ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is one of the most common hormonal disorders affecting an estimated 10 percent of women of reproductive age and is a leading cause of infertility. Franks S. 1995. Nazir et al in 1999 have reported 20.7% prevalence of polycystic ovarian syndrome in Pakistan. One of the major biochemical features of polycystic ovary syndrome is insulin resistance accompanied by compensatory hyperinsulinemia (elevated fasting blood insulin levels). Women with polycystic ovarian syndrome are currently treated according to their presenting features but it is suggested by most of the researchers that endocrinopathy which is the main cause of all these symptoms can only be treated by reducing hyperinsulinemia.

Method: We studied 60 patients (age range 20-30yrs) and they were divided into group A group B. Group A was given Clomiphene Citrate and group B was given Metformin.

Result: A non-significant effect was observed between the two groups when %age of conception and abortion was observed. While considering the ovarian hyper stimulation syndrome (OHSS) a significant difference was seen that is 10% of patients in group A showed OHSS while non in group B.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common hormonal disorders affecting an estimated 10 percent of women of reproductive age and a leading cause of infertility (Franks S., 1995). The disease is not only common in the western world but also has an increased incidence in Pakistan as well. Nazir et al. (1999) have reported a prevalence of 20.7% in Pakistan. The syndrome is characterized by anovulation and hyper-androgenism (elevated serum testosterone and androstenedione). It is associated with menstrual disturbance and altered hormonal parameters, which lead many affected women of reproductive age to attend a gynaecology or infertility clinic (Dunaif A., 1997). The etiology of the condition is unknown, but recent evidence suggests that the principal underlying disorder is one of insulin resistance, with resultant hyperinsulinaemia (Velazequez, 1994). Patients with this syndrome may complain of abnormal bleeding, infertility, obesity, excess hair growth, hair loss and acne (Saeed, 1994). In addition to the clinical and hormonal changes associated with this condition, vaginal ultrasound shows enlarged ovaries with an increased number of small (6-10mm) follicles around the periphery (Polycystic Appearing Ovaries or PAO) (Clayton et al., 1991).

Hyperinsulinaemia and PCOS?

One of the major biochemical features of polycystic ovary syndrome is insulin...
resistance accompanied by compensatory hyperinsulinemia (elevated fasting blood insulin levels). There is an increasing evidence that hyperinsulinemia produces the hyper-androgenism of polycystic ovary syndrome by increasing ovarian androgen production (particularly testosterone) and androstenedione and by decreasing the serum sex hormone binding globulin concentration. The high levels of androgenic hormones interfere with the pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhea, and infertility (Utiger R.D., 1996 and Sattar N., 1998).

Women with polycystic ovarian syndrome are currently treated according to their presenting features such as irregular menses, hirsutism, or infertility but it is suggested by most of the researchers that endocrinopathy which is the main cause of all these symptoms can only be treated by reducing hyperinsulinemia. This would in turn lead to the reduction of basal and stimulated levels of leutinizing hormone and testosterone, thereby reducing anovulation and menstrual irregularity and helping in achieving fertility (Clark and Markaverich, 1999). Metformin, a biguanide often used in non-insulin dependent diabetes, has been the most commonly used drug for the treatment of polycystic ovarian syndrome that also improve fertility. It is an oral hypoglycemic agent that increases insulin sensitivity, and has been shown to reduce serum concentrations of insulin and androgens, reduces hirsutism, and improve ovulation rates. Some of the clinicians use clomiphene (in the patients having infertility due to PCOS) not for the treatment of PCOS but for the infertility that results in hyper stimulation of ovaries and multiple pregnancies (Velazquez, 1997).

MATERIALS AND METHODS

The present study was carried out in the Gynaecology and obstetrics department of Abbasi Shed Hospital in collaboration of Hamdard College of Medicine and Dentistry, Hamdard University, Karachi from January 2004 to June 2004. We enrolled 60 women who were 20 to 30 years old. All the women had polycystic ovary syndrome, as defined by oligomenorrhea (fewer than six menstrual periods in the previous year) and hyperandrogenemia (elevated serum free testosterone concentrations), and were obese. All had hirsutism. All had normal serum prolactin concentrations and normal results on thyroid-function tests. All the women had ultrasonography findings consistent with the diagnosis of the polycystic ovary syndrome. None had taken any medications for at least two months, and none had diabetes mellitus. Thirty women were randomly assigned (Group A) to receive Clomiphene Citrate 50 mg once daily starting from the second day of menstrual cycle for five days, with a gradual increase in dose up to 200 mg over four months period and 30 women (Group B) to receive metformin 500 mg once daily starting from the second day of menstrual cycle with increase in dose up to 1500 mg per day in two weeks for four months.

The subjects were evaluated for one year after getting enrolled and were observed for conception, abortion, OHSS and multiple pregnancies. Results were analyzed statistically.

RESULTS

Table-1 shows the comparison of mean values of demographic characteristics such as, age, weight, height, body mass index and smoker status, in Group A and Group B subjects No significant difference of age, weight, Height and BMI was observed.

