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**Evaluating effect of Magnesium on cardio metabolic risk factors in infertile women with polycystic ovary**

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**A B S T R A C T**

Women with polycystic ovaries show a high incidence of ovulation failure perhaps linked to insulin resistance and related metabolic features. The aim of this study was to compare the effect of supplement Magnesium on cardiometabolic risk factors of infertile women with the polycystic ovary syndrome. This 12 week randomized parallel group trial was conducted to compare the effect of supplement Magnesium on cardiometabolic risk factors of infertile women with the polycystic ovary syndrome. In this study 69 patients were randomized to Metformin & Magnesium (34) and Metformin (35) groups. The numbers discontinuing the study prematurely were not statistically different between three groups. The mean changes of cardiometabolic factors (HDL, LDL and ...) were compared between three groups. Per protocol analysis was done for comparing treatment groups (34 and 35 patients in Metformin & Magnesium and Metformin groups, respectively). There were no significant difference in terms of age, metabolic syndrome frequency, the cause and duration of infertility between two groups. Many of the metabolic factors (BMI, BP, FBS, LDL, and cholestrol) have been decreased significantly in two groups after treatment ( $p < 0.001$ ). However this difference was not statistically significant for HDL, DHEAS, TG and testosterone. And also, in Metformin & Magnesium group, the positive changes of the parameters were more, and although this difference was not statistically significant in most cases. But, LDL, HDL and testosterone had more positive changes in Metformin & Magnesium group. Reduction rate of BMI and BP in Metformin & Magnesium group was more, but the difference was not statistically significant. In all patients, 10 patients had metabolic syndrome. Significant differences were not observed in the studied parameters between patients with and without metabolic syndrome.

**Introduction**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among reproductive-aged women with various

prevalence from 5-21% (1, 2). This syndrome is associated with wide spectrum complications in different aspects of health,

including reproductive (hyperandrogenism, hirsutism, anovulation, infertility, and menstrual disturbance), metabolic (obesity and diabetes mellitus as well as cardiovascular risk), and psychological features (mood disorders and decreased quality of life) (1, 3).

Insulin stimulates lipogenesis in arterial tissue and adipose tissue via an increased production of acetyl-Co A, and the entry of glucose and triglycerides (4). Increasing adipose tissue mass is associated with increasing levels of angiotensin II from the increased secretion of angiotensinogen by adipose tissue. Increase in angiotensin II could contribute to hypertension and aggravate insulin resistance (5).

It also has a metabolic component consisting of hyperinsulinemia and insulin resistance with increased cardiovascular disease risk, which occurs both in lean and obese women with the disorder, and has a strong association with metabolic syndrome(6-8).

Metabolic syndrome is another cluster of endocrine disturbances, including insulin resistance, dyslipidemia, obesity, and hypertension(9). In these patients, coronary artery disease(CAD) and atherosclerosis risk increases by 4-5 times, and CAD occurs with higher intensity and earlier (10). Studies have demonstrated that insulin has profound effects in the two levels of ovarian stroma and follicle, such that it induces androgen increase in the ovary.

Magnesium is the second ion found in abundance in body cells, and its role has been proven in adjustment and modification of blood pressure, improvement of peripheral vascular resistance and cardiac output, lipids metabolism, operation of different enzymes, reduction of damage

caused by free radicals, vascular endothelial damage and cardiac arrhythmias, and improvement of chronic disease risk (11). The aim of this study is to compare treatment effects of the supplements Magnesium on cardiometabolic risk factors in infertile women with PCOS.

## **Materials and methods**

In a clinical trial performed at obstetrics and gynecology department of Hamadan University of Medical Sciences on women visiting infertility clinic of Fatemiyeh Hospital for treatment of infertility, we compared treatment effects of the supplements Magnesium on cardiometabolic factors in infertile women with PCOS. The clinical trial was performed on 20-45 year-old women visiting infertility clinic of Fatemiyeh Hospital in Hamadan for treatment of infertility.

The criteria for diagnosis of PCOS were Rotterdam criteria. Inclusion criteria included abnormal menstrual cycles (oligomenorrhea and amenorrhea), polycystic ovary in sonography, chemical or clinical symptoms of hyperandrogenism (hirsutism and acne).

Exclusion criteria of the study included history of any underlying and chronic disease (chronic kidney disease, etc.), history of abdominal and pelvic surgery, abnormal hysterosalpingography, abnormal serum prolactin level, smoking, pregnancy, current or previous Statin use during the past 2 months, insulin use, use of corticosteroids, anti-obesity medication, and history of neoplastic diseases.

The selected individuals were divided in simple random form into 2 groups, and underwent treatment for 12 weeks. As Metformin is considered as part of the

routine treatment in infertility, all patients in all groups also received 1500 milligrams of Metformin every day along with the supplements received.

First group: under treatment with 75 millimoles of Magnesium (12).

Second group: who were under treatment only with Metformin.

