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RESEARCH

Comparative Effects of Metformin, Inositol, and ECoQ10 on Metabolic Parameters and Fertility Hormones in Insulin-resistance Infertile Women

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Introduction: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder with a range of associated symptoms. No unique therapy is available to restore body homeostasis. The present study aimed to treat PCOS in insulin-resistant infertile women using metformin, inositol, and ECoQ10. **Methods:** A case-comparative study with 200 PCOS patients divided into four groups (Metformin, inositol, CoQ10, and control diet). Measurements included anthropometrics, hormonal and biochemical tests, and abdominal imaging. **Results:** Metformin significantly improved BMI, glycemic control, and lipid profiles. Myo-inositol showed the greatest improvement in HOMA-IR and fasting blood sugar. CoQ10 had modest effects on BMI but significantly decreased fasting blood sugar and HOMA-IR. Metformin and myo-inositol also improved fertility hormones and lipid profiles. **Conclusion:** Metformin and myo-inositol effectively improve metabolic and hormonal parameters in PCOS, while CoQ10 enhances metabolic markers. Individualized treatment plans and further research into long-term efficacy are recommended.

Keywords: Insulin Resistance, Metformin, Inositol, ECoQ10, Infertility, PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 8-13% of women worldwide [1], characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology [2, 3].

Metformin reduces hepatic glucose production and enhances insulin sensitivity [4]. It improves menstrual regularity, fertility, and insulin levels in PCOS patients. Despite gastrointestinal side effects and rare risks like lactic acidosis and vitamin B12 deficiency, its efficacy in managing metabolic disorders and cardiovascular diseases is notable [3].

Inositol, a cyclic carbohydrate essential for cellular signalling, myo-inositol regulates glucose uptake and insulin pathways, improving hormonal balance and ovulatory function in PCOS. Both myo-inositol and D-chiro-inositol influence glucose metabolism and have a favourable safety profile, with benefits in PCOS, depression, and metabolic disorders [5-7].

Coenzyme Q10 (CoQ10) an antioxidant vital for ATP production and protecting cells from oxidative damage, CoQ10 levels decline with age, requiring supplementation for therapeutic benefits [8]. It improves conditions like cardiovascular disease and hypertension and may enhance metabolic parameters in PCOS. The present study sought to investigate the role of inositol, EcoQ10, or metformin in modulating important biochemical and hormonal parameters linked to PCOS and infertility.

2. Materials and Methods

Study Design: A comparative-case control study was conducted from November 1, 2023, to July 1, 2024. Patient consent was approved for participation in the study through a filled and signed questionnaire (questionnaire provides collective information about patients personal information, presence of compiling symptoms with PCOS, medication profile, laboratory investigations). Diagnosis starts with abdominal imaging, which then undergoes comprehensive examinations. The measurements in these studies included anthropometry and hormonal and biochemical tests. Whole blood samples of 200 PCOS patients of childbearing age women were collected at the women's health hospital and private clinic, with ages ranging between 15-35 years. Serum separated and analysed for metabolic and hormonal factors. Patients with chronic diseases were excluded or women older than 50 years. Patients were either given metformin, inositol, ECoQ10, or control therapy (Figure 1).

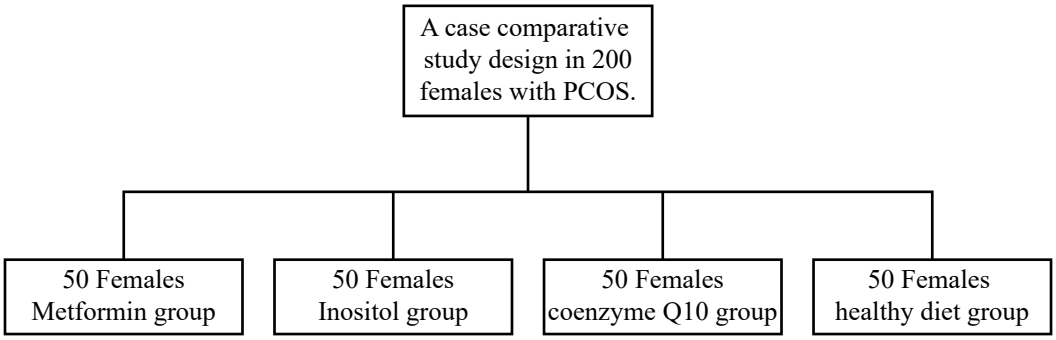

Figure 1: Scheme Diagram of the Study Design.