Table-2 shows comparison of Conception in group A and group B. In Group A 43.3% (13/30) women conceived while 56.7% (17/30) did not. In-group B 50% (15/30) Women got pregnant and 50% (15/30) did not. The percentage of women getting pregnant is high in group B (Metformin treated) as compared to group A (Clomiphene treated).
Table 1
Comparison of Age, Weight, Height and BMI Status of Group A (Clomiphene Treated) and Group B (Metformin Treated) Subjects

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (years)</th>
<th>Weight (Kg)</th>
<th>Height (m)</th>
<th>BMI (Kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A 30</td>
<td>25.06 ± 2.15</td>
<td>75.0 ± 1.17</td>
<td>1.68 ± 0.02</td>
<td>26.57 ± 0.64</td>
</tr>
<tr>
<td>Group-B 30</td>
<td>26.47 ± 1.17</td>
<td>70.01 ± 1.96</td>
<td>1.65 ± 0.59</td>
<td>25.71 ± 0.59</td>
</tr>
</tbody>
</table>

BMI: Body mass index
The values are expressed as mean ± s.e.m. The number of observation and units are given in parentheses.

Table 2
Comparison of Percentage (%) of Conception between Group A (Clomiphene treated) and Group B (Metformin treated) Subjects

<table>
<thead>
<tr>
<th>Groups</th>
<th>Conceived</th>
<th>Did not Conceive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A 30</td>
<td>13 (43.3%)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Group-B 30</td>
<td>15 (50.0%)</td>
<td>15 (50.0%)</td>
</tr>
</tbody>
</table>

The values are expressed as %age. The number of observation and units are given in parentheses.

Table 3
Comparison of Percentage (%) of Abortion, OHSS and Multiple Pregnancies between Group A (Clomiphene Treated) and Group B (Metformin Treated) Subjects

<table>
<thead>
<tr>
<th>Groups</th>
<th>Abortion</th>
<th>OHSS</th>
<th>Multiple Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A 30</td>
<td>5 (16.7%)</td>
<td>3 (10%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Group-B 30</td>
<td>3 (10%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

OHSS=Ovarian Hyper Stimulatory Syndrome
The values are expressed as %age. The number of observation and units are given in parentheses.

Table 3 shows comparison of abortion, OHSS (Ovarian hyper stimulatory syndrome) and Multiple pregnancies between the two groups. In group A 16.7% (5/30) had abortion as compared to 100% (3/30) in Group B whereas OHSS 10% (3/30) and multiple pregnancies 10% (3/30) were only observed in group A (Clomiphene treated) women.

DISCUSSION
Polycystic ovary syndrome (PCOS) is classically characterized by ovarian dysfunction (oligomenorrhoea, anovulation and infertility), androgen excess (hirsutism and acne), obesity, and morphological abnormalities of the ovaries (cystic enlargement and stromal expansion). 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. (Glueck CJ, 1999; Kolodziejczyk B et al., 2000)

Metformin is a biguanide drug whose mechanism of action is poorly understood, but it is known to enhance the peripheral action of insulin without stimulating insulin secretion. The drug is widely used in type 2 diabetes mellitus. Metformin is claimed to have a multifactorial action, with prime effects on insulin sensitivity in both the liver (where it reduces basal hepatic glucose production) and in peripheral tissues (where it increases glucose uptake into muscle in the insulin-stimulated state after meals). It reduces blood glucose concentrations without causing hypoglycaemia (except when used with alcohol).

Two important randomized, double-blind, placebo-controlled trials of metformin therapy in women with PCOS have recently been published (Morin-Papunen Lc et al., 2000). In one, 23 women with PCOS randomly allocated to treatment with either placebo or metformin (500 mg three times daily) for six months showed significant benefits in menstrual pattern, ovulation rate, insulin sensitivity, serum free testosterone levels, and gonadotropin-releasing-hormone-stimulated 17-hydroxyprogesterone levels without changes in body weight. (Moghetti P, et al., 2000). Almost 50% of the women involved developed ovulatory cycles. In the other, 20 women with obesity and PCOS and 20 with obesity only were randomly assigned to either placebo or metformin therapy (850 mg twice daily) for six months. Metformin reduced visceral fat mass and improved glucose-stimulated insulin levels, hirsutism and menstrual pattern in those with PCOS (Pasquali R, et al., 2000; Acbay O and Gundogdu S., 1996). Our study was the observation of the outcome after the use of two different medicine in our local population and we observed that 50% women conceived and 50% did not in metformin treated group while in clomiphene treated group 43.3% conceived and 56.7% did not conceive. Similarly abortion rate was high in group A (16.7%) as compared to group B (10%), while OHSS and Multiple pregnancies were not observed in group B patients. These observations indirectly show improvement in insulin resistant, menstrual pattern, ovulation rate and insulin sensitivity which are in agreement with the above mentioned studies.

**CONCLUSION**

It is concluded that the rate of conception and abortion of the two medicines is more or less same but the OHSS and multiple pregnancies were only seen in clomiphene treated group. Therefore metformin is the better choice for the treatment of infertility in patients with (PCO) polycystic ovarian syndrome. More large scale local studies are required to evaluate the effects of metformin in PCO.

**REFERENCES**


(Glueck C.J., Wang P., Fontaine R. et al. (1999). Metformin-induced resumption of normal menses in 39 of 43 (91%)
previously amenorrheic women with polycystic ovary syndrome. *Metabolism.* 48: 511-519.


