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EFFECT OF SUPPLEMENTING MYOINOSITOL AND VITAMIN D3 ON CLOMIPHENE CITRATE INDUCED OVULATION IN INFERTILE WOMEN WITH POLYCYSTIC OVARIAN SYNDROME – A RANDOMIZED CONTROL TRIAL

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Abstract: Polycystic ovarian syndrome is the major cause of an ovulatary infertility, which is mainly because of insulin resistance. Myoinositol, a nutrient belonging to vitamin B family has shown to improve hormone profile and metabolic disorders in patients with PCOS by amelioration of pre-existing insulin resistance. Vitamin D also has a positive effect on folliculogenesis. This study analyses the effect of using Myoinositol and Vitamin D3with Clomiphene Citrate on the ovulation in infertile women with PCOS. Aim: To evaluate the effectiveness of using Myoinositol and vitamin D3 with Clomiphene Citrate for ovulation induction in infertile women with PCOS. Methodology: Inpatients with PCOS and infertility, total of 94 patients were enrolled and the first group of patients received Myoinositol and vitamin D3 with Clomiphene Citrate and the second group of patients received Clomiphene Citrate alone. Results: Ovulation rate in group 1 was 32.25% and group 2 was 31. 5%. Satisfactory endometrial response rate was 25.9% in group 1 and 22.4% in group 2. Overall follicular rupture rate was 22.7% in group 1 and 25.5% in group 2. Conclusion: The addition of Myoinositol and Vitamin D3 with Clomiphene citrate in PCOS women improves the ovulation and pregnancy rates. The addition of Myoinositol and Vitamin D3 does not have any undue side effects.

Keywords: Myoinositol; Vitamin D3; Clomiphene Citrate; Ovulation Induction.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) in women of reproductive age is associated with a broad range of health conditions including hypertension, dyslipidemia, insulin resistance, hyperandrogenemia and type 2 diabetes mellitus. Globally the prevalence of PCOS is estimated between 5.5% to 12.6%.[1] In India the prevalence estimates are between 8.2% and 22.5%.[2]

PCOS is characterized by anovulation, hyperandrogenism, hirsutism and polycystic ovaries on USG. These women are at higher risk of developing Type 2 diabetes mellitus than due to insulin resistance their age and weight matched counterparts without PCOS. This syndrome is currently recognized as the leading cause of anovulatory infertility accounting for more than 80% of the cases.[3]
Clomiphene citrate is a SERM and has long been assumed as the standard first line agent in ovulation induction of PCOS patients due to satisfying ovulation rate of 85% and pregnancy rate exceeding 35%.[4]Recent evidence has shown that Myoinositol, which is a nutrient belonging to Vitamin B family may improve hormone profile and the metabolic disorders accompanying PCOS, probably through the amelioration of preexisting of insulin resistance.[5]

Vitamin D deficiency is common in PCOS. Vitamin D status is linked to reproductive function, metabolic alterations and mental health. Vitamin D therapy decreases serum androgen in PCOS patients. They have positive effect on menstrual cycle and on folliculogenesis. Women demonstrating increased VDR expression in the endometrium were more likely to get pregnant than their counterparts with decreased VDR expression. VDR expression of the granulosa cells and vitamin D content of the follicular fluid are decreased in PCOS, which also suggests that vitamin D supplementation may aid the treatment of infertility in PCOS.[6] Hence we conducted a study to analyse the effect of using Myoinositol and Vitamin $D_3$with Clomiphene Citrate on the ovulation in infertile women with PCOS.

Aim:
To evaluate the effectiveness of using Myoinositol and vitamin D_3 with Clomiphene Citrate for ovulation induction in infertile women with PCOS.

Objective:
Primary objective:
a. To compare the ovulation rate of Myoinositol and Vitamin D_3 with Clomiphene Citrate with the ovulation rate of Clomiphene citrate only.

Secondary objective:
a. To compare the pregnancy rates between the groups.
b. To compare the first trimester pregnancy outcome between the groups**.**

MATERIALS AND METHODOLOGY
After obtaining approval from the Institute Ethics Committee and Institute Research Committee, the study was started on PCOS patients with infertility undergoing ovarian stimulation in Obstetrics and Gynaecology Department in Indira Gandhi Medical College and Research Institute.