2.1. Measurement of Biochemical Parameters

2.1.1. Laboratory Procedures for Metabolic Parameters

As per manufacturer instructions provided in the kits, Glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) measured based on the chemiluminescent immunoassay (CLIA), using BS-230-MINDARY.

2.1.2. Laboratory Procedures for Testing Hormones

As per manufacturer instructions provided in the kits, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin hormone (PL), thyroid stimulating hormone (TSH), Insulin, and Testosterone hormone (TH) levels were measured by the chemiluminescent automates immunoassay system (ECL), using CL900i-MINDARY.

2.2. Measurement of Insulin Resistance (HOMA-IR)

IR can be calculated from the insulin and glucose values divided by a constant according to this formula:

Fasting glucose (mg/dL) X fasting insulin (m IU/L)/405.

If the value is greater than 2 this indicates insulin resistance.

3. Results

3.1. The Results of Metabolic Changes are Presented in Figure 2

3.1.1. Modulation of Metabolic Parameters After 8 Weeks of the Control Group

The BMI in the control group demonstrated that there is a significant decrease from a mean of 29.68 kg/m² at the beginning to 27.48 kg/m² after 8 weeks ($p = 0.001$), indicating a 7.4% improvement rate.

Regarding fasting blood sugar (FBS) levels in the control group, there is no significant change observed from a mean of 69.01 mg/dl at the beginning to 71.30 mg/dl after 8 weeks ($p = 0.226$), corresponding to a -3.3% change. Although not statistically significant, there's a slight increase in FBS levels.

In the control group, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), there is no significant decrease from a mean of 40.61 at the beginning to 40.1 after 8 weeks ($p = 0.342$), indicating a 1.2% improvement rate.

The lipid profile parameters in the control group showed negligible and statistically insignificant changes. TC increased by 1.5% ($P = 0.466$), TG decreased by 1.1% ($P = 0.351$), HDL decreased by 0.3% ($P = 0.429$), and LDL increased by 1.2% ($P = 0.733$). The p-values indicate that these variations are not statistically significant, suggesting no meaningful alterations in lipid profile parameters occurred in the control group during the study duration.

3.1.2. Modulation of Metabolic Parameters After 8 Weeks of Metformin Therapy

Metformin significantly ($p = 0.001$) decreased BMI from a mean of 29.23 kg/m² at the beginning to 25.65 kg/m² after therapy. FBS has significantly ($p = 0.015$) decreased from a mean of 87.89 mg/dl at the beginning to 83.86 mg/dl after therapy. HOMA-IR has significantly ($p = 0.001$) decreased from a mean of 41.36 at the beginning to 35.46 after therapy. There are significant improvements observed in TC levels, with a decrease from a mean of 178.27 mg/dl at the beginning to 163.67 mg/dl after 8 weeks ($p = 0.001$). TG levels also show significant improvement, decreasing from a mean of 113.71 mg/dl at the beginning to 98.09 mg/dl after 8 weeks ($p = 0.001$). However, there is no significant change observed in HDL levels ($p = 0.698$). Notably, LDL levels significantly decrease from a mean of 106.02 mg/dl at the beginning to 94.28 mg/dl after 8 weeks ($p = 0.001$).

3.1.3. Modulation of Metabolic Parameters After 8 Weeks of Inositol Therapy

Regarding BMI, there is a significant decrease from a mean of 30.81 kg/m² at the beginning to 29.10 kg/m² after 8 weeks ($p = 0.001$), indicating a 5.5% improvement rate. Regarding FBS levels, there is a significant decrease from a mean of 90.07 mg/dl at the beginning to 77.68 mg/dl after 8 weeks ($p = 0.001$), corresponding to a 13.8% improvement rate. For Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), there is a significant decrease from a mean of 40.59 at the beginning to 13.76 after 8 weeks ($p = 0.001$), indicating a remarkable 66.1% improvement rate.

