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Effects on Menstruation Pattern of Polycystic Ovarian Syndrome (Pcos) Cases in a Comparative Study of Metformin and Pioglitazone.

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Abstract
Objective: *The present comparative study was aimed to evaluate the efficacy of Pioglitazone and Metformin in improvement of menstruation patterns in symptomatic cases of PCOS patients.*
Materials and methods : *The present study was a prospective , parallel group trial in 40 proven cases of PCOS , all the patients underwent clinical evaluations and detailed menstrual history at baseline .There were two groups in this study Group A (unmarried) and Group B (married) each divided in two subgroups each having 10 patients, A_1 (unmarried Metformin) A_2 (unmarried Pioglitazone), B_1 (married Metformin), B_2 (married Pioglitazone) therapy was given for six months with regular clinical evaluations and detailed menstrual history of the patients after every two months.*
Results: *The effect of both the drugs was comparable. The study results show that 80-90% of patients with duration of menstrual period less than 3 days were reverted back to normal duration of 3-5 days with both the drug. The amount of menstrual flow increased significantly with both the drugs and significantly more women showed higher flow with pioglitazone.*
Conclusion: *It can be concluded that a six month course of metformin and pioglitazone improves menstrual cyclicity in more than 90% cases of PCOS. Therefore insulin sensitizing agents are the rational drugs for the treatment of PCOS.*
Keywords: *oligomenorrhea, insulin resistance, hyperandrogenism*

I. Introduction

Polycystic Ovarian syndrome is one of the common abnormality in reproductive aged women, occurring globally in 6% to 10% of the population. [1, 2, 3]

According to revised guidelines of PCOS Consensus Workshop Group [4] : A women to be diagnosed with PCOS must have two of the following three manifestations; irregular / absent ovulation, elevated levels of androgenic hormones and/ or enlarged ovaries containing at least 12 follicles each. Polycystic ovaries are defined as those found on ultrasound to contain at least 12 or more follicles measuring 2 to 9 mm in diameter and / or have an increased volume of 10 ml or greater. Only one ovary fulfilling these criteria is enough to meet the definition of polycystic ovaries. It should be stressed that polycystic ovaries are not a necessary feature of PCOS and that many women with polycystic ovaries do not have PCOS.

An understanding of the pathogenesis of PCOS substantiates the concept that it seems to be a multigenetic disorder. Clinical studies support an increased frequency of PCOS in first degree relatives of affected women as suggested by a higher prevalence of glucose intolerance , insulin resistance , and hyperandrogenemia .[5-7]

Many candidate genes for PCOS have been proposed. A number of these genes may alter the hypothalamic-pituitary ovarian axis and the others may play a major role in the pathogenesis of insulin resistance and the associated phenotype of this heterogeneous disorder. [8] Recent studies have demonstrated a candidate gene near the insulin receptor gene locus. [9, 10] There are no pathognomic characteristics of the syndrome, but the combination of oligomenorrhea and clinical or biochemical finding of androgen excess are most commonly noted.

The association between hyperinsulinaemia and PCOS was first noted by Burghen et. al in 1980 who found a significant positive correlation between insulin , androstenedione and testosterone levels among PCOS women. [11 ,12] It is estimated that 20-40 % of PCOS women have impaired glucose tolerance , a number approximately seven fold higher than the rates in age and weight matched women. [13, 14] Secondary hyperinsulinaemia is the key factor responsible for the hyperandrogenism characteristics of the syndrome , [15 ,16] which is attributed to an increased stimulation of the activity of the cytochrome $P_{450c\ 17\alpha}$ in the ovary. [17]

Because insulin resistance is a cardinal feature of PCOS, one therapeutic approach is to use drugs to improve insulin sensitivity and ovarian function.

Insulin sensitizing agents improve insulin action by increasing insulin sensitivity thereby decreasing hyperinsulinemia. Since almost all care insulin resistant and present with some degree of fasting or stimulated hyperinsulinaemia, the use of insulin sensitizers could therefore be suggested in most patients with PCOS.

