulating Hormones (FSH). Vaginal ultrasound shows enlarged ovaries with an increased number of small (6-10mm) follicles around the periphery.

Methods

A total of 4500 women were seen at outpatient department, out of which 650 were booked for treatment. Among these 650 booked patients 55(8.5%) were diagnosed as polycystic ovarian disease feature of PCOD:

Discussion

Hyperinsulin and PCOS?

It is not yet understood when one woman who demonstrate polycystic appearing ovaries on Transvaginal scan (TVS) has regular menstrual cycles with no sign of excess androgen while other develop Polycystic Ovarian Syndrome (PCOS). One of the unique subset of PCOS is insulin resistance accompanied by hyperinsulinaemia (Elevated fasting insulin level)[1,2].

There is increasing data that hyperinsulinaemia produces the hyperandro-genism of polycystic ovary syndrome by increasing ovarian androgen production, particularly testosterone and androstenedione and by decreasing SHBG concentration. Increased level of androgen interferes with the pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhoea and infertility. Hyperinsulinameia is also associated with increased BP, increasing clot formation and appears to be major risk factors for development of heart disease and type II diabetes.

Hyperinsulinaemia is a common endocrine abnormally observed in some women with PCOS. Elevated LH secretion is observed in the majority of women with PCOS. However, severe hyperinsulinaemia is only observed in a subset of women with PCOS[3].

How to detect insulin resistance and hyper insulinaemia

There is no clear consensus on how to detect insulin resistance and hyperinsulinaemia. Until both specific and sensitive laboratory tests are available, clinicians will need to use either clinical findings or simple laboratory tests such as fasting plasma insulin or fasting glucose to insulin ratio or both, to identify women with insulin resistance.

Table Physical finding associated with insulin resistance.

- Body mass index>27kg/m^2
- Waist to hip ratio >0.85
- Waist >100cm
- Acanthrosis Nigricans

A clincial trial was carried out at assisted conception unit of Services Hospital from January to december 2001. A total of 4500 women presented with infertility showing features of PCOS which included (oligomenorrhea, obsity, hirsutism acne and long standing infertility). In all these women after thorough history, hormonal profiles and TVS, PCOP was diagnosed. All women were looked for acanthosis nigricans and serum fasting insulin was done to see insulin resistance, which is a subset of PCOS. It was surprising that the presence of acanthosis nigricans is almost always indicative of insulin resistance, but many women with insulin resistance do not have acanthosis nigricane[6]. All these PCOD patients were given diet charts and excessive schedule to help them in reducing their weight. Women with plasma fasting level >10miu were started on metformin after certain tests like urea and creatinine.

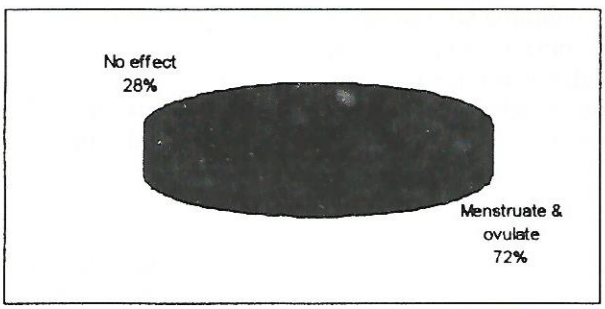
A commonly used dose of 500mg three times daily was used in women with clinical evidence of insulin resistance. To minimize gastrointestinal side effects, such as nausea, abdominal cramps and diarrhoea Metformin was started at 500mg daily for one week, followed by increasing dose upto 500mg 3 times daily for duration of 3-9 months. Regular follicular tracking and progestrone levels were measured periodically on appropriate days to determine whether ovulation has occurred or not. After 5-10 weeks of metformin. If ovulation has not occurred, then clomiphene 50mg daily for 5 days, was administered in conjunction with metformin. Those patients who became pregnant, metformin therapy were discontinued. Results were as follows.

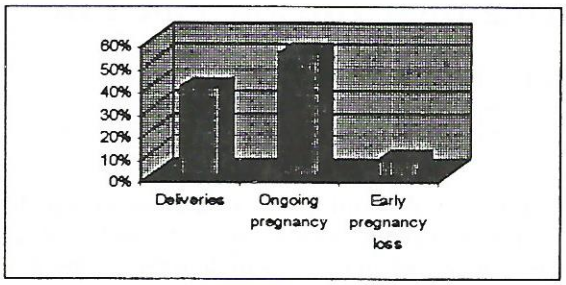
Results

Total of 55 women with POD were started on metformin 40(72%) of them started menstruating and ovulation within 3-9 months of their treatment. 13(24%) became pregnant. Outcome pregnancy were as follows:

Table 1. Outcome of patients indicated in the study.

	n=13	%age
Patient delivered	13	38
On going pregnancy	7	54
Early pregnancy loss at 29 weeks due to increase in blood pressure	1	7





Out come of menstruating ovulating patients.

Conclusion

Insulin sensitizing agents have been demonstrated to induce ovulation in infertile hyperandrogenic and insulin resistant women. Metformin showed increase in the number of ovulatory cycles in infertile women with hyperandrogenism and insulin resistance resulting into menstruation ovulation and subsequent pregnancies.

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