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Observational study of usage of a combination of inositols with alpha-lactalbumin (Ovamystic) in the treatment of menstrual irregularity in PCOS

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ABSTRACT

Objective: This observational study aimed at evaluating the effects of Ovamystic in groups of women with menstrual irregularities in Polycystic Ovary Syndrome (PCOS), treated at Mahavir Hospital and Manish IVF Center Surendranagar, Gujarat.

Materials and Methods: The study involved 126 normal weight or overweight PCOS patients aged 18 to 30 years, with menstrual irregularity and anovulation > 12 months. Patients were administered orally chewable tablets of Ovamystic (myo-inositol 1100mg + D-chiro-inositol 27.6mg + alpha-lactalbumin 50mg + chromium picolinate 400mcg + vitamin D2 400IU) twice daily for 6 months. The primary outcome was measured in terms of certain parameters like changes in body mass index (BMI), change in ovarian volume, and change in frequency and duration of menstrual cycle (M-SCORE). Alpha-lactalbumin is effective in increasing myo-inositol intestinal absorption, which is very useful in reducing the therapeutic failure of myo-inositol in some patients (inositol resistant subjects).

Results: Recovery was general, and its relevance was higher when the starting point was further away from the normal range. The most important results with Ovamystic were obtained in correcting the menstrual irregularity, and also decreasing ovarian volume and BMI. No significant adverse effects were detected in this group of patients, and Ovamystic had good tolerability and compliance.

Conclusion: This observational study demonstrated that Ovamystic improves important parameters in PCOS patients characterized by different metabolic profiles like BMI, menstrual irregularities, and ovarian volume.

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1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder in premenopausal women which presents with signs and symptoms of androgen excess & ovarian dysfunction.^{1,2} Androgen excess termed as hyperandrogenaemia causes excessive insulin production, hormonal imbalance leading to increased LH: FSH

ratio causing menstrual irregularities, acne and hirsutism. Particularly hyperandrogenism retards follicular growth, which can lead to microcysts in the ovaries, anovulation, and menstrual irregularities like oligomenorrhea or amenorrhea. The prevalence of infertility in women with PCOS can be as high as 70-80%, while almost 80% of anovulatory infertility cases are due to PCOS.³ Based on the Rotterdam criteria (2003), Polycystic Ovary Syndrome (PCOS) is diagnosed when the patients show two of the following

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clinical and endocrine features: chronic ovulatory disorder, clinical and/or hyperandrogenism, and polycystic ovaries.⁴ There is a high incidence of insulin resistance in PCOS patients. Resistance to insulin causes an increased level of insulin, decrease in sex hormone binding globulin (SHBG), increase in free androgen, and increased free testosterone level. These changes are responsible for various symptoms of PCOS. In these last years a great body of evidence has demonstrated the important role of altered insulin sensitivity in many, though not all, PCOS patients.⁵⁻⁷ Treatment of PCOS aims at decreasing insulin sensitivity, and maintaining balanced hormonal levels, which leads to regular menses and ovulation.

There is a renewed interest towards natural therapies in India to treat PCOS holistically and minimize drug related side effects and tolerability issues.⁸ Ovamystic is one such class of drug for PCOS management containing inositols and alpha-lactalbumin that have clinically proven efficacy without much of side effects.

Ovamystic consists of myo-inositol 1100mg + D-chiro-inositol 27.6mg + alpha-lactalbumin 50mg + chromium picolinate 400mcg + vitamin D2 400IU. Myo-inositol acts as an insulin sensitizer by reestablishing the depleted store of GLUT-4 protein levels and it leads to increase in cellular glucose uptake in PCOS. Through sodium/myo-inositol transporter (SMIT-1) and phosphorylated AMP-activated protein kinase (p-AMPK) dependent mechanism it increases the GLUT-4 translocation and expression on the cell membrane. (Figure 1). Myo-inositol also enhances insulin-sensitivity by metabolizing and generating Phosphatidylinositol (4,5)-biphosphate (PIP2) and Phosphatidylinositol (3,4,5)-trisphosphate (PIP3) which act as a second messenger in the insulin pathway through the activation of the enzyme phosphatidylinositol-3-kinase/protein Kinase B (PI3K/AKT).⁹

