Original Article

Metformin Plus Myoinositol Versus Metformin in Polycystic Ovarian Syndrome Women Undergoing Ovulation Induction with Letrozole

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ABSTRACT

Objectives: To assess the effect of combined metformin and myo- inositol in comparison to metformin alone on the ovarian response and improving insulin resistance parameters in PCOS infertile women undergoing induction of ovulation.

Study design : This study was a randomized controlled study conducted for a minimal total number of 60 eligible study patients (30 per group). Women recruited from a routine infertility clinic.

Results: This study was a randomized controlled study conducted for a minimal total number of 60 eligible study patients (30 per group). Women recruited from a routine infertility clinic. As regards pregnancy rate, the pregnancy rate was lower in group 2 than group 1 but there was not any statistically significant difference between both groups (p= 0.162). As regards ovarian response, there was not any statistically significant difference between the studied groups at the beginning of the study after first cycle of ovulation induction (p= 0.706). As regards ovarian response, the ovarian response at the end of the study after second cycle of ovulation induction was higher in group 1 (Myo-inositol 600mg+Metformin 500mg+Folic acid) than group 2 (Metformin 500mg) which is statistically significant (p= 0.002).

Conclusion: From this study we conclude that: -The ovarian response was notably higher in myo-inositol plus metformin group than in the metformin group. - there was a higher pregnancy rate in myo-inositol plus metformin group but there was no statistically notable difference between the two groups.

Key Words: Infertility, myoinositol, polycystic ovarian syndrome.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous, multifaceted, and complex disorder associated with metabolic and hormonal impairments, ovarian dysfunction, menstrual irregularity, and infertility[1]. Although the Rotterdam criteria have been widely accepted, it has recently become clear that dysmetabolic features of insulin resistance (IR) are a further clinical element that needs to be taken into account[2].

In the past decade, substantial in vitro and in vivo evidence has supported the pivotal role of insulin resistance and compensatory hyperinsulinemia in the pathogenesis of PCOS (which is present in 80% of obese women with PCOS, and in 30–40% of lean women)[1,3].

Nevertheless, although the role of insulin resistance and related hyperinsulinemia is widely accepted, some women who exhibit extreme obesity and insulin resistance do not develop PCOS[4]. Therefore, a prerequisite for developing PCOS may be the concomitant abnormal secretion of androgens, and a primary defect that favors androgen excess is thought to be essential for PCOS development in response to insulin or other triggering factors[5]. Whether insulin resistance or abnormal androgens secretion are the primary causes of PCOS is a subject of major debate, and constant efforts are being made to understand the complex pathogenic network underlying the syndrome[5,6].

Regardless of the initiating factor of PCOS, treatment of insulin resistance and hyperinsulinemia could return the metabolic and hormonal state to homeostasis, and thereby alleviate ovarian dysfunction, anovulation, and finally infertility. In addition to insulin-sensitizing and insulin-response modulatory effects, metformin has been studied most extensively and there is evidence that it may have metabolic and reproductive benefits[7].

In spite of being used for decades[4], metformin has not been able to show results in terms of improved live birth rates in infertile PCOS women though there is evidence of improved clinical pregnancy rate when given along with clomiphene (clomiphene citerate) as compared to

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clomiphene citerate alone[8]. Inositols act as gonadotropin second messengers in the ovary. Given the connection between ovulatory dysfunction, hyper insulinemic insulin resistance, and hyperandrogenism, inositols have been studied to assess their effects on PCOS symptoms and signs, including the possibility of improving fertility and reproductive outcomes[9].

As the two insulin sensitizers act through different mechanisms, these may be combined to act synergistically to improve metabolic and reproductive outcomes simultaneously in infertile PCOS women. Till now there is no study published to evaluate whether the combination of metformin and myo-inositol can act better than metformin alone in infertile PCOS women. The present study was planned to study the effect of combined metformin and myo-inositol as compared to metformin alone in terms of reproductive outcome and improvement in metabolic and hormonal parameters in infertile PCOS women undergoing ovulation induction cycles.

AIM OF THE WORK

The aim of this study is to assess the effect of combined metformin and myo-inositol as compared to metformin alone in terms of ovarian response and improvement in insulin resistance parameters in infertile PCOS women undergoing ovulation induction cycles.

