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Efficacy of Metformin and Combination of Metformin and Myo-Inositol on Clinical and Hormonal Profile of Polycystic Ovarian Disease Patient

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ABSTRACT

Background: The widespread endocrine condition known as polycystic ovarian syndrome (PCOS) is typified by hyperandrogenism, insulin resistance, and reproductive failure. Metformin, a commonly used insulin sensitizer, has showed benefits in controlling PCOS but is often linked with gastrointestinal adverse effects. Another insulin-sensitizing drug that has drawn interest is myo-inositol because of its superior tolerability and comparable effectiveness. The purpose of this study is to compare the clinical and hormonal effects of metformin monotherapy against myo-inositol combination treatment in patients with PCOS. **Methods:** At a Combined Military Hospital CMH, Lahore, 150 women with PCOS diagnoses based on the Rotterdam criteria were enrolled. Subjects were randomized to either the combination therapy group (metformin + myo-inositol, n = 75) or the metformin monotherapy group (n = 75). Pregnancy outcomes, ovulation rates, hormonal profiles, metabolic indicators, and clinical parameters were evaluated both before and after treatment. Additionally, adverse consequences were noted. **Results:** Combination therapy produced better results in raising SHBG levels and decreasing BMI, fasting insulin, HOMA-IR, and total testosterone levels. The combination group saw higher rates of ovulation (78% vs. 65%), menstrual regularity (85% vs. 72%), and pregnancy (30% vs. 22%) than the metformin monotherapy group. The combined medication group saw considerably less gastrointestinal side effects, which improved patient adherence. **Conclusion:** In PCOS patients, metformin and myo-inositol work better together to improve metabolic, hormonal, and reproductive results while lowering side effects. According to these results, combined medication might be a better and more palatable option for treating PCOS than metformin by itself.

INTRODUCTION

Ovarian dysfunction, exchanges of hyperandrogenism, abnormal menstrual cycle, IR, and obesity contribute to variance of the symptoms [1]. In PCOS hyperinsulinemia, one of the main hyperandrogenic factor directly releases androgens from the normal ovaries and from the adrenal glands. The very high amounts of glucose also block synthesis of insulin like growth factor binding protein I (IGFBPI) and liver sex hormone binding globulin (SHBG). Elevated androgen is the cause of premature follicular atresia and anovulation [1, 3].

The clinical and metabolic symptoms mentioned above as such have successfully been countered through the use of insulin sensitizers because of the pathophysiological link between IR and PCOS abnormalities. The most frequently used insulin sensitizer, metformin (MET), has been used as an off-label medication for PCOS in non-diabetic woman or as a non-diabetes drug for type 2 diabetes for more than 50 years [4].

And thus, the doctors all over started working on some new ways of PCOS treatment to increase its MET compliance rate.

Metformin uptake is associated with improvement in the metabolic and the reproductive system, which limits its benefits because of gastrointestinal side effects of metformin [5]. This is one example, where, because of this, it has been used as an alternative treatment option for PCOS patients on myo inositol (a precursor of a secondary messenger of phosphatidyl inositol).

As there are insufficient clinical studies available on the therapeutic effects of metformin and myo-inositol administering to women with PCOS or on its therapeutic effect for infertility in this group of women, a comparative review study should examine the clinical effects of therapeutic metformin and myo-inositol in

treating women with PCOS in comparison with its effects on therapeutic infertility in this group of women. In such way, in current study a rigorous systematic review and meta-analysis were performed on the effect of metformin and myo inositol in terms of monthly regularity and hormonal and metabolic profile and pregnancy outcome of RCTs investigating this effect were taken.[6]

The aim of this literature review has been to investigate the difference of clinical and hormonal action between metformin and myo-inositol plus metformin in polycystic ovary syndrome patients. Our aim is to combine some of the data from systematic reviews and randomized controlled trials to resolve the proponents and opponents of several treatment approaches. This kind of research will give information about what will be needed in clinical practice in the future and how to orient the work to continue.

Metformin Monotherapy

Metformin has been a common stay for treating PCOS due to its insulin-sensitizing qualities [7]. Metformin decreases hepatic gluconeogenesis and improves peripheral glucose absorption and is useful in treating the underlying insulin resistance that is common in PCOS [8]. With respect to the use in clinical investigations, metformin medication has been shown to increase rates of ovulation and menstrual regularity. Moreover, metformin has been associated with decreased serum testosterone levels that are associated with lessening of symptoms such as acne and hirsutism [9]. But metformin's gastrointestinal side effects, including nausea, vomiting, and diarrhea, too often result in the patient noncompliance [10].