The task force of AES 2006 [18] recognised four key features of PCOS: 1) ovulatory and menstrual dysfunction, 2) hyperandrogenaemia, 3) clinical features of hyperandrogenism and 4) polycystic ovaries. Clinically evident menstrual dysfunction, such as oligomenorrhea or abnormal uterine bleeding, can be observed in a majority of patients with PCOS. In large series of patients diagnosed with PCOS, approximately 75% have clinically evident menstrual dysfunction. [19-21]

An inappropriate gonadotropin secretion is associated with the classic form of PCOS. Compared with the follicular phase of the normal menstrual cycle, women with PCOS exhibit a disproportionately high LH secretion with relatively constant low FSH secreation [22 , 23] which leads to menstrual irregularities.

Several studies have been done with use of metformin in cases of PCOS which observed significant restoration or amelioration in menstrual cyclicity .[Velazquez et al [24], Glueck (1999) [25], Vibikova et al (2001) [26], Eisenhardt et al (2005) [27], Zafar (2006) [28], Sahin et al (2007) [29] but a few studies have been done to establish the role of pioglitazone in restoring the menstrual cyclicity in cases of PCOS. Therefore the present work was planned in the form of a clinical comparative study on the effects of Metformin and Pioglitazone in establishing menstrual regularity in cases of PCOS.

II. Materials And Methods

The present study is a prospective, parallel group comparative trial in 40 proven cases of PCOS. The study was carried out in department of gynaecology and obstetrics of tertiary level of hospital after taking approval from ethics committee. There were two groups in this study (Group A and Group B) each divided in two subgroups (subgroup A_1 A_2 and subgroup B_1 B_2).

Group A included 20 unmarried women with PCOS, who attended the OPD with complaints like menstrual irregularities, weight gain and cosmetic problems. Group A was randomly assigned to Metformin 500 mg thrice a day (subgroup A_1) or Pioglitazone 45 mg per day orally (subgroup A_2).

Group B included 20 married women with PCOS, who attended the OPD with complaints like menstrual irregularities, weight gain and cosmetic problems. Group B was randomly assigned to Metformin 500 mg thrice a day (subgroup B_1) or Pioglitazone 45 mg per day orally (subgroup B_2).

All the subgroup received continued treatment for 24 weeks.

Evaluation And Follow Up: All the patients underwent clinical evaluations and detailed menstrual history at baseline . Patients were evaluated after every two months, Visit 2, 3&4 were performed after 2, 4&6 months of the treatment respectively.

The menstrual patterns were according to Van Hoaff et al (1999) [30]

Regular Cycles : Length of cycle between 21 & 41 days.

Irregular Cycles

Oligomenorrhoea : Length of cycle between 42 & 180 days

Polymenorrhoea : Length of cycle 21 days or less.

Amenorrhoea : absence of menstruation for 180 days or more (two or more such irregularities during the past year).

During the study period , record of menstrual bleeding was maintained of each PCOS patient. Women were asked about duration of bleeding , length of cycle (number of days from beginning of menstrual period to the beginning of next one). Normal menstrual blood loss during one cycle is 30-60ml and number of pads and tampons changed normally is 3-6 times a day. But counting of number of pads is not a reliable method [31] so the subject's own perception was carefully recorded. Perceived daily blood loss volume was rated on a 4-point rating scale [32] as follows

Spotting : 2.5 ml

Light : 5.7 ml

Moderate : 16.1 ml

Very Heavy : 22.0 ml

The total volume of blood loss during one period was calculated by adding this daily volume of blood loss.

Menstrual bleeding before and by the end of the study period was blindly scored as amenorrhea, irregular menses or regular menses. The evaluation of increased regularity of menstrual cycles was based on this scoring procedure because other measures of evaluation were not reliable.

Statistical Analysis:

To consider the effect of drugs on menstrual cycle (non parametric data) chi square test (χ^2 test) was used.

$$\chi^2 = \frac{\sum(O-E)^2}{E}$$

where O refers to observed frequencies and E refers to the expected frequencies.