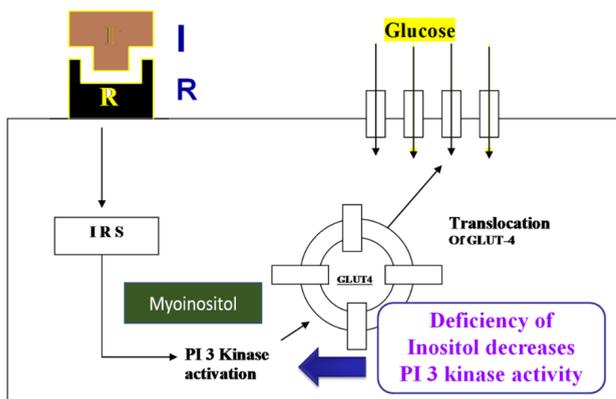


Figure 1: Mechanism of action of myoinositol I= Insulin, IR= Insulin receptor, IRS= Insulin receptor substrates, PI= Phosphatidylinositol, GLUT= Glucose transporter

The presence of abnormal ovarian ratios of myo-inositol (MI) to D-chiro-inositol (DCI) is seen in PCOS patients. D-chiro-inositol (DCI), accelerates the dephosphorylation of glycogen synthase and pyruvate dehydrogenase. Elevated DCI causes increased androgen production and abnormal ovulatory cycle.¹⁰ At the same time since some actions of insulin are mediated by inositolphosphoglycan (IPG) mediators, deficient release of a d-chiro-inositol-containing (DCI) IPG mediator may contribute to insulin resistance in women with PCOS.¹¹ Therefore, DCI should always be given with MI in a ratio of 40:1 of MI: DCI for maximum benefit in treating the cause.^{12,13}

Myo-inositol intake during meals may result in the intestinal co-presence of different sugars that may compete for the same co transporters, causing a marked decrease in myo-inositol absorption. Presence of chronic inflammatory state in PCOS leads to gut dysbiosis and metabolic disturbances.¹⁴ This can further reduce the absorption of myo-inositol, which ultimately leads to increasing insulin resistance. Myo-Inositol (MI), has been reported to be greatly correlated to ovarian function and oocyte quality in patients undergoing IVF procedures, independently from circulating plasma levels.^{15,16}

Alpha-lactalbumin is a globular whey protein that constitutes approximately 22% of the proteins in human milk and approximately 3.5% of those in bovine milk. It is an important source of essential amino acids, including tryptophan, lysine, branched-chain amino acids like leucine, and sulfur-containing amino acids. It is broken down in intestine to release bioactive peptides, which possess prebiotic, antibacterial properties, anti-inflammatory and immunomodulatory activities.¹⁷ (Figure 2)

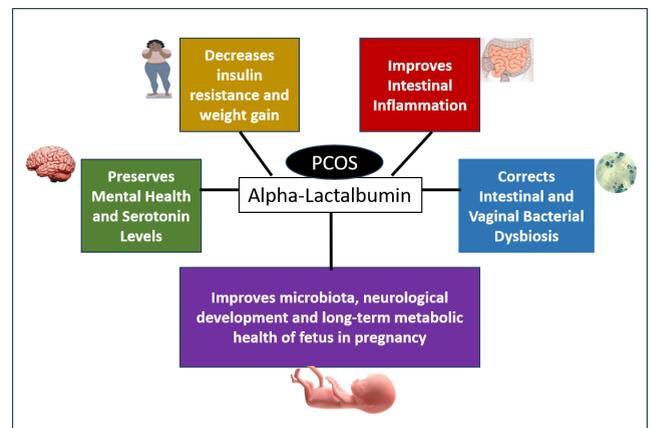


Figure 2: Alpha lactalbumin benefits

Administered orally, it passes undisturbed through the stomach, unlike all the other proteins that precipitate in the gastric environment Alpha-lactalbumin may offer a novel approach to treat inositol non-responsive PCOS patients. It can stimulate the secretion of GLP-2 (glucagon-like

peptide) which in turn increases the gene expression of SGLT-1 and GLUT-2 transporters.¹⁸ Alpha-lactalbumin (A-LA) also improves the permeability at the tight junctions of the intestinal cells that improves direct absorption of inositols. Co-administration of inositol plus alpha-lactalbumin may be more effective than inositol alone, providing a clinical efficacy even in the so-called inositol resistant patients.