Inclusion criteria
- Women in the age group of 20-35 years.
- Diagnosed as PCOS according to Rotterdam s criteria.
- Infertility

Exclusion criteria
- Women with other causes of infertility
- Women who received treatment in the past 3 months.

Infertility was defined as the failure to achieve pregnancy within 12 months or more of regular unprotected sexual intercourse. Patients with PCOS were identified by the presence of two of the following three features :1) oligo or anovulation 2) clinical signs of hyperandrogenemia or 3) polycystic ovaries on ultrasound.[12]Detailed history, examination and Infertility workup for the patients was done according to the routine department protocol. Patients satisfying the inclusion criteria were randomized into two groups.

The first group of patients received Myoinositol and vitamin D_3 with Clomiphene Citrate and identified as the MI +CC group. The second group of patients received Clomiphene Citrate alone and identified as the CC group. In the MI+CC group patients received Myoinositol 2000mg and Vitamin D_3 1000 IU orally throughout the cycle and Clomiphene Citrate 100 mg orally from the 2^{nd} day to the 6^{th} day of menstrual cycle for a maximum of three successive cycles.

In the CC group, only Clomiphene citrate 100mg was given from day 2^{nd} to 6^{th}day of the menstrual cycle for maximum of three successive cycles

In both the groups follicular monitoring was done by transvaginal ultrasonography (TVS) on alternate days from day 9 of menstrual cycle until a mature follicle detected. Follicle considered mature when attained 20mm in size or more by averaging inner two diameters of the follicle. A Single injection of 5000 IU hCG was given, if at least one follicle attained

20mm. TVS was done after 48 hours of hCG injection to determine follicle rupture. If the follicle found unruptured, TVS will be done after 72 hours of the HCG injection to detect whether follicle has ruptured or not.

The following parameters will be compared between both the groups:

1. Ovulation rate- Ovulation rate was assessed by number of mature follicle (diameter 20 -22 mm) per cycle .
2. Response of endometrium- Endometrial thickness of 7mm was considered a satisfactory response of the endometrium.
3. Follicular rupture was ascertained by the following criteria
    a. Disappearance or sudden decrease in follicular size.
    b. Increased echogenicity inside the follicle, indicating corpus luteum formation.
    c. Free fluid in pelvis (or pouch of Douglas)
    d. Replacement of triple-line appearance of endometrium by homogenous, hyperechoic "luteinized'' endometrium
    e. Chemical pregnancy – Pregnancy when diagnosed by positive beta HCG.
    f. Ongoing pregnancy – Viable pregnancy diagnosed by ultrasound.

Sample size was calculated using open epi software.
Confidence interval as 95% and power as 80%. mean as 7.7 and 8.4 for each group respectively.
The total sample size iwass 86, 43 for each group. After adjustment for loss to follow up and non response rate of 20%, final sample size is 94, 47 for each group

RESULTS

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using IBM SPSS (SPSS Inc.,IBM Corporation, NY, USA) Statistics Version 25 for Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The data were checked for normality before statistical analysis using Kolmogorov Simonov test. The unpaired t test (for quantitative data to compare two independent observations) was applied. The chi square test was used for qualitative data comparison of all clinical indicators. Level of significance was set at $P \leq 0.05$.

TABLE 1: Comparing ovulation, endometrial response, follicular rupture and pregnancy rate between the two groups across the three cycles