III. Results

Effect on menstruation cycle has been observed under these three headings:-

A. Interval between two periods.
B. Duration of one period.
C. Menstrual flow.

A. Interval between Two Periods

It has been observed that subjects of the two groups at the baseline have the irregular periods. After prescribing metformin to subgroup A_1 (unmarried metformin group) the number of subjects with regular menstrual cycle increased significantly ($\chi^2 = 8.80$ &P = 0.03)

After prescribing pioglitazone to subgroup A_2 (unmarried pioglitazone group) the number of patients with regular menstrual cycle increased significantly. ($\chi^2 = 14.66$ & P =0.001)

After prescribing metformin to subgroup B_1 (married metformin group) the number of subjects with regular menstrual cycle increased significantly ($\chi^2 = 9.04$ & P =0.002)

After prescribing pioglitazone to subgroup B_2 (married pioglitazone group) the number of patients with regular menstrual cycle increased significantly. ($\chi^2 = 12.29$ & P =0.001)

After prescribing metformin to subgroup B_1 (married metformin group) the number of patients with regular menstrual cycle increased significantly.

After prescribing pioglitazone to subgroup B_2 (married pioglitazone group) the number of patients with regular cycle increased significantly.

B. Duration of One Period

Duration of normal period is between 3-5 days. But all the patients at the baseline in both groups have the duration of one period less than 3 days. After the drug treatments the duration had been changed significantly in all four subgroups.

After prescribing metformin to subgroup A_1 (unmarried metformin group) the number of patients with duration of flow for 3-5 day cycle increased significantly.($\chi^2 = 13.14$ & P = 0.0001)

After prescribing pioglitazone to subgroup A_2 (unmarried pioglitazone group) the number of patients with duration of flow for 3-5 days cycle increased significantly.($\chi^2 = 23.2$ & P =0.0001)

After prescribing metformin to subgroup B_1 (married metformin group) the number of patients with duration of flow for 3-5 days cycle increased significantly.($\chi^2 = 23.2$ & P =0.0001)

After prescribing pioglitazone to subgroup B_2 (married pioglitazone group) the number of patients with duration of flow for 3-5 days cycle increased significantly. ($\chi^2 = 17.27$ & P =0.0001)

C. Amount of Menstrual Flow

After prescribing metformin to subgroup A_1 (unmarried metformin group) the number of patients with amount of flow for cycle increased significantly.($\chi^2 = 1.79$ & P = 0.61)

After prescribing pioglitazone to subgroup A_2 (unmarried pioglitazone group) the number of patients with amount of flow for cycle increased significantly.($\chi^2 = 2.99$ & P = 0.39)

After prescribing metformin to subgroup B_1 (married metformin group) the number of patients with amount of flow for cycle increased significantly.($\chi^2 = 9.81$ & P = 0.02)

After prescribing pioglitazone to subgroup B_2 (married pioglitazone group) the number of patients with amount of flow for cycle increased significantly.($\chi^2 = 23.2$ & P = 0.0001)

IV. Conclusion

Clinical evident menstrual dysfunction has been diagnosed with PCOS women which is in the consequence of the key features like chronic anovulation and hyperandrogenism. The main culprit behind these features is hyperinsulineaemia.So insulin sensitizers play a key role in establishment of menstrual irregularities.From the above results it can be concluded that both metformin and pioglitazone therapy ameliorates regularization of menstruation in PCOS.The amount and duration of flow is improved.Also the irregular cycles are now more regularized so it is likely that anovulatory menstrual cycles becomes ovulatory in these women when this treatment is given for a longer time.

