PRESENTATION OF POLYCYSTIC OVARY SYNDROME AND ITS MANAGEMENT WITH CLOMIPHENE ALONE AND IN COMBINATION WITH METFORMIN

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Background: This study was carried out to determine the pattern of presentation of Polycysitc ovary syndrome (PCOS) in patients presenting at our unit and to compare effects of clomiphene alone and in combination with metformin in management of PCOS. **Methods:** This study was conducted was conducted from Jan 2001-2003 at Military Hospital, Rawalpindi. All patients presenting with infertility were evaluated with a view to select 100 patients of PCOS with the help of history of oligomenorrhoea, hirsuitism and acne. Diagnosis was confirmed by ultrasonography and hormone analysis (LH, FSH, prolactin, testosterone along with LH:FSH>2). The 100 selected patients were divided into two equal groups, one was given combined clomiphene citrate (CC) and metformin for ovulation induction and the other CC alone. These patients were followed for six cycles for ovulation and conception. Follicle tracking on ultrasonography and day-21 serum progesterone level were used to detect ovulation while conception was confirmed by urine pregnancy test, serum B - HCG level and ultrasonography for gestational sac. **Results:** Hirsuitism and oligomenorrhoea were the two most common clinical features of PCOS. In the first group 34 patients (68%) ovulated as compared with 18 (36%) in the second group. In the first group 18 out of 34 women (52.9 %) conceived as compared with only 8 out of 18 (44%) in the second group. The difference was significant at >0.05 when ovulatory and pregnancy responses were compared among two groups. All patients tolerated metformin well and no teratogenic effects were observed in patients who conceived after treatment with metformin. **Conclusion:** A combination of metformin and clomiphene citrate significantly increases the ovulation and conception rates in these patients.

KEY WORDS: PCOS, metformin, ovulation induction.

INTRODUCTION

Anovulatory infertility comprises about one quarter of patients attending an infertility clinic[1]. The polycystic ovary syndrome (PCOS) is the commonest endocrine disturbance leading to anovulatory infertility and oligomenorrhoea[2]. PCOS is characterized by the presence of enlarged ovaries with multiple small cysts (2-8 mm dia) and a hypervascularized androgen secreting stroma[3]. The disease is manifested clinically by signs of androgen excess including hirsuitism, alopecia, obesity and menstrual cycle disturbance either oligomenorrhoea or amenorrhoea[4]. Normal ovulatory mechanism which includes selection of an ovarian follicle which grows in response to appropriate secretion of FSH, becomes dominant and ovulates, gets disturbed in women with PCOS due to androgen excess and hyperestrogenism[5]. Ovarian overproduction of androgens is due to hyperinsulinism, and raised insulin levels are recognized as an important feature of PCOS[6]. Insulin lowering therapies such as metformin can bring improvement in insulin resistance and ovarian hypergonadism[7]. It has also been shown that the ovulatory response to clomiphene the elective drug for induction of ovulation can be increased in PCOS by decreasing insulin secretion with metformin[8].

The objective of this study was to determine pattern of presentation PCOS in patients presenting at our unit and to compare effects of clomiphene alone and in combination with metformin.

MATERIAL AND METHODS

One hundred cases of PCOS were selected out of all patients who presented with infertility at the Department of Gynaecology and Obstetrics, Military Hospital, Rawalpindi. All patients were counseled regarding the purpose and method of study. The diagnosis of PCOS was based on the presence of polycystic ovaries on ultrasonography with two or more of the following criteria,

- Oligomenorrhoea (<6 cycles in preceding year)
- hirsuitism
- hyperandrogensim
- Elevated LH or LH : FSH >2.

All other endocrinal causes of female infertility including congenital adrenal hyperplasia, Cushing syndrome, hyperprolactinemia and thyroid disease were excluded by relevant investigations. Tubal patency was confirmed by hysterosalpingography performed jointly by gynaecologist and ultrasonologist at the Department of Radiology Military Hospital, Rawalpindi.

The following hormonal investigations were performed on all patients,

- Serum FSH and LH level alongwith LH/FSH ratio
- Serum prolactin and testosterone
- Fasting serum insulin levels.

Semen analysis of the male partner to rule out male factor infertility was also carried out.