Here, our aim is to enlarge and deepen insights through the results obtained in the observational study carried out on 126 patients, evaluating the effect of Ovamystic on menstrual irregularities, body mass index (BMI) and ovarian volume in a group of patients affected by PCOS, treated at Mahavir Hospital and IVF Center, Lati plot, Surendranagar, Gujarat.

2. Material and Methods

2.1. Subjects

A total of 126 normal weight or overweight PCOS patients aged 18 to 30 years who presented with menstrual irregularity and anovulation > 12 months were recruited for this study after informed consent. These patients were selected among a population attending the Mahavir Hospital and IVF Center, Surendranagar, Gujarat. Patients were treated with Ovamystic chewable tablets twice daily, for 12 weeks for three such cycles, which makes up a total course of 6 months. No changes of life style or diet was required from the patients, and no other concomitant therapy was given. Therefore, patients served as their own controls.

2.2. Assessment

Amenorrheic patients were studied the first time on a random day, while oligomenorrheic patients were studied on day 7 of the menstrual cycle. All parameters including vital data of the patient such as last menstrual period (LMP), dates of consultation and evaluation, full name of patient, age, as well as all efficacy parameters and side effects were recorded on a case record form (Tables 1, 2, 3 and 4 Appendix 1), and all the data was also recorded in an excel sheet for analysis on every visit throughout the course of 6 months.

A total of 3 visits for each patient were scheduled, with each visit being 12 weeks apart (1st visit on day 0, 2nd visit at 12 weeks since day 0, and, 3rd visit at 24 weeks since day 0). During each visit weight (in kgs) was recorded and BMI calculated. History regarding changes in frequency and duration of menstrual cycle was taken from each patient during their respective hospital visits. Ultrasonography (USG) was performed to see the ovarian volume and follicular maturity.

Table 1: Case record form (Appendix 1)

Ovamystic Observational Study in PCOS	
Patient ID	
Age	Years
Date of first consultation	Weight in Meters
Weight in Kg	
BMI_____W/H2	
BMI categorization (based on chart below)	
BMI	Weight status
Below 18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Obesity class 1
35.0-39.9	Obesity class 2
Above 40	Obesity class 3

Table 2: Menstrual history (Appendix 1)

Age of Menarche _____ years
LMP _____
Menstrual abnormalities since _____ months (minimum 12 months)
1. Frequency – normal / infrequent / frequent (normal range 21 – 35 days)
2. Duration – normal / prolonged (prolonged - >7 days)
3. Bleeding – normal / heavy (heavy – changing pad more frequently than 2 hours)
History of secondary amenorrhea (no period > 90 days; pregnancy ruled out) - not present / present. If present since _____ months
Diagnosis _____
Therapy Ovamystic (Myoinositol-D Chiroinositol + Alpha Lactalbumin, with VitD2 and Chromium): 1 tab twice daily started on (one tablet morning and one in evening) _____

Table 3: Patient follow up record (Appendix 1)

Menstrual Cycle	Visit 1 (Baseline day 0)	Visit 2 (12 weeks)	Visit 3 (24 weeks)
Period frequency (days)			
Period frequency category (normal/abnormal)			
Period Duration (Days)			
Period Duration category (normal/abnormal)			
Bleeding (normal/abnormal)			
Secondary Amenorrhea present			
Menstrual Abnormality Score*			

Table 4: Menstrual abnormality score (M-score) calculation (Appendix 1)

	Score 0 - normal	Score 1 - abnormal
Period frequency	21-35 days	<21 days; >35 days
Period duration	7 days or less	>7 days

BMI Evaluation	Visit 1 (Baseline-day 0)	Visit 2 (12 weeks)	Visit 3 (24 weeks)
BMI value			
BMI category			