V. Discussion

PCOS is a common disease characterized by altered (anovulatory) menstrual cycle and infertility. In fact, it is one of the important causes of infertility at the young age in women. [33, 34] The cause of PCOS is not certainly known but endocrine disturbances particularly insulin and female sex hormone levels are altered. There is evidence of insulin resistance and hyperandrogenism [12-15]

Use of Metformin and Pioglitazone in the treatment of PCOS is suggested because there is evidence of glucose intolerance and hyperinsulinemia and this is reversed by these drugs.[35-42] Infact, in a number of reports, efficacy of both the drugs have shown in the treatment of PCOS. In 1994 metformin was tried as a first ant diabetic drug for the treatment of PCOS.[43] Subsequently many aspects of meformin were explored by several workers (Nestler et al [17], De Leo [44], Glueck [25], Moghetti et al [45] Stadtmauer et al [46] , Kock et al [47], Shamsa Zafar [28] and Pillai et al [48]) Pioglitazone, another insulin sensitizer of thiazolidinediones class was also found to be effective in PCOS by Guido [49], Glintberg,[50] Christan Haigh [51] and Romouldi [52]

In the present study, subjects were divided into two groups; group A (n=20), unmarried, group B (n=20) married. Each group was further subdivided according to the treatment schedule. 10 unmarried women received Metformin after initial evaluation and remaining 10 received Pioglitazone in unmarried group. Similarly, out of 20 subjects in married group (group B), 10 received metformin and remaining 10 received pioglitazone. One patient from each subgroup dropped out from the study. Therefore 18 unmarried patients and 18 married patients completed the study.

The impact of the therapy was visible on menstrual pattern when Metformin 500 mg three times a day and Pioglitazone 45mg /day were given on daily basis for 6 months.

Effect on menstrual flow,duration and intermenstrual interval.

The menstrual cycle was grossly disturbed at visit 1 in PCOS cases as shown in above tables. The amount of blood flow was reduced (scanty menstrual), intermenstrual period was very irregular and ranged from 45-60 days and duration of each period was reduced (< 3 days). These effects are perhaps due to the influences of disregulated sex hormone levels, the notable being elevated LH levels. Normal ovulation is the correlated in midcycle LH surge. However the levels subsequently should decline for menstruation to occur. Women with PCOS exhibit a disproportionately high LH secreation with relatively low FSH secreation. [53, 54] This increased LH pulse frequency in PCOS is independent of body mass index (BMI) or adiposity. [55,56] The underlying cause of this pattern of gonadotropin secretion is linked to an accelerated gonadotropin releasing hormone (GnRH) pulse generator activity in hypothalamus and heightened pituitary response to elevated GnRH. The mechanism (s) underlying the abnormal regulation of GnRH in PCOS women has remained unclear.

It has been postulated that altered inputs to the GnRH neuronal system by insulin, IGFs and/ or sex steroids during critical development phase of adrenarche/pubertiy may induce a disregulation of GnRH pulse generator activities, a proportion constant with observations made in peripubertal girls with PCOS [57,58] These studies therefore show that persistent LH levels disrupts the menstruation cycle. Velazquez et al (1997) assessed the effect of metformin for a period of 6 months in 22 women. Restoration of menstrual cyclicity (97.7%) was observed. 13 out of 15 women who had regular menses demonstrated a serum progesterone levels within the ovulatory range (3.1-28 mg/ml).[24]

Glueck (1999) reported metformin induced resumption of normal menses in 39 of 43 previously amennoric women with PCOS in the conchrane register. [25]

Vibikova et al (2001) evaluated adrenal and ovarian steroidogenesis before and after long term (27 +/- 4 weeks) treatment. 24 women with metformin (1000 mg/day) using adrenocorticotropin (ACTH), GnRH analogue and oral glucose tolerance (OGTT) tests. The results were : in 58% of women a significant improvement of menstrual cyclicity was observed. [26]

To evaluate the early potential effects of metformin treatment, their time of onset and the rate of insulin resistance metformin efficiency Eisenhardt et al (2005) had randomly allocated 45 oligo/anovulatory Pcos women to receive either metformin or placebo and assessed before and after 4 weeks in a treatment period of 12 weeks. The main outcome criteria menstrual disturbances was successfully improved in the metformin treated group depending on insulin resistance (12/15 vs 3/17) while women without insulin resistance (4/7)Vs 4/6 had to significant amelioration of their menstrual irregularities (P0.05) Estradiol levels increased continuously only in the treatment group (P<0.005) indicating an improvement of ovulatory function. Insulin sensitivity improved within 4 weeks after beginning of metformin. [27]

