

ROLE OF METFORMIN IN POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Objective: To assess the role of Metformin in Polycystic ovarian syndrome (PCOS).

Methodology: This interventional, quasi-experimental study was conducted at Department of Obstetrics & Gynaecology, Lady Reading Hospital Peshawar from October 2004 to October 2006. A total of 35 patients with PCOS were included fulfilling Rotterdam Criteria. Metformin was given in a dose of 850 mg twice a day. Patients' reassessment was done clinically on a three monthly basis while laboratory investigations and Transvaginal scan was done after two years. Data was analysed using SPSS v. 16.

Results: The mean age of the sample was 27 ± 5.2 years. Out of 35, 29(82.8%) had primary infertility while 6(17.2%) had secondary and only 7(20%) of those conceived. Menstrual irregularities were present in 30(85.7%) patients, 27(55.5%) with oligomenorrhea, 2(5.7%) with amenorrhea and 1(2.86%) with polymenorrhea. Out of these 15, 2 and 1 showed improvement, respectively. Regarding hyperandrogenism, 22(62.8%) patients were with hirsutism, 3(9.4%) had acne and 10(28.5%) had hair loss. Out of these 0, 2 and 3 improved, respectively. Transvaginal scan showed polycystic ovaries in all patients at baseline while the cysts dissolved in 15(42.8%) patients. Biochemical investigations like Leutinizing Hormone:Follicle Stimulating Hormone(LH:FSH), Serum Testosterone, Serum Prolactin, Random Blood Sugar(RBS) and Serum Insulin was raised in 32(91.4%), 24(68.5%), 9(25.7%), 3(8.5%) and 10(28.5%) patients respectively and 17(53.1%), 13(54.2%), 4(44.4%), 1(33.3%) and 4(40%) patients improved respectively.

Conclusion: Metformin is an effective drug to improve the menstrual irregularities, LH:FSH and serum testosterone but it does not show improvement in clinical signs and symptoms of hyperandrogenism.

Key Words: Polycystic ovarian syndrome (PCOS), Metformin, Menstrual irregularities, Infertility, Hyperandrogenism, Leutinizing Hormone: Follicle Stimulating Hormone (LH:FSH).

This article may be cited as: Wahab S, Farnaz, Karim R. Role of metformin in Polycystic Ovarian Syndrome. J Postgrad Med Inst 2013; 27(2):179-83.

INTRODUCTION

Polycystic ovarian syndrome is a common disorder of reproductive age women affecting up to 10% of population^{1,2}. Pathophysiology of PCOS appears to be multifactorial, heterogeneous and

polygenic; however, exact etiology remains unknown². Polycystic ovary is characterized by peripheral cysts (10 or more) less than 10 mm in sizes in an enlarged ovary with significant increase in central stroma³. Polycystic ovarian syndrome is characterized by the disruption of regular process leading to multiple ovarian cyst formation, anovulation, menstrual irregularities like oligomenorrhea, hyperandrogenism (i.e., acne, hirsutism, hair loss) and/or biochemical disturbances such as raised level of LH:FSH, serum testosterone, serum prolactin, serum insulin and random blood sugar^{4,5}.

Metformin is a biguanide with an action to decrease insulin levels, reduces insulin resistance and lower the total and free circulating androgen levels. This results in improvement of the clinical sequelae of hyperandrogenism and signs and symptoms of PCOS.

At a joint consensus meeting of the American Society of Reproductive Medicine (ASRM) and the European Society of Human

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Date Received: December 22, 2011

Date Revised: December 26, 2012

Date Accepted: December 30, 2012

Reproductive and Embryology (ESHRE) held in Rotterdam, in May 2003, a refined definition of the PCOS was agreed which is called Rotterdam criteria^{6,7}.

