



Assessing the Efficacy of Inositol Based Nutraceutical Formulation in Management of Infertility Associated with PCOS

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is a complex and highly prevalent endocrine disorder affecting women of reproductive age. It is characterized by reproductive, metabolic consequences, including BMI, insulin resistance and infertility.

Objective: This article summarizes a case study, evaluating the efficacy of the marketed formulation Gestinova sachets (Myo-inositol + D-Chiro-inositol + NAC+ Melatonin+ Vitamin D+ Folic acid + Chromium) on metabolic parameters and fertility outcomes, in lean and obese PCOS patients.

Methods (Case Study): Patients with confirmed PCOS attempting to conceive were categorized by Body Mass Index (BMI) into lean and obese groups. Lean patients received Gestinova, while obese patients were divided into groups receiving either a combination of Gestinova and Metformin or Metformin alone. The key parameters monitored throughout the study were BMI, HbA1c, menstrual cycle interval days and end point considered was confirmed conception.

Results: The case study data revealed that lean patients taking Gestinova experienced a reduction in average cycle length from 36 to 28 days. Obese patients taking Gestinova combined with Metformin experienced significant improvements in BMI (from 30.5 to 27.2) and HbA1c (from 6.06% to 5.74%), with an average conception time of 19 weeks. Obese patients taking only Metformin showed no significant improvement in BMI (from 28.9 to 28.8) or HbA1c (from 6.01% to 5.86%), and conceived in an average of 26 weeks.

Conclusion: Gestinova alone is highly effective for lean PCOS patients in normalizing menstrual cycles and aiding conception. For obese PCOS patients, a combination of Gestinova and Metformin provides a synergistic effect over Metformin alone, providing better control over metabolic parameters, cycle regularization, and fertility outcomes.

Keywords: Polycystic Ovary Syndrome (PCOS); MI+DCI (Myo-inositol and D-Chiro-inositol); Infertility Metabolic Parameters

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women in fertile age. It is an endocrine and metabolic disorder characterized by oligo-anovulation, hyperandrogenism and insulin-resistance [1]. PCOS causes infertility in about 10-15% of women in reproductive age [3].

Polycystic Ovary Syndrome broadly classified into Lean PCOS and Obese PCOS, differentiated primarily based on body weight (For Lean: BMI <25, Obese: BMI ≥25).

Obese PCOS often showing more severe insulin resistance, higher testosterone, and worse metabolic markers (like HOMA-IR,

lipid profile), while lean PCOS can present with less pronounced metabolic issues but still hormonal imbalances, making it challenging to diagnose as symptoms like hirsutism and irregular periods overlap, requiring different management approaches.

Standard pharmacotherapy protocol for PCOS involves Combined Oral Contraceptive Pills (COCPs), Metformin, Antiandrogens, Anti-obesity agents, Inositols based on severity of symptoms.

Women suffering from PCOS tend to show elevated levels of inflammatory markers and a decrease in antioxidant capacity stress [12]. Several studies have documented alterations in intra-ovarian ratio of Myo- Inositol to D-chiro- Inositol, levels of melatonin, vitamin D.

Recently, inositols - myo-inositol (MI) and D-chiro-inositol (DCI) - have shown to be an efficient and safe alternative in PCOS management, as both inositol isoforms are able to counteract downstream consequences of insulin resistance [3]. MI and DCI are also involved in a number of biochemical pathways within oocytes. PCOS women have lower serum DCI levels and elevated urinary loss of D-chiro-Ins- phosphoglycan. In PCOS, the metabolism of inositol is dysregulated, highlighting the subtle connection between insulin resistance and inositol deficiency in PCOS patients. An increased activity of epimerase in the cells of ovaries of PCOS women is associated with a consistent reduction in the intra-ovarian ratio of MI to DCI. In women with PCOS, insulin resistance and compensatory hyperinsulinemia due to dysregulation of inositol metabolism may actually be the major underlying cause of the disorder.

Women with PCOS frequently suffer from metabolic disturbances. Current evidence suggests that vitamin D deficiency may contribute to the development of the metabolic syndrome (MS) [15]. Low vitamin D levels are also associated with features of the MS in PCOS women.

Another hormone that may have a role to play in PCOS is melatonin. Melatonin modulates its effects on the female reproductive physiology via its receptors in hypothalamic, pituitary, and ovarian sites. Melatonin is also a potent free radical scavenger that protects the oocytes against oxidative stress.

N- acetyl cysteine is also a potent free radical scavenger. When used in combination with clomiphene citrate or letrozole, NAC increases ovulation and pregnancy rate in infertile females suffering from PCOS and positively affects the quality of oocyte [12].

A rational combination of Myo-inositol (MI) and D-chiro-inositol (DCI) in the optimal 40: 1 ratio, vitamin D, and melatonin and N-acetyl cysteine may help modify the pathogenic abnormalities occurring in women with PCOS and infertility.

