ORIGINAL ARTICLE

Effect of Metformin Versus Diet and Exercise on Ovulation & Menstrual Regularity in PCOS

Nasim Karim, Khalid Mustafa, Talea Hoor, Riffat Farooqui

ABSTRACT:

Objective: To compare the effects of metformin with diet & exercise on ovulation & menstrual regularity in PCOS infertile women .
Study Design: Randomized clinical trial.
Place & Duration of study: Private hospital infertility clinic at Karachi from 2001-2004.
Patients & Methods: One hundred & eleven PCOS women with primary infertility were enrolled. and divided into group A & B with 57 & 54 patients respectively. Group A received tablet metformin 500mg thrice daily along with diet & exercise advice while group B was kept on diet & exercise alone (30-60 minutes walk daily & avoidance of oily foods, red meat & bakery products) for a period of 90 days. Menstrual regularity & plasma progesterone level were evaluated at day-0 and day-90. Fasting serum glucose, insulin, follicle stimulating hormone, luteinizing hormone, prolactin, testosterone & ultrasound pelvis were done at day- 0 for diagnosis of PCOS.
Results: 100 patients completed the study. 50 patients in each group.In group A, 44 (88%) patients developed regular cycles with statistically significant increase in serum progesterone whereas in group B only 3(6%) patients developed regular cycles with non-significant increase in serum progesterone level from day-0 to day-90. Group A showed ovulation in 82% patients in comparison to Group B where ovulation occurred in only 6% of patients.
Conclusion: Metformin produced beneficial effects in comparison to diet & exercise alone in PCOS infertile women.
Key Words: Polycystic ovary syndrome , Metformin, Diet & exercise, Menstrual regularity, Ovulation.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a prevalent disorder that affects approximately 6-10% of women of child bearing age.[1,2]Insulin resistance and hyperinsulinemia appears to play an important pathogenic role in both obese and lean women with PCOS.[3,4,5] These women are at increased risk for type II diabetes, dyslipidemia, hypertension & atherosclerosis due to associated insulin resistance.[6,7,8]It is characterized by chronic anovulation with either oligomennorhea or amenorrhoea & hyperandrogenism.PCOS is the most common cause of anovulatory infertility.[9] There is ample evidence that hyperinsulinemia results in increased ovarian androgen biosynthesis in vivo and in vitro and decreased sex hormone binding globulin (SHBG) synthesis from the liver, leading to increased bioavailability of free androgens [10]. This excess in local ovarian androgen production augmented by hyperinsulinemia causes premature follicular atresia and anovulation [11]

Hyperinsulinemia may have a direct effect on the hypothalamus and/or pituitary to increase serum luteinizing hormone (LH) concentrations and therefore indirectly increasing LH-dependent ovarian androgen biosynthesis possibly resulting in abnormal LH and follicle stimulating hormone (FSH) release and subsequent oligomenorrhoea. Hyperinsulinemia may also directly affect the folliculogenesis and may arrest growth of antral follicles after they have reached a diameter between 5 and 8 mm.In PCOS serum concentration of estradiol lie within the normal ranges for the early follicular and midfollicular phases of the cycle[12] but the pattern of secretion differs from that in the normal menstrual cycle because there is no pre-ovulatory or midluteal increase in estradiol concentrations. The action of estradiol on the hypothalamic pituitary axis and on the endometrium is unopposed because of a lack of cyclical progesterone secretion [13].

A pathophysiologically rationalized therapeutic approach should take into account the fact that reproductive and cardiometabolic abnormalities coexist in PCOS[14]. Metformin have been introduced as a pharmaceutical option targeting not only insulin resistance (IR), but several other aspects of the syndrome including reproductive abnormalities.[15] It decreases hyperstimulation & cycle cancellations.[16]It appears to affect the ovarian function in a dual mode, through the alleviation of insulin excess acting upon the ovary & through direct ovarian effects. This later effect directly stimulates several steroidogenic enzymes in the ovary like 17α hydroxylase/ 17, 20- lyase and 3β-hydroxysteroid dehydrogenase, P450 side chain cleavage and StAR protein.[17]Insulin action on steroidogenesis at the ovary is presumed despite the co-existance of peripheral insulin resistance.[18] Lifestyle intervensions focusing predominantly on diet & physical exercise is considered the first line treatment for metabolic complications in overweight & obese women with PCOS & may have the potential to improve ovulatory function.[19] Shedding even a modest amount of weight may help.Loosing less than 10% of initial body weight has been shown to cut high levels of body fats and blood sugar. Weight loss also improves insulin resistance.[20] Thus insulin resistance & associated compensatory hyperinsulinemia play a central role in the pathogenesis of PCOS. [21]

✉ **Nasim Karim**
Professor of Pharmacology, BUMDC, Karachi
Email:nsm_karim@yahoo.com

Khalid Mustafa
Associate Professor, Pharmacology, BUMDC, Karachi

Talea Hoor
Asst. Professor, Pharmacology, BUMDC, Karachi

Riffat Farooqui
Assistant Professor, Pharmacology, BUMDC, Karachi

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With this background present study was designed to evaluate the effect of metformin in comparison to diet & exercise on ovulation & menstrual regularity in patients having polycystic ovarian syndrome.