PCOS has strong genetic and environmental components⁸. It is thought to be associated with increase weight gain during puberty. High BMI of 30 kg/m² has strong co-relation with abnormal clinical and biochemical features⁹. It is also characterized by hyperinsulinemia which indicate significant insulin resistance¹⁰ and plays a causal role in pathogenesis and hyperandrogenism of syndrome¹¹.

METHODOLOGY

This interventional, quasi-experimental study was conducted at Department of Obstetrics and Gynecology, Lady Reading Hospital, Peshawar, from October 2004 to October 2006. Patients who presented with primary or secondary infertility with signs and symptoms of hyperandrogenism (like acne, hirsutism and hair loss) and/or menstrual irregularities only due to polycystic ovarian syndrome were included in the study. All unmarried patients and patients with infertility, hyperandrogenism and menstrual irregularities due to causes other than PCOS were excluded from the study.

A total of 35 patients of PCOS fulfilling the inclusion criteria were approached for informed consent after educating them about side effects of metformin. They were assessed by performing laboratory investigations including LH:FSH (Normal Range upto 3:1), serum prolactin (Normal value up to 400Miu/l), serum testosterone (Normal

Range between 0.5-3nmol/l), serum insulin levels (Normal Range up to 60pmol/l) and random blood sugar (Normal Range 110-140 mg/dl). A transvaginal scan was also performed.

Metformin was given in a dose of 850 mg twice a day for six months. Patients' were reassessed clinically for the improvement in signs and symptoms on a three monthly basis. The compliance of patients was ensured by educating the patients and attendants regarding the use of metformin and asking regularly in every follow up visit.

At the end of two years, final assessment was done by performing the same laboratory investigations including LH:FSH, serum prolactin, serum testosterone, serum insulin levels and random blood sugar. A transvaginal scan was also performed after two years.

The data was entered in a pre designed proforma and was analysed using SPSS v.16. Paired t test was used to compare the pre and post intervention values.

RESULTS

The sample of the study included patients between 20 to 35 years age with a mean age of 27±5.2 years. Among these 35 patients, 29 (82.8%) had primary infertility and 6 (17.2%) had secondary infertility. Six (20.6%) out of 29 patients of primary and 1 (16.7%) out of 6 of secondary infertility, did conceive by the end of the study (Table 1).

Menstrual irregularities were present in 30(85.7%) patients, 27(55.5%) with oligomenorrhea, 2(5.7%) with amenorrhea and 1(2.86%)

Table 1: Clinical Signs and Symptoms of PCOS and the role of metformin (n=35)

Signs and Symptoms		Baseline	Improved after 2 years	t	P-value
Infertility	Primary	29	6 (20.6%)	2.915	0.006
	Secondary	6	1 (16.7%)		
Menstrual Irregularities	None	5	-	6.000	0.000
	Amenorrhea	1	1 (100%)		
	Oligomenorrhea	27	15 (55.5%)		
	Polymenorrhea	2	2 (100%)		
Hyperandrogenism	Hirsutism	22	0 (0%)	2.380	0.023
	Acne	3	2 (66.7%)		
	Hair loss	10	3 (30%)		

P-value < 0.05 was considered significant

Table 2: Hormone level and the role of metformin (n=35)

Hormone Level	Deranged at Baseline	Improved after 2 years	t	P value
LH:FSH	32	17 (53.12%)	6.971	0.000
Testosterone	24	13 (54.16%)	5.527	0.000
Prolactin	9	4 (44.44%)	2.543	0.016
Random Blood Sugar	3	1 (33.33%)	0.118	0.907
Serum Insulin	10	4 (40%)	1.237	0.225

P-value < 0.05 was considered significant

with polymenorrhea. Fifteen (55.5%) out of 27 with oligomenorrhea and all with amenorrhea and polymenorrhea showed improvement (Table 1).

Regarding hyperandrogenism, 22(62.8%) patients were with hirsutism, 3(9.4%) had acne and 10(28.5%) had hair loss. No improvement was seen in cases of hirsutism while 2 out of 3 and 3 out of 10 did improve for acne and hair loss respectively (Table 1).