The patients were divided into two groups. First group of fifty patients were given Metformin (Glucophage-Efroze) 500 mg three times daily alongwith clomiphene citrate(cerophene-Hilton) 50 mg daily for five days starting from 2nd day of menstrual cycle. The second group comprising of fifty patients was started on clomiphene citrate 50 mg daily for five days starting on 2nd day of menstrual cycle. The first group was labelled as metformin plus CC group and the second only CC group. All patients were followed for six cycles for evidence of ovulation and conception. Ovulation was detected by follicle tracking on ultrasonography by experts who were blind to the therapy being given to the patients. Dominant follicles on 9th day with absent follicles on day 16th indicated occurrence of ovulation. Day-21 serum progesterone levels were noted and a value of >26 n mol/L (>8 mg/ml) was indicative of ovulation. Conception was confirmed by positive urine pregnancy test, serum B- HCG levels >25 miu/ml and presence of gestational sac on ultrasonography. All the hormonal investigations were done at the department of endocrinology Armed Forces Institute of Pathology, Rawalpindi by chemiluminescent essay method using DPC immulite kits Los Angeles USA.

The findings of both the groups were compared. These were analysed statistically by application of Chi-square test and student t-test. Descriptive data was analysed by SPSS version 10 Chicago USA.

RESULTS

Patient in the metformin plus CC group and CC group didn't differ significantly in age, age at menarche, duration and type of infertility (Table–1).

Table–1: Clinical data of women with PCOS In both groups

Demographic Data	Metformin –CC n = 50	Only CC n = 50
Age (yrs)	26.52±2.3	26.88±2.4
Menarche (age)	13.12±1.33	13.84±1.59
Duration of infertility	4.16±1.4	4.88±1.42
Primary infertility	56%	68%
Secondary infertility	44%	32%

Hirsuitism and oligomenorrhoea were the commonest clinical features seen in both study groups, other features are detailed in (Table - 2).

Table-2: Clinical features of women with PCOS in both groups

Clinical Feature	Metformin – CC n = 50	Only CC n = 50
Normal Menstrual Cycle	32%	28%
Amenorrhea	8%	4%
Oligomenorrhea	52%	64%
Polymenorrhea	4%	4%
Dysmenorrhea	52%	56%
Hirsuitism	64%	66%
Galactorrhoea	28%	32%

Baseline hormone profile and fasting insoulin level were found raised alongwith testosterone levels (Table - 3).

Table–3: Hormonal investigation for patients With PCOS in both groups

Hormonal Investigation	Metformin + CC Group n = 50	Only CC Group n = 50
Serum LH levels (mIu / ml)	12.67 + 4.14 up to 15	11.78 + 3.70
Serum FSH levels (mIu / ml)	6.16 + 4.14 up to 11	5.52 + 1.60
LH : FSH	2 : 1 > 2 : 1	2 : 1
Serum Prolaction (mIu / ml)	324.8 + 170.3 up to 470	251.44 + 149.75
Serum Testosterone (n mol / L)	0.8 – 3.2 n mol / L	0, -3.5n mol / L

In the study group receiving metformin 68% ovulated whereas 36% in only CC group. Ovulatory response varied in both groups. Rising trend was seen in metformin group and falling in CC group (Table-4). Different rates of conception were observed. 52.9% in first group and 44% in only CC group (Table – 5).

Table-4: Ovulatory response in patients with PCOS

Outcome	Metformin – CC n = 50	Only CC n = 50
No of women who ovulated	34	18
% of women who ovulated	68%*	36%

**: P<0.05*

Table–5: Conception rate in patients with evidence of ovulation

Outcome	Metformin – CC n = 34	Only CC n = 18
No of women who conceived	18	8
% of women who conceived	52.9%*	44%

**: P<0.05*

Out of the patients who received metformin only six had mild nausea and diarrhoea in the initial three weeks of treatment. None of the patients had severe side effects of lactic acidosis. No teratogenic effects were observed in patients who conceived after treatment with metformin for ovulation induction and ever its continuation upto 12 wks of pregnancy.

DISCUSSION

The most common clinical features of PCOS include menstrual irregularities, hirsuitism and obesity.[9,10]. In a study carried out by Balen et al[11] oligomenorrhoea was found in 47% of the cases whereas hirsuitism was present in 66.2% of the cases. These figures correlate well with our findings as far as hirsutism is concerned which was present in 65% of our cases. Oligomenorrhoea was present in 60% of our cases as compared to 47% in patients of Balen et al[11]. The reason for this lower frequency of oligomenorrhoea in patients of Balen et al was the presence of other menstrual irregularities like amenorrhoea in greater proportion in their patients. Amenorrhoea was present in 19.2% the patients of Balen et al as compared to 6% in our patients.

In a study carried out by Fauzia et al[12] on Pakistani patients oligomenorrhoea was found in 75% of their cases which is comparable to 64% in our cases. In the same study[12], hirsuitism was found in 84.6% of cases which is quite high as compared to 65% in our cases. The higher incidence of hirsuitism in the cases of Fauzia et al may be due to smaller number of patients (52) in this as compared to larger number of patients (100) included in our study.