Objective of the Study

To evaluate the efficacy of Inositol based nutraceutical formulation in PCOS patients metabolic parameters, pregnancy rates of a combined formulation of Myoinositol (MI) and D-chiro-inositol (DCI) in the optimal 40 : 1 ratio, vitamin D, melatonin and N- acetyl cysteine in women with PCOS related infertility.

Methodology

An observational study conducted at a tertiary care centre. 36 participants with symptoms of PCOS and trying to get conceived, were categorized based on BMI as either lean or obese PCOS groups.

The inclusion criteria was women confirmed symptoms of PCOS, with a history of infertility since at least 2 years, women who had undergone previous treatment for infertility at least 3 months ago or were treatment naïve, women with a history of miscarriages.

The exclusion criteria were women diagnosed with PCOS (based on clinical, biochemistry and/or ultrasound findings) who had undergone treatment for infertility over the past 3 months, women with hypersensitivity to any of the components of the treatment protocol, women with a history of heart disease or any other disease which would preclude their recruitment in the study.

Women in intervention groups were treated with the marketed preparation containing Myo-inositol (2g), D-Chiro inositol (50 mg), Melatonin (2 mg), NAC (300 mg), Folic acid (100mcg), Vit D (400 IU) and Chromium picolinate (200 mcg). (Product name GestiNova Sachets, Marketed by Edence Life Sciences Private Limited, Mumbai).

Key parameters monitored were: BMI, HbA1c and Menstrual cycle interval days. Treatment given as follows:

- Lean PCOS (BMI range 18-24) 11 subjects with average age 26 years: GestiNova sachet: OD
- Obese PCOS (BMI range 25-30+) 13 subjects with average age 30 years: GestiNova sachet+ Metformin Tab.: OD
- Obese PCOS (BMI range 25-30+) 12 subjects with average age 30 years: Metformin Tab.: BD

After 12 weeks follow-up, all considered parameters were evaluated. Treatment was continued in patients of respective groups till confirmation of gestation.

Results and Observations

Lean PCOS Group GN (GestiNova) :

- No significant improvement in BMI and HBA1c of Lean PCOS patients (Initial values were not so critical i.e. <6)
- Average cycle length reduced to 28 days from 36 days. (Reduced by 8 weeks)
- All patients conceived in about 13 weeks of treatment.
- Conception outcome observed only on or after 8th week of treatment in this group.

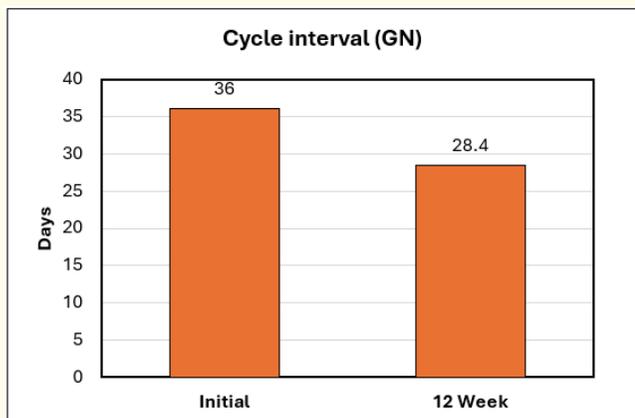


Figure 1

Obese PCOS Group 'A' (GestiNova + Metformin):

- Significant improvement in BMI and HBA1c and cycle intervals of obese PCOS patients.
- Average treatment duration till conception for this group was 19 weeks.

- Conception outcome observed only on or after 16th week of treatment in this group.

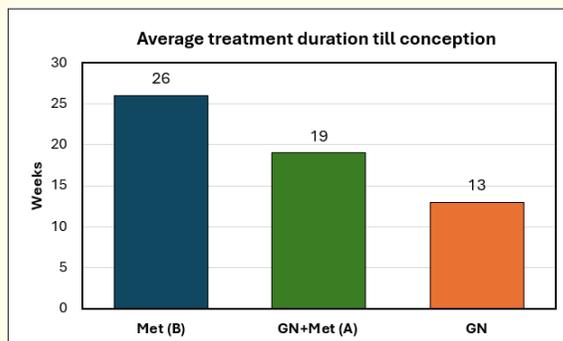


Figure 2

Obese PCOS Group 'B' (Metformin)

- No improvement in BMI and HBA1c of obese PCOS patients but average cycle length reduced to 29 days from 40 days.
- Average treatment duration till conception for this group was 26 weeks.
- Conception outcome observed only on or after 20th week of treatment in this group.