Following Inositol use, there are significant improvements observed in TC levels, with a decrease from a mean of 155.16 mg/dl at the beginning to 120.60 mg/dl after 8 weeks ($p = 0.001$), indicating a notable

22.3% improvement rate. TG levels also show significant improvement, decreasing from a mean of 125.99 mg/dl at the beginning to 107.56 mg/dl after 8 weeks (p = 0.001), corresponding to a 14.6% improvement rate. Although not statistically significant, there is a slight decrease observed in HDL levels (p = 0.058). Furthermore, LDL levels significantly decrease from a mean of 101.34 mg/dl at the beginning to 94.15 mg/dl after 8 weeks (p = 0.013), indicating a 7.1% improvement rate.

3.2. Effects of ECOQ-10 on Glycemic Parameters and Lipid Profile

Regarding BMI, there is no significant change observed from a mean of 30.21 kg/m² at the beginning to 30.23 kg/m² after 8 weeks (p = 0.796), indicating a negligible -0.06% change. Regarding FBS levels, there is a significant decrease from a mean of 87.04 mg/dl at the beginning to 77.34 mg/dl after 8 weeks (p=0.001), corresponding to a 10.8% improvement rate. For Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), there is a significant decrease from a mean of 41.21 at the beginning to 13.73 after 8 weeks (p = 0.001), indicating a substantial 66.7% improvement rate.

Following ECOQ-10 use, there are significant improvements observed in TC levels, with a decrease from a mean of 175.76 mg/dl at the beginning to 150.70 mg/dl after 8 weeks (p = 0.001), indicating a notable 14.3% improvement rate. TG levels also show significant improvement, decreasing from a mean of 123.87 mg/dl at the beginning to 102.73 mg/dl after 8 weeks (p = 0.001), corresponding to a 17.1% improvement rate. However, there is no significant change observed in HDL levels (p = 0.207). Notably, LDL levels significantly decrease from a mean of 123.38 mg/dl at the beginning to 99.33 mg/dl after 8 weeks (p = 0.001), indicating a 19.5% improvement rate.

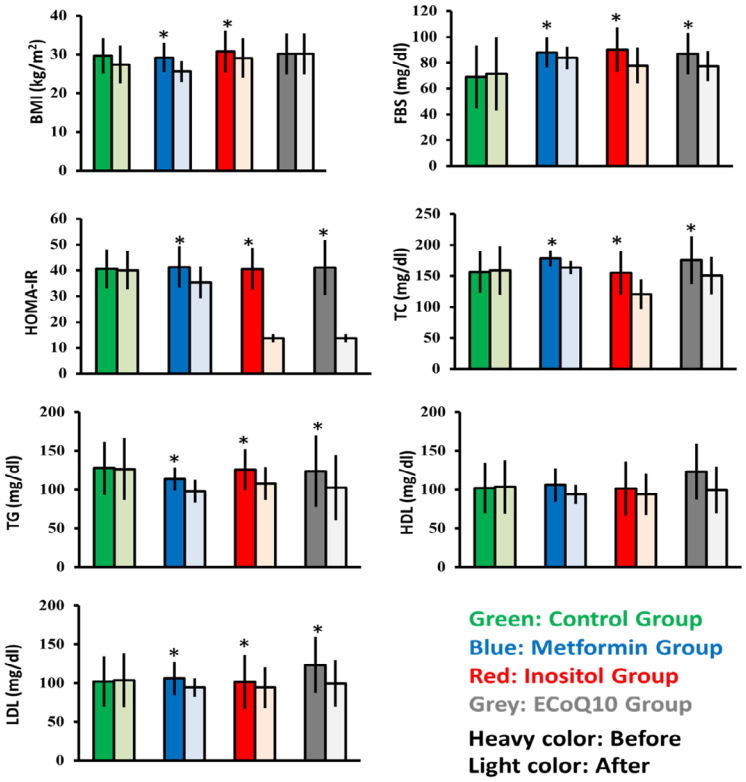

Figure 2: Metabolic Changes in the Studied Groups. Data Expressed as mean± SD (N=50 each group), * Indicates a Significant Difference at p<0.05 One Sample t-test to Compare Before and After in the Same Group.

3.3. The Results of Hormonal Changes are Presented in Figure 3

Hormonal Changes After 8 Weeks of Control Group: The changes in fertility hormones in the control group over eight weeks, revealed minimal and statistically insignificant alterations. Serum PL levels decreased by 0.7% (P = 0.532), FSH levels decreased by 1.6% (P = 0.088), LH levels decreased by 0.6% (P = 0.714), TSH levels increased by 0.7% (P = 0.685), and testosterone levels decreased by 1.0% (P = 0.667). The p-values indicate that none of these changes are statistically significant, suggesting that there were no substantial fluctuations in fertility hormone levels in the control group during the study period.