Ultrasound Parameters	Visit 1 (Baseline-day 0)	Visit 2 (12 weeks)	Visit 3 (24 weeks)
Ovarian volume			

Date	Type	Severity (mild/moderate/severe)	Spontaneous resolution (yes/no)	Was therapy stopped or changed (yes/no)
-				

3. Results

The above observational study shows changes in frequency and duration of menstrual cycle noted as M score (Figure 3) where in first visit M-SCORE of 1 patient was zero while that of 125 patients was one. During second visit, M-SCORE of 15 patients was zero and that of 111 patient was one. At the time of third visit, M-SCORE of 58 patient was zero and for 68 patients it was one (0 – period frequency 21-35 days and period duration of 0-7 days) while (1- period frequency <21 days or >35 days or period duration of > 7 days).

Changes in the ovarian volume (Figure 4) were seen where in first visit it was zero for 120 patients and one for 6 patients. In second visit it was zero for 41 patients and one for 85 patients. While during third visit it was zero for 17 patients and one for 109 patients (0 which is considered as normal while 1 denotes decreased but not normal ovarian volume).

BMI was noted in every visit by recording the weight and converting it to BMI, and then the average of all BMI readings was taken during every visit which was 24.512 during first visit, 24.264 during second visit and 24.104 during third visit respectively (Figure 5). From the above-mentioned values, we can say that there was a mild decrease in the BMI (i.e. from average of 24.512 to 24.104).

So, from the study data collected and analysed in this 6-month periods there was evidence of marked positive changes in our desired parameters.

No significant adverse effects were seen, and patients showed good tolerability and compliance to Ovamystic.

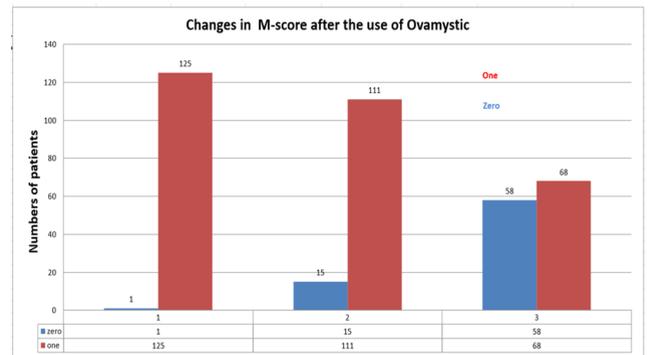


Figure 3: Changes in frequency and duration of menstrual cycle is plotted as M-SCORE (0 – period frequency 21-35 days and period duration of 0-7 days) and (1- period frequency <21 days or >35 days or period duration of > 7 days)

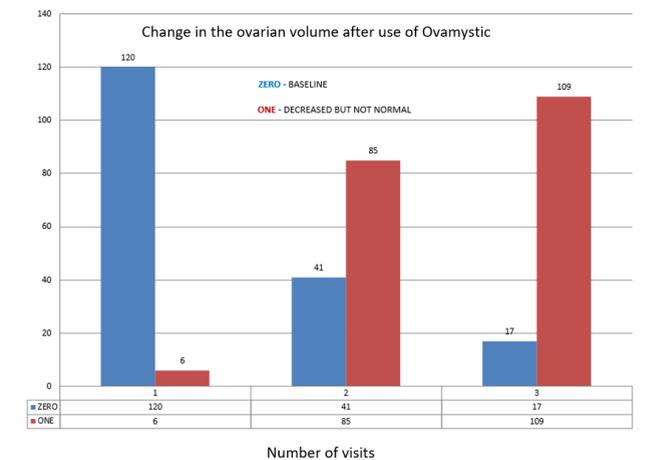


Figure 4: Changes in the ovarian volume where volume at the time of first visit is taken as 0 (which is considered as baseline) while 1 denotes decreased but not normal ovarian volume

4. Discussion

The present observational study report shows that that treatment with myo-inositol with alpha-lactalbumin in PCOS patients positively affects metabolic parameters (i.e. insulin sensitivity and body mass index) as well as hormonal parameters like ovulation and ovarian volume. PCOS is indeed the most common cause of female infertility.^{19–21} This data supports the hypothesis of a primary role of IPG as second messenger of insulin signal and is in agreement with previous studies that demonstrate that MI and DCI administration significantly affect the hormonal milieu in PCOS patients.^{21–24}

