



## Gynaecology

## AN OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF METFORMIN VERSUS A COMBINATION OF METFORMIN, CALCIUM AND VITAMIN D SUPPLEMENTATION ON MENSTRUAL CYCLE, BODY MASS INDEX AND HYPERANDROGENIC STATE IN POLYCYSTIC OVARIAN SYNDROME.

**Dr Smriti Anand\***

Resident, Dept of Obstetrics and Gynecology, Meenakshi Medical College, Main Gate, Balaji Nagar, Enathur, Kanchipuram- 631552, Tamil Nadu \*Corresponding Author

**Dr. A Kala**

MD, DGO, Resident, Dept of Obstetrics and Gynecology, Meenakshi Medical College, Main Gate, Balaji Nagar, Enathur, Kanchipuram- 631552, Tamil Nadu

**ABSTRACT**

**Introduction:** Polycystic Ovarian Syndrome was originally described in seven women in whom the syndrome could at best be described as the combination of hirsutism, obesity, amenorrhea, and enlarged bilateral polycystic ovaries.<sup>(1)</sup> Since then, our understanding of PCOS has evolved so far that none of the originally described features is considered to be a consistent finding in PCOS—not even the appearance of numerous tiny ovarian “cysts” for which the syndrome was named.<sup>(2)</sup>

**Materials and Methods:** After obtaining approval of the ethics committee, a prospective, randomized, clinical controlled study was conducted for 1 and 1/2 years. Patients were randomly allocated to one of the two groups, group D (n=50), received oral Tab Metformin 500mg BD, Tab Calcium 500mg OD, Tab Vitamin-D-1000 IU OD for 3months and group M (n=50), received oral Tab Metformin 500mg BD for 3months. Age, Menstrual irregularities, BMI, Hirsutism score Cases with hirsutism score >8, Acne, Alopecia, USG ovarian volume, S.LH, S.FSH, S. Total Calcium, S. Vitamin D and Free insulin were recorded both before treatment and after treatment in both groups. Patients were also observed for adverse reaction. Data was statistically analyzed using Epi info 7 computer software version: 7.2.1.0.

**Results:** Both groups were comparable with regard to demographic characteristics (p>0.05). There was statistically significant difference between the two groups regarding Body Mass Index, USG ovarian volume and S.Vitamin D. However there was no statistically significant difference between the two groups regarding Menstrual irregularities, Hirsutism score Cases with hirsutism score >8, Acne, Alopecia, S.LH, S.FSH, S. Total Calcium and Free insulin.

**Conclusion:** This study showed the positive effects of metformin, calcium & vitamin D supplementation on Body Mass Index, Serum Vitamin D and Ovarian volume in women with polycystic ovary syndrome.

**KEYWORDS :** PCOS; Metformin; Vitamin D; Calcium

**INTRODUCTION**

Polycystic Ovarian Syndrome was originally described in seven women in whom the syndrome could at best be described as the combination of hirsutism, obesity, amenorrhea, and enlarged bilateral polycystic ovaries.<sup>(1)</sup> Since then, our understanding of PCOS has evolved so far that none of the originally described features is considered to be a consistent finding in PCOS—not even the appearance of numerous tiny ovarian “cysts” for which the syndrome was named.<sup>(2)</sup>

PCOS is one of the most common endocrine disorders occurring in women. Epidemiological studies have resulted in estimates of prevalence, in women of reproductive age, that range from 6.5% to 8% using biochemical and/or clinical evidence,<sup>(3-6)</sup> and ultrasound-based studies have reported a prevalence of 20% or more.<sup>(7-10)</sup>

Evidences suggested that weight loss and metformin administration could improve hyper androgenic signs and symptoms of patients with PCOS possibly due to decreasing in androgen levels. Others demonstrated that changing in dietary habits, even without any significant weight loss may also improve endocrine feature and reproductive functions in this group of patients.<sup>(11)</sup>

The role of calcium (500 mg) and Vitamin D (400 unit) consumption and its deficiencies in different features of PCOS have been studied in some previous studies.<sup>(12-14)</sup> Their effectiveness is mainly due to their effect on body weight and follicular maturation. Both calcium and Vitamin D deficiency are considered as potential risk factors for obesity.<sup>(12-14)</sup>

**METHODOLOGY**

The study was conducted in Meenakshi medical college & research institute, Kanchipuram in department of Obstetrics & Gynaecology. The study was prospective in nature. All the patients were explained clearly about the purpose and nature of the study in the language they can understand who participated in the study. Patients were included in the study only after obtaining written informed and consent duly signed by them. A cross sectional analysis was made at the time of presentation. We collected the data for 1 1/2 years and analyzed the data statistically after clearance from the ethical committee. Inclusion criteria included patients with chronic unovulation and clinical or biochemical evidence of hyper androgenism and exclusion criteria included females below 20 and above 40 year of age, Cushing

syndrome, Renal failure (Cr ≥1.5), Androgenic ovarian and adrenal tumor, Primary and secondary hyper parathyroidism, Osteomalasia, Cancers and Mental retardation. Patients were divided into two Groups M and D where in each group 50 patients were taken (randomly allocated by chit method). Group M patients received Tab Metformin 500 mg BD and Group D patients received Tab Metformin 500 mg BD, Tab Calcium 500 mg OD and Tab Vitamin-d-1000 iu od. Treatment was given for 3months in both the groups. Following parameters were Body Mass Index, Menstrual abnormalities, Hirsutism score, Hirsutism, Acne, Alopecia, USG ovarian volume, Leutenizing Hormone, Follicle Stimulating Hormone, S.Calcium, S.Vitamin D and Free Insulin were noted before-treatment and after treatment.