Ovulation	**Group 1**		**Group 2**		**p- value**
	Total women	No. of ovulation	Total women	No. of ovulation	
1st cycle	47	13(27.7%)	47	10(21.3%)	0.001
2nd cycle	43	14(32.5 %)	45	18(40 %)	0.003
3rd cycle	34	13(38.2%)	41	14(34.1%)	0.000
1st cycle	27.7%		21.3%		0.001
2nd cycle	32.5%		40%		0.003
3rd cycle	38.2%		34.1%		0.000
Overall ovulation rate	32.25%		31.5%		0.000
Endometrial response (ER)	**Group 1**		**Group 2**		**p- value**
	Total women	Satisfactory ER	Total women	Satisfactory ER	
1st cycle	47	11(23.4%)	47	7(14.9%)	0.54
2nd cycle	43	12(28 %)	45	13(28%)	0.88
3rd cycle	34	9(26.4%)	41	10(24.3%)	0.92
1st cycle	23.4%		14.9%		0.7
2nd cycle	28%		28%		
3rd cycle	26.4%		24.3%		
Overall ER	25.9%		22.4%		
Follicular rupture (FR)	**Group 1**		**Group 2**		**p- value**
	Total women	FR	Total women	FR	0.9
1st cycle	10	11(23.4%)	10	7(14.9%)	
2nd cycle	12	12(28 %)	13	13(28%)	
3rd cycle	10	9(26.4%)	13	10(24.3%)	
Overall FR	22.7%		25.5%		
Pregnancy rate	**Group 1**		**Group 2**		
1st cycle	4	8.5%	2	4.2%	

2nd cycle	8	18%	4	8.8%	
3rd cycle	6	18%	8	19.5%	

In group MI+CC among the 47 participants, 27.7% of women achieved mature follicle size whereas 21.3 % in CC group achieved mature follicle size in first cycle. In the 2nd cycle, higher percentage of women achieved mature follicle size in CC group (40%) compared to MI + CC group(32.5%). This difference in both groups were statistically significant. In group MI+CC among the 34 participants, 38.2% achieved mature follicle size whereas in group CC among the 41 participants 34.1% achieved mature follicle size. This difference was found to be statistically significant. Ovulation rate was assessed by number of mature follicle (diameter 20 -22 mm) per cycle. In MI+CC group the ovulation rate in 1st cycle was 27.7% which was statistically significant in compared to the ovulation rate of CC group which was 21.3%. In the MI+CC group the ovulation rate in 2nd cycle was 32.5% whereas 40% in CC group. In the MI+CC group, the ovulation rate in 3rd cycle was 38.2% whereas 34.1% in CC group which was statistically significant. All the women who achieved mature follicles in both groups achieved only one follicle per cycle. The overall ovulation rate in MI+CC group was 32.25 % which was higher than the CC group in which the ovulation rate was 31.5% with a significant P value of 0.000. In the 1st cycle in MI+CC group, 23.4% achieved satisfactory endometrial response whereas in CC group it was 14.9% with a P value of 0.54. In the 2nd cycle in both the MI +CC group and CC group, 28% achieved satisfactory endometrial response with P value of 0.88, both not statistically significant. In the 3rd cycle in MI + CC group, 26.4% achieved satisfactory endometrial response whereas in CC group it was 24.3% which was not statistically significant. Response of endometrium was assessed by the Endometrial thickness of 7mm which was considered a satisfactory response. In group MI+CC in the 1st cycle, 23.4% achieved satisfactory endometrial response whereas in CC group it was 14.9 %. In the 2nd cycle, both the groups achieved satisfactory endometrial response of 28%. In the 3rd cycle in MI +CC group, 26.4% achieved satisfactory endometrial response whereas in CC group it was 24.3%. The overall endometrial response was 25.9% in MI + CC group whereas 22.4% in the CC group with a P value of 0.7 which was not statistically significant . In both MI + CC and CC group, the follicular rupture in first cycle was 21.3%. In the 2nd cycle, the follicular rupture was 25.5% in MI +CC group whereas in CC group it was 27.7%. In the MI + CC group, the follicular rupture was 21.3% whereas in CC group it was 27.7% in the 3rd cycle. The overall follicular rupture rate in MI+ CC group was 22.7% and in CC group it was 25.5%. These differences are not statistically significant. Pregnancy rate was assessed by both Ultrasonagraphy and positive urine pregnancy test. In the MI + CC group, the pregnancy rate in 1st cycle was 8.5% wheras in CC group it was 4.2%. In the MI + CC group, the pregnancy rate in2nd cycle was 18% whereas in CC group it was 8.8%. In the MI + CC group, the pregnancy rate in 3rd cycle was 18% whereas in CC group it was 19.5%. The overall pregnancy rate in MI + CC group was 15% and 11% in CC group, with significant P value of 0.000. In the MI + CC group, Pregnancy rate in first cycle was 8.5%, in the second cycle it was 18% and in third cycle it was 18%. In the CC group, Pregnancy rate in first cycle was 4.2%, in the second cycle it was 8.8% and in third cycle it was 19.5%. Of all the women who became pregnant, within the first trimester 94.4% had viable pregnancy, 5.5 % had abortion in MI+CC group. In CC group there were 78.5% viable pregnancy, 14% abortion and 7% ectopic pregnancy among those who became pregnant. But these differences were not statistically significant. There were no multiple pregnancies in both the groups. There were no side effects like OHSS, ovarian enlargement, ovarian cyst formation and gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain between both the groups.