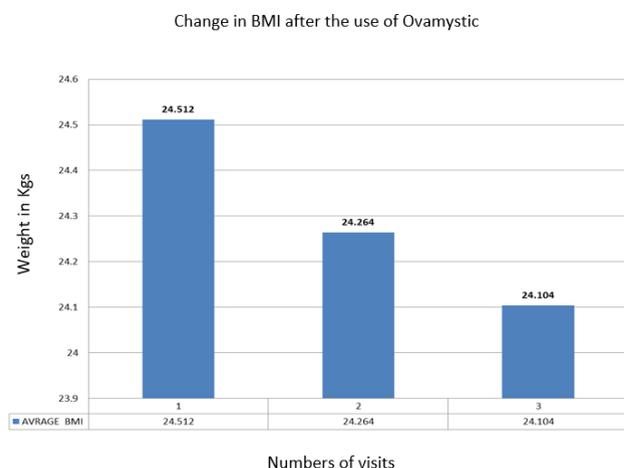


Figure 5: Change in BMI is taken as average values obtained during individual visits

Although inositol supplementation is an effective treatment for a large proportion of PCOS patients, around 35% are inositol nonresponsive (inositol resistant).²⁵ Therefore addition of alpha-lactalbumin can ensure a much higher treatment response by increasing inositol absorption. In a volunteer study, the addition of alpha-lactalbumin showed a significant increase in myoinositol absorption with a 32.4% and 27.5% higher increase in maximum blood concentration (C_{max}), and area under the curve (AUC_{0–300}) respectively, as compared to MI alone. While the MI C_{max} showed a 3-fold rise from baseline when given alone, there was a 4-fold rise in MI C_{max} from baseline when given with alpha-lactalbumin.²⁶

The effect of combining alpha-lactalbumin with myoinositol (MI) has been seen earlier in clinical trials. In a study of PCOS patients, with anovulation and infertility > 1 year non responsive to MI alone, 86% of these women ovulated after combined treatment with alpha-lactalbumin. Their MI plasma levels were found to be significantly higher (almost double of baseline). Hormonal and lipid profile parameters also showed significant improvement.²⁷

In another study, normal weight or overweight women aged 18 to 40 years, with anovulation and infertility > 1 year and insulin resistance diagnosed by HOMA (Homeostatic Model Assessment for Insulin Resistance) index were evaluated.²⁷ Patients were given 2 g MI + 50 mg alpha-lactalbumin with 200 µg folic acid for 6 months. Significant decrease at 3 and 6 months was seen in HOMA-index, insulin levels, androgen (testosterone and androstenedione) levels, and metabolic parameters. The improvement was more relevant when the starting point was further away from the normal range, as seen in this observational study as well. The reductions in testosterone and lipid parameters in this study were similar to the study discussed earlier.²⁸ No significant adverse effects were detected in both groups of patients.

However, the current observational study is the first time that the combination of MI-DCI with alpha-lactalbumin has been evaluated in PCOS, and its positive impact on menstrual cycle regularity demonstrated in the real-world clinical setting.

5. Conclusion

Ovamystic supplementation is one of the treatment options for managing menstrual irregularities, ovarian volume and body weight in PCOS patients. Majority of women showed improvement and regularization in the pattern of menstrual cycle including periods frequency and periods duration after the treatment of 6 months. Duration of the cycle in many patients became near normal (i.e. between 0-7 days) and frequency of the cycle became regular (i.e. 21-35 days). There was mild decrease in the BMI in many patients after the treatment of 6 months. The observational study has also shown mild decrease in the ovarian volume, but the decrease was subnormal. Inositol therapy is already established in PCOS, but since inositol resistance may reduce treatment response, combining MI-DCI with alpha-lactalbumin can help increase inositol absorption, increase response rate and also impart other benefits in PCOS. Larger clinical and real-world studies can add further insights and value in this direction of PCOS therapy.

6. Source of Funding

None.

7. Conflict of Interest

None.

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