The sampling method was the simple sampling method, and any individual with the inclusion criteria of the study was gradually included in the study. Random assignment was performed with the block-randomized method as follows. 5 pieces of paper reading Magnesium, and 5 pieces of paper reading Metformin were placed in a plastic bag and mixed, and then, for each patient included in the study, one piece of paper would be taken out of the bag, and the patient would be assigned one of the groups based on what was written on it, and the procedure would be followed for 15 patients, and then, the other patients were selected with this procedure.

Blood samples were taken from all groups at the beginning of the study after 8 to 12 hours of nighttime fasting. All of the cardiometabolic factors such as systolic blood pressure, diastolic blood pressure, blood sugar, insulin, total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), testosterone, and Dehydroepiandrosterone (DHEA) as well as the serum level of the received supplement were examined. At the end of the treatment period, blood samples were again obtained after nighttime fasting to measure the aforementioned cardiometabolic factors as well as the received supplement.

Adult Treatment Panel III (ATP-III) criteria:

1. A waist circumference of more than 102 cm in men and 88 cm in women

2. A triglyceride level over 150 or administration of drugs for the treatment of high TG
3. An HDL level below 40 or administration of drugs for the treatment of low HDL
4. An FBS level higher than 100
5. A Blood pressure (BP) higher than 130/80 or administration of Hypertension (HTN) drugs.

Patients who met three of the aforementioned five criteria were diagnosed with the metabolic syndrome.

The waist circumference of patients was measured in centimeters by the project resident.

In the Metformin & Magnesium group 3 patients were excluded because of their discontent with the tests and 2 patients were omitted because of their unwillingness for follow ups. In the Metformin group, 2 patients were excluded for their unwillingness to consume drugs, 3 were omitted because of diarrhea and one was excluded because of pregnancy using Intracytoplasmic Sperm Injection (ICSI).

### **Ethical Considerations**

All of the patients participated voluntarily in this study and the required information was presented to all of the patients under study in a comprehensible way. The patients were included in the study after completing the informed consent form which was approved by the ethics and research committee of the university. Patients were charged no additional costs and all of the medications and supplements were provided to the patients for free. All patients were free to leave the study and all of the information will remain confidential.

### **Statistical Analysis**

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean  $\pm$  SD. Continuous (quantitative) variables were compared by Independent samples, Paired T test and ANOVA test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value  $\leq 0.05$  was considered statistically significant.

### **Possible Problems and Solutions**

Lack of patient's consent: In order to solve this problem, we talked to the patients to the possible extent and provided them with the required explanations. Their questions about the study were also answered properly in order to win their consent and encourage them to participate in the study with full consent.

### **Result and Discussion**

This clinical trial that was carried out in the Department of Obstetrics and Gynecology of Hamedan University of Medical Sciences on women who visited the infertility clinic of Fatemiyeh Hospital to receive treatment for infertility. The effects of supplementary treatments (including Magnesium, Vitamin D, and Calcium) on the cardiometabolic factors of infertile women with PCOS were examined and compared. The following results were obtained from the examinations:

In this study, 70 patients were studied. Of the 69 patients, 35 were put in the Metformin & Magnesium group and 35 were put in the Metformin group. Finally, 5 patients were excluded from the study while 35 in the Metformin & Magnesium group

and 30 in the Metformin group finished the study.

The average age of patients in the Metformin & Magnesium group and the Metformin group was  $28.82 \pm 4.81$  and  $27 \pm 4.49$  years, respectively ( $p=0.107$ ). Results of analysis of other demographic parameters of patients are presented in Table (1).

According to the ATP-III criteria, the metabolic syndrome was observed in 10 patients. Of the patients with the metabolic syndrome, 7 in the Metformin & Magnesium group and 3 in the Metformin group.

Table (2) shows the changes in the parameters under study after the treatment as compared to the parameters before the treatment. Results presented in this table suggest that no significant difference existed between the changes in the levels of the following parameters in the three groups: Body Mass Index (BMI) ( $p=0.154$ ), SBP ( $p=0.610$ ), DBP ( $p=0.546$ ), FBS ( $p=0.627$ ), cholesterol ( $p=0.516$ ), TG ( $p=0.827$ ) and DHEA-S ( $p=0.450$ ). However, the reduction in LDL was significantly higher in the Metformin & Magnesium group ( $P=0.016$ ). In addition, the increase in the level of HDL was not significantly higher in the Metformin & Magnesium group ( $p=0.074$ ). The increase in the level of blood testosterone was not significantly higher in the Metformin & Magnesium group ( $p=0.106$ ).

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder amongst women of reproductive age. Antioxidant supplementation has been shown to improve insulin sensitivity and other health threatening conditions in women with PCOS (13-14). Despite the important role of

alternative medicine especially antioxidants in management of PCOS women, there are not many well-designed papers or detailed literature reviews report in this field, especially in Iran. In the other hand, the available studies addressing antioxidant use in PCOS women yielded controversial

results, because of their sample sizes or the diversity in the prescribed antioxidant or outcomes assessed in them. For overcoming these limitations, updating our knowledge on this field and a critical appraisal of all available studies might be helpful to guide clinical practice.