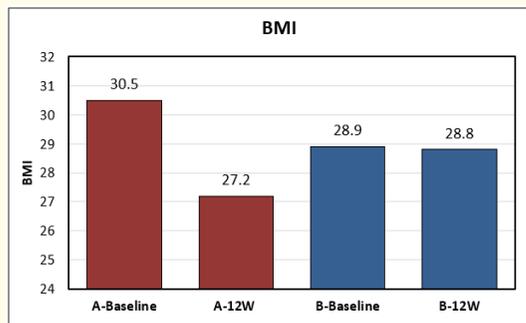


Figure 3

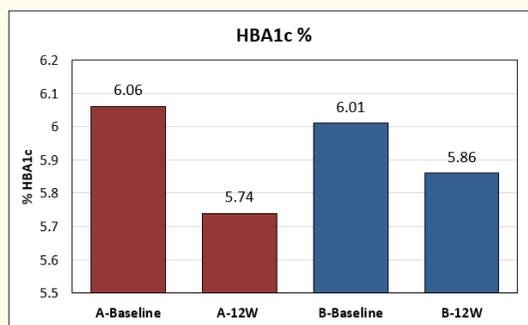


Figure 4

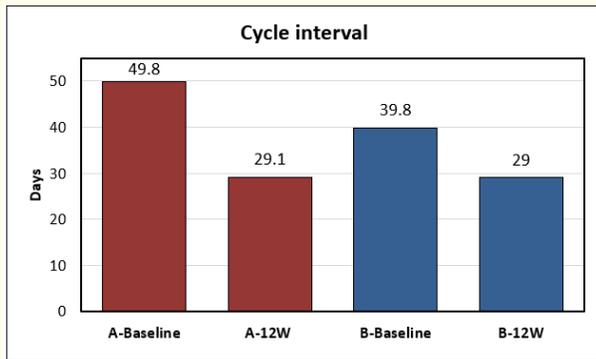


Figure 5

Other positive findings were a reduction in weight, and symptoms of acanthosis nigricans. No adverse effects were reported in any patient. The treatment was well tolerated. The BMI analysis indicates that overweight and obesity were commonly observed among women with PCOS in this study, suggesting that increased body mass may contribute to metabolic disturbances and reproductive dysfunction associated with the syndrome.

Discussion

Polycystic ovarian syndrome (PCOS) is the commonest endocrine disorder in women of a reproductive age, occurring in approximately one in seven women. Of these women approximately two-thirds will not ovulate on a regular basis and consequently may therefore seek treatment for ovulation induction. Women with PCOS are potentially at an increased risk of miscarriage [2]. Besides the hormone disorders and subfertility that are common in the polycystic ovary syndrome (PCOS), in obesity the adipocytes act as endocrine organ. The adipose tissue indeed, releases a number of bioactive molecules, namely adipokines that variably interact with multiple molecular pathways of insulin resistance, inflammation, and oocyte differentiation and maturation. Moreover, endometrial implantation and other reproductive functions are affected in obese women with complications including delayed conceptions, increased miscarriage rate, reduced outcomes in assisted conception treatment [7].

After exclusion of other significant causes of sub-fertility the pragmatic approach to ovulation induction is to commence with weight reduction, diet therapy and clomiphene citrate for ovulation induction. The goal of ovulation induction is the development of a single ovulatory follicle and the avoidance of a multiple gestation.

Second line therapies consist of gonadotrophin therapy and laparoscopic ovarian drilling, the place of metformin therapy is believed to lie in the management of woman with impaired glucose tolerance [2]. Evidence suggests that both clinicians and patients are not satisfied with the timeliness of diagnosis and treatment options [4].

It is imperative to look at the pathogenic events at the cellular level to understand and develop a more rational pathogenic process driven treatment approach. An increased activity of epimerase has been demonstrated in theca cells of ovaries of PCOS women is associated with a consistent reduction in the intraovarian ratio of Myo-Ins to D-chiro-Ins. These experimental data are in line with the so-called D-chiro- Ins ovarian paradox posited by Carlomagno, *et al.* these investigators advanced the hypothesis that epimerase activity is increased in the ovaries of PCOS subjects, resulting in a local Myo-Ins deficiency responsible for the oligoovulation and poor oocyte quality of the disorder. This hypothesis has drawn attention to the importance of Myo-Ins and D-chiro-Ins supplementation in a physiological ratio in order to restore normal ovary functionality. In fact, a correlation between Myo-Ins concentration in the follicular fluid and high oocyte quality was found and a number of studies have reported that Myo-Ins supplementation is able to improve oocyte quality [3].