Transvaginal scan showed polycystic ovaries in all patients at baseline while the cysts dissolved in 15(42.8%) patients.

Biochemical investigations like LH: FSH, Serum testosterone, Serum Prolactin, RBS and Serum Insulin was raised in 32(91.4%), 24(68.5%), 9(25.7%), 3(8.5%) and 10(28.5%) patients respectively. The improvement was seen in 17(53.1%) out of 32, 13(54.2%) out of 24, 4(44.4%) out of 9, 1(33.3%) out of 3 and 4(40%) out of 10 patients on LH:FSH, Serum testosterone, Serum Prolactin, RBS and Serum Insulin respectively.

The use of Metformin showed improvement in weight reduction and the average weight loss was 4.7 kg.

DISCUSSION

The basic etiology behind anovulation in PCOS is insulin resistance and hyper-insulinaemia. Therefore the reduction of insulin concentration is of great importance, for which insulin sensitizing agent such as metformin is indicated. Metformin not only decreases hyperandrogenism and insulin resistance but also improves ovulation and pregnancy rates¹². But current evidence suggests that metformin alone is not a first line treatment in the management of PCOS¹³.

In a study by Kocak M et al, in 2002¹², it was concluded that metformin improves ovulation and pregnancy rates, which is evident in our study

as well. Another study by Hwu YM et al, in 2005¹⁴ showed that in 40 patients treated with Metformin, 6 (15%) conceived, which is also comparable with our study. Another study, which was conducted by Legro RS et al¹⁵ showed much different result, that is, 15 (7.2%) of 208 patients in Metformin treated group. The difference may be due to small sample size of our study.

Conway in 1989 found that 75-80% of women with PCOS had amenorrhea and oligomenorrhea while 4-14% patients had polymenorrhea, menorrhagia and dysfunctional uterine bleeding¹⁶. Our results are comparable to this study. However, the difference may be due to small sample size in our study.

Approximately 4% of women of reproductive age present with hyperandrogenism and anovulation¹⁷. Approximately three-fourths of patients with PCOS (Diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia^{18,19}. Kocak M et al, in his study in 2002, concluded that Metformin decreases hyperandrogenism¹². In our study, none of the patients with hirsutism showed improvement but some of the patients with acne and hair loss did improve which means that metformin has overall, low anti-androgenic effect.

Metformin showed to improve majority of the patients with deranged LH:FSH in our study which is comparable to the study by Valezquez EM et al²⁰. On the contrary, Kazerooni T et al in their study have shown no significant changes in the LH:FSH²¹.

Circulating testosterone levels, among women with PCOS are higher than among normally cycling non hirsute women¹⁶. Our study showed improvement in majority of the patients with deranged serum testosterone which is comparable to the results of Valezquez EM et al and Kazerooni T et al^{20,21}.

Prolactin levels were improved in less than half of our patients which was in accordance with the study by Kazerooni T et al and contradictory to the results of the study by Evangelia B et al^{21, 22}.

Approximately 50% of patients with PCOS are thought to be obese. In our study, the use of metformin showed improvement in weight reduction and the average weight loss was 4.7 kg. This has also been shown in a study by Haas DA et al where metformin was shown to produce significant reductions in BMI²³. Barbieri RL, in his study in 2003, has also mentioned that in obese woman, Metformin plus low caloric diet may be associated with more weight loss than a low caloric diet alone²⁴.

CONCLUSIONS

Metformin is an effective drug to improve the menstrual irregularities, LH:FSH and serum testosterone but it does not show improvement in clinical signs and symptoms of hyperandrogenism. It is suggested that further long term studies be conducted to evaluate the uses of Metformin in PCOS.

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CONTRIBUTORS

SW conceived the idea, planned and wrote the manuscript. F & RK did the data collection, analyzed the study & helped in write up of the manuscript. All the authors contributed significantly to the research that resulted in the submitted manuscript.