**Table.1** Demographics finding of patients in three groups

|                         | Groups                |                | P     |
|-------------------------|-----------------------|----------------|-------|
|                         | Metformin & Magnesium | Metformin      |       |
| Age(year)               | 28.82 ± 4.78          | 27.00 ± 4.49   | 0.107 |
| Height                  | 161.38 ± 6.10         | 158.80 ± 5.18  | 0.062 |
| Weight                  | 72.71 ± 12.93         | 67.54 ± 12.81  | 0.100 |
| Waist Circumference     | 89.38 ± 10.44         | 80.09 ± 11.18  | 0.001 |
| Hip Circumference       | 106.74 ± 12.14        | 101.00 ± 11.91 | 0.052 |
| Duration of infertility | 3.94 ± 2.91           | 5.01 ± 3.94    | 0.203 |

**Table.2** Analysis of the studied parameters among the two groups

|              | Groups                |                | P     |
|--------------|-----------------------|----------------|-------|
|              | Metformin & Magnesium | Metformin      |       |
| BMI          | -0.57 ± 0.44          | -0.38 ± 0.56   | 0.154 |
| SBP          | -5.00 ± 6.53          | -4.22 ± 5.25   | 0.610 |
| DBP          | -4.46 ± 5.67          | -3.59 ± 5.42   | 0.546 |
| FBS          | -6.25 ± 10.05         | -5.27 ± 3.53   | 0.627 |
| LDL          | -11.14 ± 13.53        | -4.37 ± 4.08   | 0.016 |
| Cholesterol  | -11.96 ± 20.51        | -15.10 ± 15.92 | 0.516 |
| HDL          | 1.21 ± 5.04           | -.98 ± 4.13    | 0.074 |
| TG           | -9.96 ± 28.31         | -8.70 ± 11.60  | 0.827 |
| Testosterone | 0.19 ± 0.48           | 0.03 ± 0.19    | 0.106 |
| DEAH-S       | 0.14 ± 0.77           | 0.02 ± 0.14    | 0.450 |

Women with PCOS have an increased risk of presenting with insulin resistance (IR) (15), impaired glucose tolerance (IGT) (16), type 2 diabetes mellitus (DM2) (16), obesity (15), and dyslipidemia (17). In addition to presenting with these traditional risk factors for CVD, women with PCOS also show evidence of an increase of nontraditional, novel CVD risk factors, such as subclinical

atherosclerosis (18) and an elevation in inflammatory markers (19).

The prevalence of obesity among women with PCOS in the USA is 70 to 80%, almost twice as much as in the general US female population (15, 20). Most studies report the prevalence of obesity in affected women outside the USA to be between 38 and 50%

(15, 20). Differences in diagnostic criteria, environmental factors, ethnicity, and lifestyle contribute to these variations (15, 21-22). Although less obesity is reported outside the USA, the prevalence of obesity among PCOS women outside the USA is still higher than that of women in the general population outside the USA (20).

Obesity in PCOS increases the patient's risk of developing cardiovascular disease. Among PCOS women, the prevalence of the metabolic syndrome, as in the general population, increases with increasing BMI and is highest in obese women with PCOS (23). Studies report the prevalence of the metabolic syndrome in PCOS women in the USA to be 43–47%, twice more than in the age- and BMI-matched control population, suggesting that PCOS per se, possibly by promoting abdominal fat accumulation, increases the risk of acquiring the metabolic syndrome (23).

In studies by Apridonidze and Gluek, incidence of metabolic-syndrome in patients with PCOS had been reported as 43% and 46% (24-25).

In a study performed by Dr. Azizi and et al., incidence of metabolic-syndrome in general population of Iran was reported as 30% (26). In our study, 10 patients among all suffered metabolic-syndrome before the study, which means lower incidence of metabolic-syndrome in our study than in the above studies, and there was also no significant difference between rates of changes in the parameters under study in the patients with and without metabolic-syndrome.

However, by examining the role of Magnesium in occurrence of PCOS in a study conducted in Iran (2011), Sharifi and et al., demonstrated that Magnesium shortage increases risk of suffering the

syndrome by 19 times (27). In our study, in the patients receiving Magnesium, the rates of the positive changes in the parameters under study was higher than in the other groups, and although this difference was not statistically significant in most cases, in regard to LDL, HDL, and testosterone, the rates of the positive changes in the Metformin and Magnesium group patients were significantly better than in the other two groups.

### **Conclusion**

In this study, we examined the effects of simultaneous reception of Magnesium as supplement in patients with PCOS, and the results suggest the effectiveness of use of these supplements in the suffering patients. Moreover, in the patients receiving Magnesium, the rates of the positive changes in the parameters under study was higher than in the other groups, and although this difference was not statistically significant in most cases, in regard to LDL, HDL, and testosterone, the rates of the positive changes in the Metformin and Magnesium group patients were significantly better than in the other two groups. The decrease rates of BMI and BP were higher in the patients receiving Magnesium, but this difference was not statistically significant. 10 patients among all suffered metabolic-syndrome before the study. There was no significant difference between rates of changes in the parameters under study in the patients with and without metabolic-syndrome.

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