Zafar (2006) conducted a study in 50 women with PCOS metformin at a dose 1500 mg/day for 6 months. Menstrual cyclicity, fasting insulin and blood sugar levels, medluteal progesterone to assess ovulation and weight in Kg were measured after 6 months. Menstrual cycles were established in 86% women. [28]

Sahin et al (2007) evaualated the effects of metformin therapy in lean women with PCOS in a prospective clinical study. 2550 mg/day of metformin was administered for 6 months in 20 non obese PCOS women. Before and after the treatment metabolic parameters were evaluated. There was decreased LH, total testosterone, free

androgen index, slightly increased SHBG levels. Metformin treatment resulted in resumption of regular menses in 12 (60%) patients. [29]

Romoualdi et al (2003) evaluated the effectiveness and safety of pioglitazone (45mg/day) on clinical and endocrine-metabolic features of PCOS. In 18 obese PCOS patients. [52]

The effect of both the drugs was comparable and effective in restoring menstrual cycle in pcos which is in accordance to earlier studies . The study results show that 80-90% of patients with duration of menstrual period less than 3 days were reverted back to normal duration of 3-5 days with both the drug. The amount of menstrual flow increased significantly with both the drugs and significantly more women showed higher flow with pioglitazone. Therefore, it can be concluded that a six month course of metformin and pioglitazone improves menstrual cyclicity in more than 90% cases of PCOS.

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Table1:Comparison of menstrual regularity in number of patients in subgroups of the unmarried groups & married groups using chi square test.

(A_1=unmarried metformin group A_2= unmarried pioglitazone group B_1= married metformin group B_2= married pioglitazone group)

	Visit 1		Visit 2		Visit 3		Visit 4		χ^2 value P value
	Regular	Irregular	Regular	Irregular	Regular	Irregular	Regular	Irregular	
A_1	0	9	0	9	2	7	4	5	$\chi^2 = 8.80$ P = 0.03
A_2	0	9	0	9	3	6	6	3	$\chi^2 = 14.66$ P =0.001
B_1	0	9	0	9	3	6	4	5	$\chi^2 = 9.04$ P =0.002
B_2	0	9	0	9	4	5	5	4	$\chi^2 = 12.29$ P =0.001

Table 2: Comparison of duration of one period in number of patients in subgroups of the unmarried groups & married groups using chi square test.

(A_1=unmarried metformin group A_2= unmarried pioglitazone group B_1= married metformin group B_2= married pioglitazone group)

	Visit 1		Visit 2		Visit 3		Visit 4		χ^2 value
	<3days	3-5 days	<3days	3-5 days	<3days	3-5 days	<3days	3-5 days	P value
A_1	7	2	8	1	5	4	1	8	χ^2 = 13.14 P = 0.0001
A_2	9	0	8	1	4	5	0	9	χ^2 = 23.2 P =0.0001
B_1	8	1	8	1	5	4	1	8	χ^2 = 15.42 P =0.0001
B_2	8	1	7	2	4	5	0	9	χ^2 = 17.27 P =0.0001

Table 3: Comparison of amount of flow in one period in number of patients in subgroups of the unmarried groups & married groups using chi square test.

(A_1=unmarried metformin group A_2= unmarried pioglitazone group B_1= married metformin group B_2= married pioglitazone group)

	Visit 1		Visit 2		Visit 3		Visit 4		χ^2 value
	Spotting	Light	Spotting	Light	Spotting	Light	Spotting	Light	P value
A_1	6	3	6	3	4	5	2	7	χ^2 = 1.79 P = 0.61
A_2	5	4	4	5	4	5	1	8	χ^2 = 2.99 P = 0.39
B_1	9	0	6	3	4	5	3	6	χ^2 = 9.81 P = 0.02
B_2	9	0	5	4	1	8	0	9	χ^2 = 23.2 P = 0.0001