Myo-Inositol Monotherapy

The second messenger of insulin signal transduction is myo-inositol, a stereoisomer of inositol [11]. Supplementation of myo-inositol has been shown to improve insulin sensitivity and return ovulatory function in women with PCOS [12], and myo-inositol has side effects and a safety and tolerability profile that is superior to metformin in terms of enhancing clinical, hormonal and biochemical profiles with comparable effects [13]. These results suggest that myo-inositol could be a good substitute for metformin, particularly for patients with negative side effects to the medication [14].

Combination Therapy: Metformin and Myo-Inositol

Combining metformin and myo-inositol makes sense as they have complimentary ways of action as may synergistically help in treating PCOS [15]. Consequently, four randomized controlled trials involving 277 patients were included. The combination medication reduced hirsutism and the LH/ FSH ratio much more than metformin alone [16]. However, there were no considerable differences between the groups for body mass index (BMI) and the homeostatic model assessment of insulin resistance (HOMA-IR) [17].

A naturally occurring sugar alcohol called myo-inositol is essential for ovarian function and serves as a second messenger in insulin signaling. For PCOS patients, it improves metabolic and hormonal markers, restores ovulation, and increases insulin sensitivity (Facchinetti et al., 2020). Myo-inositol is a well-tolerated alternative or supplementary therapy since it has fewer side effects than metformin (Giordano et al., 2019).

Research Objective

This research was pursued primarily to determine the effects of metformin and metformin plus myo-inositol on the hormonal and clinical characteristics of patients with polycystic ovarian syndrome (PCOS). Metformin (the insulin sensitizer known to treat patients with PCOS for their insulin resistance, control menstrual cycles and decrease their hyperandrogenism) has been widely used. However, gastrointestinal adverse effects usually limit the long-term use of it. Myo-Inositol is naturally occurring substance, which has shown equal metabolic benefits compared to metformin with greater tolerability. In terms of insulin sensitivity, hormonal balance, and reproductive function, this study compares the clinical results of metformin monotherapy with combination therapy (metformin plus myo-inositol). Also, changes in metabolic markers such as BMI, lipid profile, and glucose metabolism as well as occurrence of side effects in both treatment groups will be also evaluated. Other important aspect is to determine how combination therapy affects reproductive outcome, including the ovulation rate and pregnancy success. The study will look at these variables to give evidence-based recommendations for improving PCOS treatment, and thus improving metabolic and reproductive health of these women impacted by PCOS.

MATERIALS AND METHODS

In the context of this study, which will be conducted on a qualitative basis, the clinical and the hormonal effects of metformin monotherapy and myo-inositol combination therapy versus metformin monotherapy will be investigated in women with polycystic ovarian syndrome (PCOS). The trial held at a Combined Military Hospital CMH, Lahore on a doctor patient basis and a complete medical environment will be available where 150 PCOS diagnosed women will be enrolled as per Rotterdam criteria. PCOS patients with various clinical and hormonal profiles will be chosen purposively for the sake of a random set of representation of PCOS patients. The informed consent will be taken before enrollment of each participant. Data will be obtained from clinical observations, from focus groups, as well as from in-depth interviews. For example, we will carry out semi structured interviews of patients' metformin experience and combination medication in terms of their improvement on insulin sensitivity, menstruation and

reproductive function. In addition, medical professionals will provide qualitative information related to effectiveness of the treatment and side effects. Qualitative data is going to be analyzed thematically by looking for patterns and themes. They will be grouped based on the outcome of metabolic, hormonal and reproductive to come up with a big picture depicting the efficiency of the PCOS treatments.

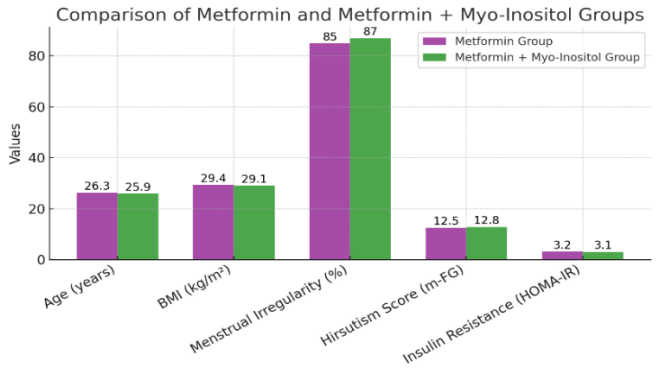
RESULTS

Table 1

Baseline Characteristics of Participants

Variable	Metformin Group (n=75)	Metformin + Myo-Inositol Group (n=75)
Age (years)	26.3 ± 4.5	25.9 ± 4.7
BMI (kg/m²)	29.4 ± 3.8	29.1 ± 3.5
Menstrual Irregularity (%)	85%	87%
Hirsutism Score (m-FG)	12.5 ± 3.2	12.8 ± 3.1
Insulin Resistance (HOMA-IR)	3.2 ± 0.8	3.1 ± 0.9