DISCUSSION

In our study oral Myoinositol and vitamin D_3along with Clomiphene citrate was compared to Clomiphene citrate group in infertile women with PCOS. In the first group Myoinositol was administered at the dose of 2000 mg, Vitamin D_3 1000 IU throughout the cycle and Clomiphene citrate 100 mg orally once a day was given for 5 days from day 2 to day 6 of menstrual cycle for three successive cycles. In the second group 100 mg clomiphene citrate was given for 5 days from day 2 to day 6 of the menstrual cycle.

The study was done on 94 women with PCOS. On 47 women, oral Myoinositol, vitamin D3 and Clomiphene citrate was used and in 47 women, only Clomiphene citrate was used as ovulation induction agent. The primary outcome assessed was to compare the ovulation rate between Myoinositol, vitamin D_3 along with clomiphene citrate and with clomiphene citrate alone. The secondary outcome was to assess the pregnancy rate and first trimester pregnancy outcome between both the groups.

The mean age of the participants in both the groups were 29.11 ± 3.272 versus 28.45 ± 5.311 and was not statistically significant. The mean BMI was higher in Myoinositol and Clomiphene citrate group when compared to Clomiphene citrate group which was 26.500 ± 2.0703 versus 24.902 ± 2.0035 which was statistically significant. In our study ovulation rate was higher in the Myoinositol group in spite of patients being of a higher BMI but the difference was not statistically significant. This could suggest that Myoinositol with Vitamin D_3 has a positive effect on the metabolic abnormalities of PCOS. So Myoinositol with VitaminD_3 has a better outcome when it was used along with clomiphene citrate. Similar results were proved by Constantino et al,[5] among 42 patients in the Myoinositol group plasma triglycerides and total cholesterol was significantly decreased with a P value -0.003. Also the whole body insulin sensitivity significantly

increased and total serum Testosterone was significantly reduced with the P value – 0.01 in the myoinositol group. Ovulation was restored in 69% women in the myoinositol group with a significant P value- 0.001. In a study by Gerli S, Mignosa M et al,[7] the inositol group shows significant reduction in weight with a significant P value – 0.01. But the HDL and also the metabolic benefits of inositol treatment were not observed in morbid obesity which shows a inverse relationship between BMI and myoinositol therapy.

Comorbidities in both the groups were similar and the difference was not statistically significant. In our study 40.4% had family history of comorbidities which was statistically significant.

In our study, the ovulation rate was higher in Myoinositol, Vitamin D_3 and Clomiphene citrate group which was 32.25% when compared to clomiphene citrate 31.5%. The ovulation rate also increases progressively from 1st cycle to 3rd cycle in myoinositol group, these results suggest that Myoinositol with Vitamin D_3 can be used for a few months before starting ovulation induction treatment. This can have a favourable outcome on achieving ovulation and pregnancy.
Similar results were proved by Papaleo et al,[8] where the ovulation rate is 72% in myoinositol group. The dosage used in their study was 4 grams over a period of 6 months. In our study 2 grams over 3 months was used which shows a favourable response of ovulation at low dosage. In the study by Reffone et al,[9] a comparison between Myoinositol and Metformin which shows 65% ovulation rate in Myoinositol and 50% in metformin group. Pundir J et al,[10] reviewed a meta analysis on Myoinositol and concluded that inositol was associated with significantly improved ovulation rate (RR - 2.3 ; 95% CI 1.1 - 4.7)