SUBJECTS AND METHODS

The clinical trial was carried out from 2001-2004 in which 111 women were selected from an infertility clinic of a private hospital at Karachi. Eligibility criteria included women of reproductive age group with ages between 20-40 years having primary infertility, oligomenorrhoea, obesity, hirsutism, fasting hyperinsulinemia (>10µU/ml) and fasting serum sugar level < 6.1mmol/L as ≥ 6.1mmol/L is WHO diabetic criteria, 2000.Consent was taken from each study participant before they were enrolled in the study.Preliminary data, date of follow up visit & laboratory investigations were recorded on a specially designed proforma. The patients were divided into two groups A & B randomly.Even number of proformas for group A (57 patients) metformin treated group & odd number of proformas for group B (54 patients) diet & exercise treated group.Tablet metformin HCl (escalation dose) was started at 500mg once daily per orally for one week & was increased to thrice daily for a period of 3months. The initial week was excluded from the study.Group B patients were advised for exercise (30-60 minutes walk daily) & change in diet pattern (avoidance of oily foods, red meat & bakery products). Menstrual cyclical changes were noted & serum progesterone was evaluated at day-0 & day-90 of the study as an indicator of ovulation (progesterone cut off value for ovulation was ≥ 4ng/ml).

Analytical method: Analysis for the serum progesterone was performed on automated random access immunoassay analysis "Immulite" from Diagnostic Product Corporation (DPC) by using commercial kits supplied by DPC.

Statistical Analysis: The observations were recorded on day 0 and day 90 for menstrual cyclical changes and serum progesterone (P). Statistical evaluation was done by using student (paired) t-test utilizing SPSS Version 10

RESULTS

A total of 100 patients completed the study period with 50 patients in each group. All patients presented in the infertility clinic with complain of no issue that is they had primary infertility. In group A out of 50 patients 35 (70%) had oligomenorrhoea & 15 (30%) had irregular cycles. In group B out of 50 patients 41 (82%) had oligomenorrhoea & 9 (18%) had irregular cycles (Table 1).

Physiological, metabolic, endocrinologic parameters along with clinical features & ultrasound pelvis were done for making diagnosis of PCOS in Group A and B (Table 2a, 2b)

In group A following 90 days of treatment with metformin 33 (66%) patients out of 35(70%) developed regular cycles, while 2 (4%) patients had no change. Out of 15 (30%) patients who had irregular cycles at day-0, 11 (22%) patients showed regularity in their cycles at day-90 while 4 (8%) patients had no change in their menstrual cyclicity. In group B after 90 days of diet & exercise treatment 39 (78%) patients out of 41(82%) had no change, while 2 (4%) patients developed regular cycles. Out of 9 (18%) patients with irregular cycles only 1(2%) patient showed regularity in cycles. (Table3).

In group A serum progesterone level showed an increase from a mean ±SD of 1.3±0.3ng/ml to 9.5±5.1ng/ml from day-0 to day-90. On statistical evaluation it was found to be significant with P-value of 0.001. In group B serum progesterone level showed an increase from a mean ±SD of 1.6±0.6 to 1.74±1.1ng/ml from day-0 to day-90. On statistical evaluation it was found to be non-significant with P-value of 0.067 (Table 4).

All patients (100%) showed increase in their progesterone level in group A but in group B 32(64%) patients showed increase, 17 (34%) patients had a decrease & 1(2%) had no change in the serum progesterone level (Table 5).

This increase in serum progesterone was divided into 2 groups (a) < 4 ng/ml and b) > 4 ng/ml. In group A 9 (18%) patients had an increase which was < 4 ng/ml while 41 (82%) patients had an increase which was > 4 ng/ml. This latter value was taken consistent with ovulation. In group B 48 (96%) patients had serum progesterone level < 4 ng/ml while 2 (6.25%) patients had an increase in level which was > 4 ng/ml. This latter value was taken consistent with ovulation (Table 6).