Hormonal Changes After 8 Weeks of Metformin Therapy: Following metformin use, there is a significant reduction in serum PL levels from a mean of 15.73 ng/ml at the beginning to 14.04 ng/ml after 8 weeks (p = 0.001), indicating a 10.7% improvement rate. While FSH levels show a negligible decrease of -0.3%, it is not statistically significant (p = 0.814). However, there are significant reductions in LH and TSH levels, with 20.9% and 19.5% improvement rates, respectively (p = 0.001 for both). Additionally, testosterone levels significantly

decreased by 26.8% (p = 0.001). These findings suggest that metformin treatment in Group I leads to notable improvements in fertility hormone levels, particularly in reducing LH, TSH, and testosterone levels, which may contribute to better reproductive health outcomes in individuals with PCOS.

Hormonal Changes After 8 Weeks of Inositol Therapy: Following Inositol use, there are significant reductions in serum PL levels from a mean of 15.07 ng/ml at the beginning to 13.26 ng/ml after 8 weeks (p = 0.001), indicating a 12.0% improvement rate. While FSH levels show a slight decrease of 1.6%, it is not statistically significant (p = 0.101). However, there are significant reductions in LH levels, with a 20.0% improvement rate (p = 0.027). Additionally, TSH levels decrease by 10.1% (p = 0.073). Furthermore, testosterone levels significantly decreased by 24.2% (p = 0.001). These findings suggest that Inositol treatment in Group II leads to notable improvements in fertility hormone levels, particularly in reducing LH, TSH, and testosterone levels, which may contribute to better reproductive health outcomes in individuals with PCOS.

Hormonal Changes After 8 Weeks of ECoQ10 Therapy: Following ECoQ10 use, there are no significant changes observed in serum PL levels (p = 0.725) and FSH levels (p = 0.241), LH levels show a modest but significant decrease by 6.0% (p = 0.045), suggesting a potential effect on ovarian function. Additionally, TSH levels decreased by 6.3%, although this change is not statistically significant (p = 0.251). Notably, there is a small but significant decrease of 2.3% in testosterone levels (p = 0.012). These results suggest that ECOQ-10 treatment in Group III may have a limited impact on fertility hormone levels, with slight reductions observed in LH and testosterone levels, which may contribute to improved reproductive health outcomes in individuals with PCOS.

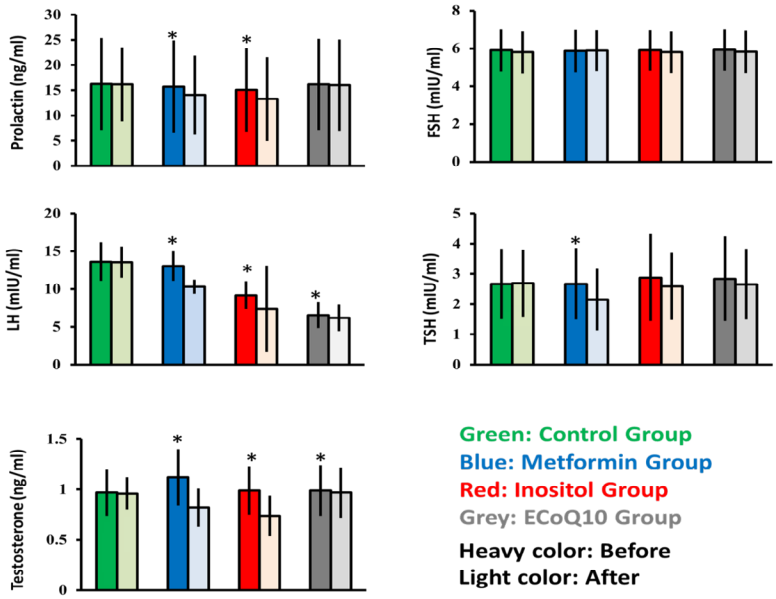

Figure 3: Hormonal Changes in the Studied Groups. Data Expressed as mean± SD (N=50 each group), * Indicates a Significant Difference at p<0.05 One Sample t-test to Compare Before and After in the Same Group.