Although amenorrhoea and oligomenorrhoea are the most common findings, normal menses may be present in PCOS,[11,13] Balen et al[11] found normal menses in 29.7% of their cases which is in agreement with our figure of 30% patients who had normal menses. The figures for normal menses in other two studies carried out by Goldzieher et al[10] and Lobo et al[13] are half of what was noted by Balen et al,[11] and our study. The reason may be a very strict criteria for selection of patients in the studies carried out by Goldzieher[10] and Lobo et al[13].

PCOS demonstrates the levels of sex steroids in relatively steady state in contrast to the fluctuating levels in normal menstrual cycle. An exaggerated response of serum LH to gonadotrophin releasing hormone as compared with that occurring in various phases of normal menstrual cycle has been well documented in PCOS since long.[14,15] As serum FSH may be low and LH may not always be elevated, it has been suggested that the use of the LH : FSH ratio would be most discriminatory for a hormonal diagnosis and a ratio of greater than two in the presence of suggestive clinical features and ultrasound finding is taken as diagnostic.[3,13] The increased LH in PCOS results from a heightened pituitary sensitivity to GnRH stimulation secondary to hyper-estrogenism.[16] This has been supported by statistical correlations observed by Lobo & Carmina[13] between estrogens and with LH and the LH : FSH ratio in PCOS. In our study a raised LH was found in 35% of cases which is comparable to 39.8% patients in study of Balen et al[11]. All our cases of PCOS had LH : FSH > 2. Another feature of hyperestrogenism in PCOS is mild increase in serum prolactin in

some patients[17]. In our study raised level of serum prolactin were found in 18% of the cases which is comparable to the figure of 12% in Lobo & Carmina.[13] Ovarian hyperandro-genism is a cardinal feature of PCOS and elevation of serum testosterone is a frequently encountered finding in these patients.[13]

The basic problem in the ovary is the conversion of normal estrogen microenvironment to abnormal androgen environment. This is due to failure of granulosa cells to convert testosterone produced by ovary to estrogen[18]. The androgen excess in PCOS is milder than that observed in ovarian tumours & hyperethicosis and circulating testosterone level doesn't generally exceed 150 ng/dl.[19] In our study all cases had raised serum testosterone levels which is in conformity with all other studies.

Insulin resistance giving rise to hyperandrogenism with resultant anovulation is a recently realized important pathogenetic mechanism in PCOS.[5,6,20] Insulin resistance occurs not only in obese women with PCOS, where it might be expected because obesity is often associated with insulin resistance, but also in 50% of normal weight women with PCOS.[21] Clomiphene citrate and gonadotrophins were most commonly used drugs for ovulation induction in PCOS, but realization of this pathogenetic mechanism has given a new direction to the treatment of PCOS with insulin sensitizing drugs, giving promising results and significantly higher success rates of ovulation and pregnancy[22,23] as compared with clomiphene citrate.[23,24] Among these drugs metformin is most widely used being safe without any teratogenic effects.[7,8]

After this new development many studies have been carried out world wide to establish the role of metformin in patients of PCOS[8,24,25], but only one such study on Pakistani population is available before our study.[26] In a study carried out by Vandermolen et al[24] 75% of the patients taking metformin and clomiphene citrate ovulated whereas only 27% of the patients taking CC only ovulated, conception rate in those who ovulated in metformin group was 75% whereas in only CC group it was 33%. In another study carried out by Malikawi and Qublan[25] ovulation rate (68.8%) in patients who took CC plus metformin were significantly higher than the patients who received only CC 25%. Pregnancy rates in metformin +CC and only CC group were 56.3% and 16.6% respectively. Imtiaz et al[26] studied the role of metformin in ovulation induction and subsequent conception in Pakistani patient of PCOS having hyperinsulinaemia, 72% of his patients ovulated within 3-9 months of treatment of metformin, and 32.5% of those who ovulated conceived. In our study, addition of metformin alongwith CC significantly increased the ovulation and the conception rate during six months treatment 68% of our patients who took a combination of metformin and CC ovulated whereas only 36% of the patients who received only CC ovulated. Conception rate in those who ovulated with metformin + CC was 52.9% as compared with 44% in cases who ovulated with clomiphene only. Our findings on the role of metformin in increasing the ovulation rate and subsequent conception are in agreement with the results of above quoted studies. [24-26] In our study comparatively increased ovulatory rates in the CC group was probably due to the fact that clomiphene resistance was not the criteria for enrollment in our study. Another limitation of our study is that we didn't screen the woman for insulin resistance and obesity was not a criteria for inclusion so our results are applicable to unselected PCOS patients.

CONCLUSION

Menstrual irregularities and hirsuitism are the two most common clinical presentation of PCOS.

A combination of metformin and clomiphene citrate significantly increases the ovulation and conception rates in these patients. Further studies in a larger population are needed to determine the minimum dose and length of treatment to achieve the desired effects.

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