DISCUSSION

The etiology of PCOS remain obscure & the variability in phenotype expression continues to render the clinical care & research concerning this heterogenous condition challenging.[22]In women with PCOS the ovary does not make the hormones needed for the eggs to fully mature. Follicles may start to grow and build up fluid but none of the follicle becomes large enough. Instead some follicles may remain as cysts. Since no follicle becomes large enough and no egg matures or is released, ovulation does not occur and the hormone progesterone is not made. Without progesterone, a woman's menstrual cycle becomes irregular or ceases. In addition the cysts so produced make male hormones, which also prevent ovulation in thse women[23].

In group-A the metformin treated group 35 (70%) patients had oligomenorrhoea and 15 (30%) had irregular cycles and anovulation as confirmed by their low serum progesterone levels (mean±SD of 1.3±0.3 ng/ml). In group A 33 (66%) patients developed regular cycles after 3 months of metformin therapy while 11 (22%) patients who previously had irregular cycles experienced improvement in menstrual flow & had regular cycles. Remaining 6 patients did not had any change. Out of these 44 patients, 41 (82%) ovulated as confirmed by their serum progesterone level > 4 ng/ml. Velazquez [24] has reported the results of 22 women with PCOS completing 6 months of metformin therapy 500 mg three times per day. All patients in his study had chronic

TABLE 1
PRESENTING CHARACTERISTICS OF PATIENTS
(n=100)

S.NO	SYMPTOMS	NO. OF PATIENTS Group A	%	NO. OF PATIENTS Group B	%
1.	No issue (infertility)	50	100	50	100
2.	Oligomenorrhoea	35	70	41	82
3.	Irregular cycles	15	30	9	18

Group A= Metformin treated group Group B = Diet & Exercise treated group

TABLE 2a
BASELINE DIAGNOSTIC CHARACTERISTICS OF PATIENTS

S.NO.	CHARACTERISTICS (n=100 patients)	RANGE Group A	MEAN±SD Group A	RANGE Group B	MEAN±SD Group B
	A: Physiological				
1.	Weight (Kg)	45.0-102	69.4±11.8	52.4-92.5	75.4±8.8
2.	Height (m)	1.4-1.7	1.6±0.1	1.4-1.7	1.6±0.1
3.	BMI (Kg/m^2)	16.7-39.2	27.5±4.8	20.7-41.7	30.0±4.8
	B: Metabolic				
4.	Fasting serum glucose mg/dl)	65-110	92.74±13	75-110	92.00±11.1
5.	Fasting serum insulin (ul/ml)	10.4-51	20.6±11	10.2-30.4	18.8±5.0
	C: Endocrine				
6.	Serum progesterone(ng/ml)	0.6-1.9	1.3±0.3	0.7-3.0	1.6±0.6
7.	Serum FSH (ng/ml)	0.3-32.5	4.2±5.8	0.5-16.1	4.8±3.1
8.	Serum LH (ng/ml)	1.8-105.5	16.6±17.9	3.4-41.0	16.1±7.4
9.	Serum prolactin (ng/ml)	3.7-34.8	12.4-6.8	5.0-27.2	12.0-4.8
10.	Serum testosterone (ng/ml)	0.7-4.9	3.0±0.8	1.3-4.9	3.1±0.7

Group A= Metformin treated group Group B= Diet & Exercise treated group

TABLE 2b
BASELINE CHARACTERISTICS OF PATIENTS
(n=100)

S.NO.	CHARACTERISTICS	GROUP A (n=50)		GROUP B (n=50)	
		NO. OF PATIENTS	%	NO. OF PATIENTS	%
1.	Acanthosis nigricans	04	8	03	6
2.	Male type baldness	05	10	03	6
3.	Acne	13	26	17	34
4.	Hirsutism (face, arms & legs)	33	66	39	78
5.	Ultrasound pelvis (multiple small ovarian cysts)	37	74	39	78

TABLE 3
CYCLICAL CHANGES FROM DAY-0 TO DAY-90
(n=100)

S.NO.	CYCLICAL PATTERN	GROUP A (50)			GROUP B (50)		
		DAY-0	CHANGES	DAY-90	DAY-0	CHANGES	DAY-90
1.	Oligomenorrhoea	35 (70%)	Regular cycles	33 (66%)	41 (82%)	Regular cycles	2 (4%)
			No change	2 (4%)		No change	39 (78%)
2.	Irregular cycles	15 (30%)	Regular cycles	11 (22%)	9 (18%)	Regular cycles	1 (2%)
			No change	4 (8%)		No change	8 (16%)

TABLE 4
SERUM PROGESTERONE FROM DAY-0 TO DAY-90
(n=100)

GROUPS	CHARACTERISTICS	DAY-0 MEAN±SD	DAY-90 MEAN±SD	P VALUE
A	Serum progesterone (ng/ml)	1.3±0.3	9.5±5.1	0.001*
B	Serum progesterone (ng/ml)	1.6±0.6	1.74±1.1	0.067

* P-value significant. Using student t-test (paired) for comparison from Day-0 to Day-90.