4. Discussion

This study's findings demonstrated a beneficial effect of metformin on BMI, there is a significant difference between the beginning and end of the study. Metformin significantly reduced BMI compared to the diet-only group. This is related to increased intestinal production of growth differentiation factor-15(GDF-15), which penetrates the blood-brain barrier and provides a satiety signal and has been described by Patel *et al.* [9]. Metformin decreased FBS as compared with the diet group, which could be related to the effectiveness of metformin in lowering hepatic glucose production, which primarily lowers baseline (fasting) glycaemia an enhanced intestinal anaerobic glucose metabolism and enhanced peripheral glucose excretion induced by insulin [10, 11]. The study revealed a significant improvement in HOMA-IR with metformin treatment compared to the diet-only group, as evidenced by a notable reduction from baseline to endpoint. This agrees with the study conducted by Halawa *et al.* [12].

The present study demonstrates that metformin exerts significant beneficial effects on lipid metabolism. The findings reveal a significant improvement in TC with metformin use compared to a diet-only group. Similarly, a significant improvement in TG levels was observed, along with a reduction in LDL. These findings align with the study conducted by Sangeeta [13], who reported significant reductions in LDL, VLDL, TC, and TG after three months of metformin therapy. This consistency reinforces the efficacy of metformin in improving lipid profiles over a relatively short duration.

However, the impact of metformin on HDL levels

presents a contrasting picture. In our study, HDL levels elevated slightly but non-significantly. Sangeeta [13] reported a significant increase in HDL levels after six months of metformin therapy, indicating a potential time-dependent effect of metformin on HDL. The difference in study durations (two months in our study versus six months in theirs) may explain the divergent results. It is plausible that HDL levels initially remain stable before increasing with prolonged metformin use, suggesting that a longer treatment duration might be necessary to observe significant improvements in HDL [13].

The current study's findings demonstrate significant improvements in fertility hormone levels following 8 weeks of metformin treatment in women with PCOS. Specifically, significant reductions were observed in serum PL, LH, TSH, and testosterone levels, while FSH levels showed a negligible, non-significant improvement. Sohrevardi *et al.* [14] found a non-significant change in testosterone and LH levels between PCOS patients and a control group after 4 months of metformin treatment. This contrasts with our findings, where testosterone and LH levels significantly decreased. The difference in results may be attributed to variations in study duration, sample size, or participant characteristics. However, both studies highlight metformin's potential to regulate hormonal disorders in PCOS patients [14].

Our study observed a non-significant decrease in FSH levels, which contrast with the findings of prior studies showing a significant decrease in FSH levels. This discrepancy could be due to differences in study protocols or the specific methods used to measure FSH levels [14]. Another study by Jindal *et al.* [15] documented that there was no significant change in FSH levels before and after treatment with metformin. Additionally, they revealed a significant reduction in mean value in PL after 6 months of treatment [15].

A study conducted by Nemati *et al.* [16] found a significant change in TSH levels three months after treatment with metformin. A significant reduction in TSH levels, reaching which supports our result [16]. The current study's findings demonstrate significant improvements in BMI following 8 weeks of inositol treatment in women with PCOS compared to the diet-only group. In a meta-analysis conducted by Zarezadeh *et al.* [17], it was found that inositol significantly decreased BMI scores in individuals with overweight or obese BMI. Myoinositol had the strongest effect on reducing BMI when compared to other inositol stereoisomers [17].

The present study showed improvements in FBS levels after 8 weeks of inositol treatment in women with PCOS compared to the diet-only group, which is consistent with the findings of Unfer *et al.* [18], who observed that in 247 women treated with myoinositol (MI) or MI combined with D-chiro-inositol (DCI) and folic acid, MI alone significantly decreased fasting insulin levels.

This study revealed improvements in the HOMA-IR in inositol-treated women with PCOS compared to the diet-only group. These findings are supported by a study conducted by Unfer *et al.* [18]. Inositol improved lipid profile compared with the control group, and there was a significant reduction in TC, TG, and LDL which do agree with a study conducted by Costantino *et al.* [19]. Despite that no changes occurred with HDL, this agrees with a study done by Ravn *et al.* [20].