**STATISTICAL ANALYSIS:**

Results were presented as mean ± SD, ranges, numbers and percentages. Data were analyzed using Student t-test and Chi-square test.

**OBSERVATION & RESULTS**

In the above study it was observed that before-treatment Body Mass Index (BMI) in group M was 24.84 ± 3.34 and in group D it was 25.17 ± 3.41. After treatment Body Mass Index (BMI) in group M was 23.90 ± 2.58 and in group D it was 22.59 ± 2.65 which was statistically significant with (p value = 0.013). It was observed that before-treatment Ultrasonographic volume of ovaries in group M was 10.98 ± 1.49 and in group D it was 10.70 ± 1.52. After treatment Ultrasonographic volume of ovaries in group M was 8.36 ± 1.99 and in group D it was 7.2 ± 1.46 which was statistically significant with (p value = 0.001). It was observed that before-treatment Serum Vitamin D values in group M was 22.88 ± 5.59 and in group D it was 22.59 ± 6.52. After treatment Serum Vitamin D values in group M was 22.87 ± 5.55 and in group D it was 27.06 ± 5.15 which was statistically significant with (p value = 0.002). Following parameters had no Statistically significance among both the groups age, Body Mass Index, Menstrual abnormalities, Hirsutism score, Hirsutism, Acne, Alopecia, USG ovarian volume, Leutenizing Hormone, Follicle Stimulating Hormone, S.Calcium, S.Vitamin D and Free Insulin were noted before-treatment and after treatment.

**DISCUSSION**

In 1935 Stein and Leventhal related bilateral polycystic ovaries in a clinical syndrome consisting of menstrual irregularity, masculine type of hirsutism and less consistently obesity. The condition was for a long time called Stein – Leventhal syndrome.<sup>(3)</sup>

PCOS is one of the most common endocrine disorders occurring in women. Epidemiological studies have resulted in estimates of prevalence, in women of reproductive age, that range from 6.5% to 8% using biochemical and/or clinical evidence,<sup>(3-6)</sup> and ultrasound-based studies have reported a prevalence of 20% or more.<sup>(7-10)</sup>

Evidences suggested that weight loss and metformin administration could improve hyper androgenic signs and symptoms of patients with PCOS possibly due to decreasing in androgen levels. Others demonstrated that changing in dietary habits, even without any significant weight loss may also improve endocrine feature and reproductive functions in this group of patients.<sup>(11)</sup>

The role of calcium (500 mg) and Vitamin D (400 unit) consumption and its deficiencies in different features of PCOS have been studied in some previous studies.<sup>(12-14)</sup> Their effectiveness is mainly due to their effect on body weight and follicular maturation. Both calcium and Vitamin D deficiency are considered as potential risk factors for obesity.<sup>(12-14)</sup> In addition, it is well established that increased body weight has a considerable negative effect on 25(OH) Vitamin D and 1, 25(OH)<sub>2</sub> Vitamin D<sub>3</sub> concentration in women with PCOS.<sup>(13)</sup>

The role of Vitamin D (50,000 unit) in the reproductive system has been also demonstrated in several studies.<sup>(15,21)</sup> Impaired calcium regulatory system could cause follicular arrest. Moreover, animal studies in this field indicated that the calcium has a crucial role in oocyte maturation as well as resumption and progression of follicular development.<sup>(22)</sup> **Hatav et al**<sup>(65)</sup> conducted a study in which before treatment BMI in metformin group and in metformin with calcium and vitamin D group after treatment BMI is comparable to our study. **Veena Gupta et al**<sup>(70)</sup> conducted a study in which group with before treatment BMI in metformin group and in metformin with calcium and vitamin D group was comparable to our study. **Hatav et al**<sup>(65)</sup> conducted a study in which before treatment Mean Vitamin D values in metformin group and in metformin with calcium and vitamin D group after treatment BMI is comparable to our study. **Veena Gupta et al**<sup>(70)</sup> conducted a study in which before treatment Mean Vitamin D values in metformin group and in metformin with calcium and vitamin D group after treatment BMI is comparable to our study.

## CONCLUSION

- This study showed the positive effects of metformin, calcium & vitamin D supplementation on Body Mass Index, Serum Vitamin D and Ovarian volume in women with polycystic ovary syndrome.
- Metformin is an effective treatment for anovulation in women with polycystic ovary syndrome and there is some evidence of benefits on variables of the metabolic syndrome.
- Vitamin D deficiency is one of the commonest cause of PCOS, hence metformin, vitamin D with calcium supplementation have shown beneficial effects over metformin alone. This leads to support of vitamin D in future has therapeutic role in women with PCOS.
- Therefore, further research with high quality randomized controlled trials is warranted to establish the impact of vitamin D supplementation in the management of PCOS.

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**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Ethics Committee

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