The satisfactory endometrial response rate was 28.9% in Myoinositol, Vitamin $D_3$and Clomiphene citrate group and 22.4% in Clomiphene citrate group which was not statistically significant. The response was slightly higher in Myoinositol group. These results suggest Myoinositol can be used in PCOS women undergoing IVF treatment to increase the endometrial thickness. These similar results were proved by Wdowiak et al,[11.] on the effect of myoinositol, vitamin D_3 and melatonin on the oocyte quality and pregnancy in IVF where the endometrial thickness in the study group was 12.40 ± 1.22 and 9.89 ± 1.11 in the placebo group which was statistically significant <0.001.

Antonio Regidor et al,[12] in PCOS women undergoing IVF treatment.72% of the women achieved ovulation in Myoinositol group. The number of oocytes retrieved in the myoinositol group is 233 oocytes in compared to placebo where the number of oocytes retrieved is 300. Out of 233, 136 oocytes where fertilized in myoinositol group. Out of 300,128 oocytes were fertilized in placebo group also the duration of stimulation and usage of FSH was lower in myoinositol group

Mohammedi S et al,[13] demonstrated that the number of oocytes retrieved; number of M II oocytes number of embryos transferred ,clinical and chemical pregnancy was higher in the Myoinositol group but they are not statistically significant. But the ovarian sensitivity index and fertilization rate were significantly higher in the myoinositol group ($p > 0.05$) also the dosage of gonadotropins is significantly reduced in Myoinositol group.

The follicular rupture rate in myoinositol group was 22.7% while in CC group it was 25.5% with a P value of 0.9 which was not statistically significant but CC group has a little higher rupture rate so it suggests that adding clomiphene citrate with myoinositol instead of myoinositol alone can improve ovulation in PCOS women .These results were proved by Smith S et al,[14] study of folliculometry on spontaneous and clomiphene citrate induced ovulation and showed the disappearance of follicle in 36% and presence of fluid in POD by 52% compared to disappearance of follicle in 40% and appearance of fluid in POD by 48 % in spontaneous cycle

Pregnancy rate in MI + CC group was 15% whereas in CC group it was 11% which was statistically significant with a P value of -0.000. Also in our study, in MI + CC group pregnancy rates were more in second and third cycle compared to first cycle (8.5% ,18%,18%in each of the three cycles respectively). This suggests that longer use of Myoinositol improves ovulation rate and pregnancy rates Even in the Clomiphene citrate group pregnancy rates increased progressively from first to third cycle.

Comparing the first trimester pregnancy outcome, there were 94.4% viable pregnancy, 5.5% abortion in MI+CC group. In the CC group there were 78.5% viable pregnancy ,14% abortion and 7 % ectopic pregnancy. No multiple pregnancy was noted and ovarian hyperstimulation was also not seen in both the groups. This suggests that usage of Myoinositol can increase the pregnancy rate and has a higher viable pregnancy, hence myoinositol can help to restore and improve fertility in PCOS women. These results were proved in similar study by Artini et al.[15] Among the 45 participants the pregnancy rate was 60% in myoinositol group which was significant with the P value of 0.005.Viable pregnancy outcome was 32% in myoinositol group with P value of 0.05. Similarly in study by Raffone et al,[33] the pregnancy rate was 48.4% in myoinositol and 36.6% in metformin group ,abortion rate was 20.6% in myoinositol and 22.7% in metformin group. Even though these rates were high but both the results are statistically not significant. In a study conducted by Papaleo E ,Unfer V et al,[32]

among the 25 participants the pregnancy rate was 40% and the abortion rate was 40 % compared to the placebo group these results are statistically significant .

In a similar study by Papaleo E, Unfer V Baillargeon JP et al,[16] the pregnancy rate in myoinositol group was 26.6% vs 23.3% in placebo group but the abortion rate is higher in placebo group 28.5% than in myoinositol group which was 25 % but these are not statistically significant.

CONCLUSION

The addition of Myoinositol and Vitamin D_3 with Clomiphene citrate in PCOS women improves the ovulation and pregnancy rates. The addition of Myoinositol and Vitamin D_3 does not have any undue side effects.

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