Inositol supplementation decreased serum PL, LH, and testosterone. In comparison with other studies done by Nisa *et al.* [21], LH level was significantly improved. Our study observed a non-significant decrease in FSH which contrasts with the study's findings of a significant decrease in FSH levels. This discrepancy could be due to differences in study protocols or the specific methods used to measure FSH levels [21].

Another study by Azizi Kutenaei *et al.* [22] showed a significant decrease in testosterone levels, as circulating androgens, were observed in the PCOS patients who received myo-inositol supplementation compared to those who received the metformin supplementation. Another study approved our result done by Genazzani *et al.* [23]. Whose study showed myo-inositol decreased hormonal parameters such as LH, testosterone and PRL after 12 weeks of treatment [23]. The study by Nordio *et al.* [24] contrasts with Our study's finding of a non-significant change in TSH levels. The difference in study durations (two months in our study versus six months in theirs) may explain the divergent results [24].

The results demonstrate the effect of ECOQ-10 on BMI after 8 weeks in Group III compared with thus didn't use ECOQ-10. The findings indicate no significant change in BMI, with values remaining relatively constant from the beginning to after 8 weeks compared with the control group, reflecting a negligible -0.06% change. The results of the current study agree with those of a study conducted by Bader et al., a randomized double-blind clinical trial [25]. The present study showed that Q10 improved in glycemic control. FBS levels decreased compared to the control group. This result aligns with the study conducted by Bader et al., which reported significant improvements in FBG in the cases group after two months of treatment with coenzyme Q10 200 mg daily, compared to the control group receiving a placebo [25].

Our study revealed a significant improvement in HOMA-IR with Coenzyme Q10 treatment compared to the diet-only group, as evidenced by a notable reduction from baseline to endpoint. This significant reduction in HOMA-IR suggests a notable improvement in insulin sensitivity. These findings are consistent with the study conducted by Liu *et al.* [26].

The ECOQ-10 group showed improvements in TC, TG, and LDL, this result agrees with the study conducted by Zhang *et al.* [27], this study was a randomized double-blind placebo-controlled trial in which 64 type 2 diabetic patients were randomly assigned to receive either 200 mg Q10 or a placebo daily for 12 weeks.

However, there was no significant change observed in HDL levels. This agrees with the prior literature, a

total of twenty-one controlled trials (514 patients and 525 controls) were included. The meta-analysis indicated a significant reduction in serum levels of TG. CoQ10 supplementation also decreased TC and increased LDL while its effect on HDL was not statistically significant [28].

ECOQ-10 demonstrated a notable decrease in LH and testosterone levels. The FSH levels showed non-significant changes, these results were approved with a study done by Izadi *et al.* [29]. We observed no significant changes in serum PL levels, which agreed with a study done by Thakur *et al.* [30]. Additionally, TSH levels showed a non-significant decrease, this finding is consistent with the results of Gharakhani Bahar *et al.* [31], who similarly reported a non-significant decrease in TSH levels compared to the placebo group after treatment.

5. Conclusion

Metformin and myo-inositol have shown significant efficacy in ameliorating both metabolic and hormonal imbalances in women with Polycystic Ovary Syndrome (PCOS), offering a promising therapeutic strategy for managing this multifaceted endocrine disorder. Metformin, primarily an insulin-sensitizing agent, has been extensively studied and is known to enhance glucose metabolism and reduce hyperinsulinemia, which subsequently mitigates hyperandrogenism—one of the hallmarks of PCOS. Similarly, myo-inositol, a naturally occurring carbohydrate that plays a crucial role in insulin signalling pathways, has demonstrated potential in improving ovarian function and metabolic profiles by normalizing insulin levels and reducing androgen concentrations. Additionally, Coenzyme Q10 (CoQ10), an antioxidant involved in mitochondrial function, has emerged as a supportive treatment due to its positive effects on lipid profiles and oxidative stress markers in PCOS patients. However, given the heterogeneity of PCOS manifestations among individuals, these treatments should be tailored to each patient's specific metabolic and hormonal presentation to maximize their benefits. Moreover, while current evidence supports the effectiveness of these interventions in short-term applications, longitudinal studies are imperative to ascertain their long-term efficacy and safety profiles. This comprehensive approach not only optimizes individual care plans but also underscores the necessity for continued research into sustainable management practices for PCOS.

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