PATIENTS AND METHODS

Patients:

This study will include 60 patients after obtaining approval from the Ethics committee of Faculty of Medicine of Alexandria University. The study population will be recruited from a routine infertility clinic.

Methods:

All cases will be subjected to the following:

1. Complete history taking (gynecological, obstetric, medical and surgical).

2. Complete general and local examination including weight, height and BMI.

3. Routine laboratory investigations to exclude co-morbidities.

4. Assessment of prolactin level, thyroid profile level and semen analysis for the husband.

5. Transvaginal ultrasound to diagnose polycystic ovaries and confirm eligibility.

6. Initial assessment of baseline Homeostatic Model Assessment of insulin resistance (HOMA IR) mmol/L level and body mass index (BMI) for all patients.

7. All patients will receive Aromalock tablet (Letrozole 2.5mg) twice daily for one cycle starting from day two to day seven of menstrual cycle.

8. *Patients will be randomly allocated into 2 groups:*

- Group A: (*n*= 30) will receive Glucophage tablet (Metformin 500mg) twice daily and Inofolic (Myo-inositol 600mg+Folic acid 0.24mg) orally twice daily for 3 months.

- Group B: (*n*= 30) will receive Glucophage tablet (Metformin 500mg) twice daily for 3 months. After 3 months each group will receive Aromalock tablet (Letrozole 2.5mg) twice daily for one cycle starting from day two to day seven of menstrual cycle.

- In both groups, first visit will be at day 9 for folliculometry and then serial transvaginal sonography will be done till one or more follicles reach the size of 18mm.

9. Then after the second cycle of induction HOMA IR, BMI and another folliculometry will be done.

10. Comparison of the results of the 2 groups will be done before and after the use of Inofolic.

Statistical method:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Significance of the obtained results was judged at the 5% level.

The used tests were:

1- Chi-square test.

For categorical variables, to compare between different groups.

2- Fisher's Exact.

Correction for chi-square when more than 20% of the cells have expected count less than 5.

RESULTS

As regards HOMA–IR, there was not any statistically significant difference between the studied groups at the beginning of the study (*p*= 0.952). And there was not any statistically significant difference between the studied groups at the end of the study (*p*= 0.207) (Table 1).

As regards pregnancy rate, the pregnancy rate was lower in group 2 than group 1 but there was not any statistically significant difference between both groups (p= 0.162) (Tables 2 and 3).

Ovarian response In form of serial transvaginal sonography will be done till one or more follicles reach the size of 18mm. As regards ovarian response, there was not any statistically significant difference between the studied groups at the beginning of the study after first cycle of ovulation induction (p= 0.706) (Table 4).

As regards ovarian response, the ovarian response at the end of the study after second cycle of ovulation induction was higher in group 1 (Myo-inositol 600 mg+Metformin 500mg+Folic acid) than group 2 (Metformin 500mg) which is statistically significant (p= 0.002).

Table 1: Comparison of the two groups based on HOMA–IR:

HOMA–IR	Group I (n= 30)	Group II (n= 30)	U	p
Before				
Min.–Max.	1.80–9.60	1.80–9.60		
Mean ± SD.	3.69±2.19	3.73±2.21	446.00	0.952
Median (IQR)	3.0(2.50–3.80)	3.0(2.50–4.0)		
After				
Min.–Max.	0.80–5.0	1.20–4.50		
Mean±SD.	1.87±0.96	2.08±1.0	365.00	0.207
Median (IQR)	1.65(1.0–2.80)	1.70(1.40–2.20)		

Table 2: Comparison between the two studied groups regarding positive pregnancy (before treatment):

Positive pregnancy	Group I (n = 30)		Group II (n = 30)		χ^2	p
	No.	%	No.	%		
Before treatment						
Negative	25	83.3	28	93.3	1.456	^{FE}p= 0.424
Positive	5	16.7	2	6.7		

Table 3: Comparison between the two studied groups regarding positive pregnancy (After treatment):

Positive pregnancy	Group I$^{\#}$ (n = 25)		Group II$^{\#}$ (n = 28)		χ^2	p
	No.	%	No.	%		
After treatment						
Negative	18	72.0	25	89.3	2.578	^{FE}p= 0.162
Positive	7	28.0	3	10.7		

Table 4: Comparison of the two groups based on ovarian response:

Ovarian response	Group I (n= 30)		Group II (n= 30)		χ^2	p
	No.	%	No.	%		
Before treatment						
No	25	83.3	27	90.0	χ^2= 0.577	^{FE}p= 0.706
Yes	5	16.7	3	10.0		
After treatment	(n= 25)$^{\#}$		(n= 28)$^{\#}$			
No	9	36.0	22	78.6	9.859*	0.002*
Yes	16	64.0	6	21.4		

DISCUSSION

Polycystic ovary syndrome (PCOS) is one of most common endocrine disorder that affects women of reproductive age. Infertility and anovulation are the most common effects of PCOS. The two main components of this condition are compensatory hyperinsulinemia and insulin resistance. Studies have demonstrated the

efficacy of insulin-sensitizing agents, like metformin and myoinositol, as pharmacological treatments to induce ovulation in PCOS-affected women. The two agents can be used singly or in combination to achieve an additive effect. Additionally, a number of studies have explained why metformin and myoinositol are better when used together, with improved endocrine, metabolic, and reproductive outcomes. These findings align with our hypothesis-driven research. In Our study Patients randomly allocated into 2 groups: - Group 1 (*n*= 30) received (Myo-inositol 600mg+Folic acid 0.24mg) and (Metformin 500mg) twice daily orally twice daily for 3 months. - Group 2 (*n*= 30) received (Metformin 500mg) twice daily for 3 months. - Each group received (Letrozole 2.5mg) twice daily for one cycle starting from day two to day seven of menstrual cycle once before the treatment and once after the treatment. The aim of the study is to examine the effects of myo-inositol and metformin alone vs combined therapy for insulin-resistant infertile polycystic ovarian syndrome .

BMI: Our study observed BMI decreased after the treatment in both groups. But was almost similar in both groups. The mean BMI in group 1 (Myoinositol and Metformin) was 29.9±2.25 before treatment and decreased to 27.8±2.66 after treatment,while in group 2 (metformin alone) mean BMI was 29.7±1.97 before the treatment and decreased to 27±1.84 after the treatment by comparison of BMI between 2 groups after treatment there was no statistically significant difference between the two groups (p>0.05).

HOMA IR: Every individual had evidence of insulin resistance. The clinical diagnosis of insulin resistance was made using the HOMA IR level. This was justified by the fact that glucose intolerance and diabetes are typically diagnosed using fasting plasma glucose (FPG) and Hba1c. They are insufficient, therefore, to identify glucose intolerance in its early stages with Discussion 36 clarity. Our study also observed HOMA IR level decreased after the treatment in both groups. The mean HOMA IR in group 1 (Myoinositol and Metformin) was 3.69±2.19 and decreased to 1.87±0.96 after the treatment while the mean HOMA IR in group 2 (Metformin alone) was 3.73±2.21 before the treatment and decreased to 2.08±1.0 after the treatment. By comparing the HOMA IR level after the treatment between both groups there was a decrease in HOMA IR level in group 1 more than group 2 but it was statistically not significant (P= 0.207).

Ovarian response: We observed ovarian response In form of serial transvaginal sonography will be done till one or more follicles reach the size of 18 mm (mature follicle), after treatment for 3 months we started a cycle of ovulation induction with letrozole for both groups and observed the ovarian response , the ovarian response was higher in group 1 (Myo-inositol 600mg+Metformin 500mg+Folic acid) 16 women out of 25 women developed mature follicle which was higher than group 2 (Metformin 500mg) 6 women out of 28 developed mature follicle (64.0% versus 21.4%) which is statistically significant (p= 0.002).

Pregnancy rate During the treatment in group 1 (Myo-inositol 600mg+Metformin 500mg+Folic acid) 5 women out of 30 got pregnant,while group 2 (Metformin 500mg) 2 women out of 30 got pregnant (16% vs 6.7%) After the treatment and induction in group 1 (Myoinositol and Metformin) 7 women out of 25 got pregnant,while in group 2 (Metformin alone) 3 women out of 28 got pregnant (28% vs 10.7) So we observed the pregnancy rate was higher in group 1 in comparison to group 2 after the treatment but there was not any statistically notable difference between both groups (p= 0.162).

CONCLUSION

From this study we conclude that: -The ovarian response was notably higher in myo-inositol plus metformin group than in the metformin group. - there was a higher pregnancy rate in myo-inositol plus metformin group but there was no statistically notable difference between the two groups.

CONFLICT OF INTERESTS

There is no conflict of interests.

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