The synergistic action of Myo-Ins and D-chiro-Ins has been suggested as they regulate different biological processes. In fact, the combination of MI, DCI, NAC, Melatonin, Folic acid, Vitamin D and Chromium picolinate, may be particularly beneficial in overweight PCOS women, considering that Myo-Ins improves the ovulatory function and D-chiro-Ins rapidly reduces the peripheral hyperinsulinemia. Evidence suggests that MI 2g given bid improves pregnancy outcomes [11,12]. 40:1 ratio between myo- inositol and D-chiro-inositol is the optimal combination to restore ovulation in PCOS women [5]. MI-DCI treatments are able to significantly improve the regularity of the menstrual cycle, the Acne Score, the endocrine and metabolic parameters and the insulin-resistance in young, overweight, PCOS patients [1]. Myo-inositol combined with D-chiro-inositol is particularly efficacious in menstrual recovery [8]. MI enhances the effect of metformin and clomiphene on the fertility of PCOS women seeking pregnancy [6,9].

Women with PCOS frequently suffer from metabolic disturbances, in particular from insulin resistance. Accumulating

evidence suggests that vitamin D deficiency may contribute to the development of the metabolic syndrome (MS) [15]. Low Vitamin D levels are associated with features of the metabolic syndrome in PCOS women.

Folic acid plays a critical role in managing PCOS by reducing elevated homocysteine levels, improving insulin resistance, and enhancing ovum quality. It helps regulate menstrual cycles and supports fertility by promoting ovulation, particularly when combined with MI to combat metabolic and hormonal imbalances. Another hormone to be considered in women with PCOS is melatonin. The effects of melatonin on female reproductive physiology are mediated via its receptors in hypothalamic, pituitary, and ovarian sites. Melatonin is also a potent free radical scavenger that exerts protective effects in female reproductive organs; for instance, it is involved in the protection of the oocyte against oxidative stress, particularly at the time of ovulation. It can also be used to protect the developing fetus from oxidative stress. In women with PCOS, follicular fluid has lesser melatonin levels compared to the healthy condition. Melatonin may promote follicular maturation and ovulation through the protection of follicles against oxidative stress and their rescue from atresia. Furthermore, melatonin has shown protective effects on corpus luteum against reactive oxygen species (ROS) via its antioxidant effects. Melatonin administration in PCOS patients significantly affects body characteristics including reduced body weight, body mass index and intra-abdominal fat. During the ovulatory process, ROS are produced within the follicles; for this reason, the scavenging activity of melatonin plays an important role during ovulation. Melatonin reduces oxidative stress and causes oocyte maturation [10].

Women suffering from PCOS tend to show elevated levels of inflammatory markers and a decrease in antioxidant capacity. N-acetyl cysteine is a potent antioxidant which has been studied in women with PCOS. When used in combination with clomiphene citrate or letrozole, NAC increases ovulation and pregnancy rate in infertile females suffering from PCOS and positively affects the quality of oocytes and number of follicles ≥ 18 mm. Moreover, it is well tolerated with a low prevalence of side effects [12].

Chromium is a trace mineral that improves insulin sensitivity, reduces insulin resistance, and aids in regulating metabolism and hormonal imbalances in women with PCOS. Supplementation of

chromium picolinate, helps lower BMI, reduce free testosterone, and improve ovulation as well as menstrual cycle regularity.

In our study 92% women conceived at the end of treatment. This finding indicates the possible synergistic benefit of myo-inositol (MI) and D-chiro-inositol (DCI) in the optimal 40:1 ratio, vitamin D, melatonin and N-acetyl cysteine in women with PCOS related infertility.

This lends credence to the hypothesis that it is important to modify the pathogenic abnormalities occurring in women with PCOS and infertility to improve pregnancy rates in these women.

This study was a small observational study. A large randomized double blind study would be needed to corroborate the findings if our study

Conclusion

Understanding the key pathogenic abnormalities in PCOS will help in using a more rational treatment protocol for the management of women with PCOS. Using a combination of myo-inositol (MI) and D-chiro-inositol (DCI) in the optimal 40 : 1 ratio, Melatonin, NAC, Vitamin D, Folic acid and Chromium may help modify the pathogenic abnormalities occurring in women with PCOS and infertility and improve outcomes of treatment in women with PCOS related infertility. The combination of myo-inositol (MI) and D-chiro-inositol (DCI) normalized the cycle length, reduced insulin resistance, reduced testosterone. It was effective across the BMI range indicating that it is effective in improving outcomes in obese as well as underweight women.

GestiNova supplementation alone found effective in lean PCOS patients in terms of conception outcome by normalizing menstrual cycle intervals.

In obese PCOS patients GestiNova add on with Metformin, showed synergistic outcome by significant reduction in BMI, HbA1C and menstrual cycle interval as compared to only Metformin treated group. Conception outcome was also noticed 7 weeks earlier in GN+Met group than only Met treated group.

MI+DCI combination with Metformin can be a better choice of treatment in obese PCOS patients to get effective control over metabolic parameters, menstrual cycle regularization and fertility outcomes.

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