TABLE 5
CHANGE IN SERUM PROGESTERONE AT DAY-90
(n=100)

Group	Decrease in serum progesterone		Increase in serum progesterone		No change in serum progesterone	
	No.	%	No.	%	No.	%
A (50)	0	0	50	100	0	0
B (50)	17	34	32	64	1	2

TABLE 6
INCREASE IN SERUM PROGESTERONE FROM DAY-0 TO DAY-90
(n=100)

Groups	Parameter	Sub-Groups	Change in level	Day-0	Day-90
A (50)	**Serum progesterone (ng/ml)**	A	<4 ng/ml	50 (100%)	9 (18%)
		B	> 4 ng/ml	0	41 (82%)
B (50)	**Serum progesterone (ng/ml)**	**A**	**<4 ng/ml**	50(100%)	48 (96%)
		B	**> 4 ng/ml**	0	2(6.25)

oligomenorrhoea or amenorrhoea, hirsutism and polycystic ovaries as assessed by ultrasound at baseline. Kolodziejczyk[25] and Vandermolen[26] have documented that metformin administered at a dose of 500 mg three times daily increased menstrual cyclicity and improved spontaneous ovulation. These findings are coinciding with our results whereas Acbay[27] and Ehrmann[28] have failed to demonstrate salutary effect of metformin in PCOS. In the later study the mean body mass index of the women approached 40 kg/m^2 and metformin is said to be ineffective in cases of morbid obesity.

We have observed a significant increase in the serum progesterone level from 1.3±0.3 to 9.5±5.1 ng/ml. All patients treated with metformin showed an increase with 41 (82%) patients an incline > 4 ng/ml (considered consistent with ovulation) while 9 (18%) patients showing an increase in the serum progesterone from baseline but < 4 ng/ml (considered inconsistent with ovulation). Vandermolen[26] used the serum progesterone level ≥ 4 ng/ml to determine whether participants had ovulated or not. We have also taken the same cut-off value. Velazquez[24] reported ovulation in 13 out of 15 patients with an ovulation percentage of 86.7%. All 13 patients had regular menses and serum progesterone values in the ovulatory range (3.1-28 ng/ml). Fleming[29] have found 37 out of 45 patients ovulating that is 82% ovulation rate. This is in complete accordance to our study. Jakubowicz[30] have observed a significant increase in the serum progesterone level from 70.3±5.4 to 123.7±12.4 pmol/L in 26 PCOS patients after 4 weeks of metformin therapy. All these are coinciding with our study. In contrast to this Nestler[31] has observed a decrease in the serum progesterone level from 3.1±0.3 to 2.2±0.2 mmol/L at the end of 4-6 weeks of metformin therapy. He included 31 PCOS women all having normal weight or thin built with BMI between 18 to 23.7 Kg/ m^2 whereas mean BMI in our patients was 27.5 Kg/m^2.

In group-B out of 50 patients 41(82%) had oligomenorrhoea while 9(18%) had irregular cycles. After 12 weeks of diet & exercise in the former group 39(78%) patients did not had any change while 2(4%) developed regular cycles. Whereas in the latter group with irregular cycles only 1(2%) developed menstrual cycle regularity. Moghetti et al.[32] has observed in 23 caucasian women with PCOS oligomenorrhoea in 20 (86.95%) patients & irregular cycles in 3(13%) patients which is coinciding with us. Kiddy et al.[33] found among 24 PCOS women that 11 patients lost less than 5% of their body weight & only 1(12.5%) had regularity over a 7 months period with strict low calorie diet.In our study mean weight reduction was 1.1 Kg & only 3(6%) showed menstrual regularity after 3 months of diet restriction & exercise regularly. Hutchison[34] has reported a reduction of 1.6 kg in mean body weight of PCOS kept on exercise & diet restriction which is more or less the same as our finding. However Nestler [35] has reported a non-significant increase in serum progesterone level of 12 PCOS women given placebo for 4-6 weeks. Out of 26 women only 1(4%) patient ovulated spontaneously.We have also found non-significant increase in the progesterone level of 50 women kept on diet control & exercise for 12 weeks & only 2(4%) patients ovulated in this group.

CONCLUSION

Metformin has produced beneficial effects on the reproductive function in comparison to diet & exercise alone in PCOS infertile women. It produced cyclical regularity in 88% of cases with an ovulation rate of 82% in comparison to diet & exercise treated group where menstrual regularity occured in 6% of cases with an ovulation rate of 6%. However conception rate & the live birth rate could not be ascertained in these females due to financial constraints.

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