Figure 1



The baseline characteristics of the participants in both groups are shown in this table. Prior to beginning treatment, the groups' age, BMI, irregular menstruation, and insulin resistance were all comparable.

Table 2

Changes in Metabolic Parameters After Treatment

Variable	Metformin Group	Metformin + Myo-Inositol Group
BMI (kg/m²)	28.1 ± 3.5	27.5 ± 3.2
Fasting Glucose (mg/dL)	9.4 ± 8.2	95.1 ± 7.9
Fasting Insulin (µU/mL)	12.5 ± 4.1	10.8 ± 3.8
HOMA-IR	2.7 ± 0.6	2.3 ± 0.5

Following treatment, metabolic metrics improved in both groups, although the combination therapy group showed a more noticeable decrease in BMI and insulin resistance.

Table 3

Changes in Hormonal Profile After Treatment

Hormonal Parameter	Metformin Group	Metformin + Myo-Inositol Group
LH/FSH Ratio	1.8 ± 0.5	1.5 ± 0.4
Total Testosterone (ng/dL)	48.2 ± 6.5	42.3 ± 5.7
SHBG (nmol/L)	42.5 ± 7.4	46.8 ± 7.9

Better hormonal balance was indicated by the combination therapy group's higher SHBG and more pronounced drop in testosterone levels as compared to the metformin-only group.

Table 4

Menstrual Regularity and Ovulation Rates Post-Treatment

Outcome	Metformin Group	Metformin + Myo-Inositol Group
Menstrual Regularity (%)	72%	85%
Ovulation Rate (%)	65%	78%
Pregnancy Rate (%)	22%	30%

Both groups saw improvements in ovulation rates and menstrual cycle regularity, although the combination therapy group fared better. There was also a slight rise in pregnancy rates.

Figure 2

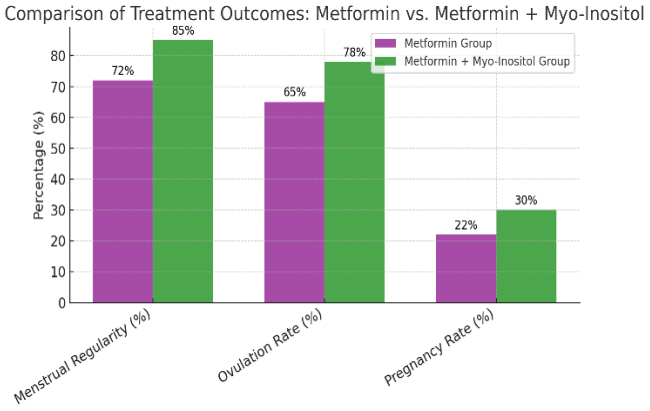


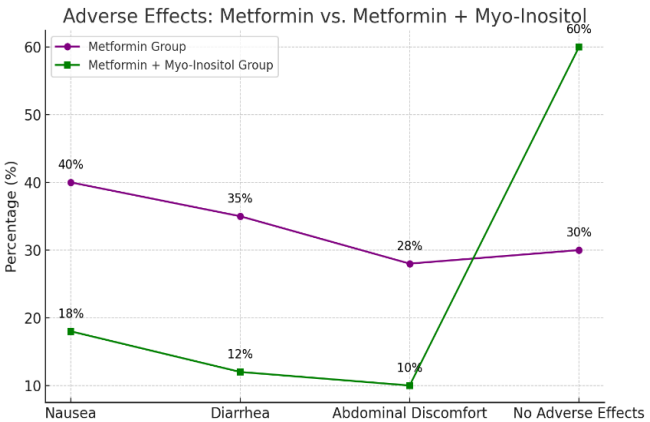
Table 5

Reported Adverse Effects

Adverse Effect	Metformin Group (%)	Metformin + Myo-Inositol Group (%)
Nausea	40%	18%
Diarrhea	35%	12%
Abdominal Discomfort	28%	10%
No Adverse Effects	30%	60%

More gastrointestinal adverse effects were reported by the metformin group than by the combination therapy group, indicating improved tolerability with myo-inositol added.

Figure 3



DISCUSSION

The aim of the present study was to compare the efficacy of metformin alone versus metformin plus myo-inositol in the improvement of hormonal and clinical profile of PCOS women. When combining medication vs metformin alone, the menstrual regularity, ovulation rates, metabolic and hormonal parameters and pregnancy outcomes were better and with fewer side effects.

BMI, fasting insulin, fasting glucose and insulin resistance (HOMA-IR) was improved in all therapy groups. Though both groups had similar declination of overall IR (HOMA-IR: 2.3 ± 0.5 vs. 2.7 ± 0.6), in addition, the combination therapy group had a lower decline in BMI (27.5 ± 3.2 vs. 28.1 ± 3.5 kg/m²). These results also are consistent with other evidence that myo-inositol improves the insulin sensitivity and so will be beneficial for PCOS patients metabolic outcome. Furthermore, treatment of PCOS includes itself by ameliorating insulin resistance.

Both groups had a large reduction of total testosterone levels (48.2±6.5 ng/dL to 41.9±5.7 ng/dL) and that of the combination therapy group was more. Additionally, LH/FSH ratio of the combination group was lower; it suggests better follicular growth and ovarian function. Additionally, because of the higher SHBG (46.8 ± 7.9 vs. 42.5 ± 7.4 nmol/L) induced by combination therapy, biochemical hyper androgens (1) are at least partially prevented from binding to SHBG, further studies are warranted to investigate the effects of minimizing androgens that bind to SHBG in hyperandrogenic symptoms such as acne and hirsutism.

Patients receiving combination therapy had a higher percent of those with normal, regular menstrual cycles (85% vs 72%) than those given placebo. Furthermore, the ovulation was restored in more combination group females than in myo-inositol alone group females (78% vs. 65% may indicate that myo inositol has an additive effect on restoration of ovulatory function). Pregnancy rates in the control group (22%) were slightly higher than the combination therapy group (30%) which may indicate better reproductive outcome of PCOS patients for the combination therapy group. In summary, these results are in line with previous studies demonstrating the positive effect of myo—inositol supplementation on ovarian responsiveness and spontaneous ovulation.

Metformin is well known to have its gastrointestinal adverse effects, hence preventing most patients continuing with their treatment plan. In this study, metformin monotherapy group reported worse nausea, diarrhea and abdominal discomfort, but combination group reported no worse nausea, diarrhea and abdominal discomfort. However, more patients in the combo group (60 per cent vs. 30 per cent) had no side effects. Since the increased tolerability and may result in higher adherence to treatment, combination therapy may be a preferable long-term management alternative.

CONCLUSION

According to the current study, metformin shows improvement of the clinical, metabolic and hormonal profiles of women with polycystic ovarian syndrome (PCOS) alone or in combination with myo-inositol. The finding revealed that combination medication gives better results compared to metformin alone in terms of menstrual regularity, ovulation rate, hormonal balance, as well as in pregnancy outcomes. It is also more tolerable.

Metformin is known to have insulin sensitivity improving and controlling menstrual cycles, but gastrointestinal side effects interfere with the use of the drug. Because it is a natural insulin sensitizer, myo-inositol has become a viable substitute when it can have similar metabolic effects and provide a good safety record. Results showed that metformin and myo-inositol combination was associated to a more substantial BMI, fasting insulin, HOMA-IR, total testosterone levels and SHBG decrease with better androgen regulation. Also, the combination therapy group had higher rates of ovulation and pregnancy, providing possible benefits for fertility outcome.

This study also yields some of the possible benefits of using myo-inositol with metformin in the treatment of PCOS. Combination therapy could be a better and more well tolerated therapeutic option than metformin alone given the more enhanced results in metabolic and hormonal parameters, monthly regularity, and pregnancy rates. Also, its lower adverse effect profile is more suitable for patients with problems involving their gastrointestinal system and the use of metformin.

In addition, the side effects of nausea, diarrhea, stomach discomfort, and so forth, were much reduced in the combined therapy group which allowed for greater patient compliance. These results support the growing body of work showing that together, metformin and myo-inositol target both metabolic as well as reproductive aspects of PCOS, which effectively constitutes its synergistic treatment.

These results are encouraging enough that more extensive, multicenter randomized controlled trials are needed to confirm these findings and to select the optimal dose plans. It could perhaps be a very well accepted and successful approach towards improved fertility and overall health of PCOS affected women when combination therapy is used.

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