The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4802-4807

Role of Choline and Inositol Treatment for Patients with Polycystic Ovarian Syndrome: A Clinical Study

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ABSTRACT

Background: The most frequent cause of infertility, hyperandrogenism, and ovulatory problems is polycystic ovarian syndrome (PCOS). One of the most common diseases in the world. Management of insulin resistance, which is based on dietary habits, exercise, and other molecules like inositol, is crucial in the treatment of PCOS. In polycystic ovary syndrome, inositol is useful in restoring ovarian function and enhancing oocyte and embryo quality.

Objective: Comparison of the effectiveness of choline and inositol vs metformin and non-insulin sensitizers in polycystic syndrome patients.

Materials and Methods: A case-control research carried out in the Iraqi city of Nasiriyah from March 2021 to December 2021. There were 150 PCOS patients. There were three categories of patients: Metformin with clomiphene citrate in Group 1, choline and inositol with clomiphene citrate in group 2 and clomiphene citrate alone in group 3. Six months of drug therapy were provided to all groups, followed by evaluation.

Results: During follow-up, mean BMI decreased significantly by an average of 1.9 ± 4.2 kg/m^2 ($p = 0.001$). Regarding cycling, regular cycling was significantly higher in the metformin group ($p = 0.001$). The mean change in follicle size was 2.9 mm, which decreased significantly after treatment initiation ($p=0.001$). Both LH and FSH increased significantly after treatment initiation ($p=0.0001$). Subsequent LH distribution was not significantly different between the drug groups ($p=0.5$), whereas subsequent FSH distribution was significantly higher in the metformin group ($p=0.04$). Although women taking choline and inositol + clomiphene citrate or metformin + clomiphene citrate were more likely to conceive than women taking clomiphene citrate alone, there was no significant difference between the two groups ($p = 0.19$).

Conclusion: There were no notable differences between any of the groups in terms of the respective medicines. There were no discernible differences between the two groups, despite the fact that women using either metformin or choline and inositol were more likely to become pregnant than those in the third group.

Keywords: Clomiphene citrate, Choline, Inositol, Infertile patients, Metformin, Polycystic ovarian syndrome.

INTRODUCTION

A diverse condition called polycystic ovarian syndrome (PCOS) is characterized by prolonged anovulation and hyperandrogenism. The hypothalamic-pituitary-ovarian axis is disrupted by ovulatory dysfunction, which is typically defined by signs and symptoms of androgen excess [(1)]. Hirsutism, menstrual abnormalities, persistent anovulation, and infertility are typical clinical characteristics [(2)].

Inadequate hypothalamic-pituitary feedback, luteinizing hormone (LH) hypersecretion, early luteinization of granulosa cells, aberrant oocyte maturation, and early arrest of activated primary follicles are all factors in persistent hyperandrogenism [(3)].

This syndrome is linked to 80% of instances of obesity and 30% to 40% of metabolic syndrome patients with insulin resistance, which aggravate PCOS. Blood levels of free androgens rise as a result of hyperglycemia's inhibition of sex hormone-binding globulin formation in the liver, whereas androgen production in theca cells is increased by insulin resistance. Only people with type 2 diabetes and glucose intolerance should take prescription insulin sensitizers like metformin [(4)].

Uncertainty surrounds the specific signaling processes that cause follicular activation. Going to sleep or waking up is presumably influenced by a variety of elements in balance. Follicle density appears to be one of these determinants. Up to the antral phase, initial follicle development is gonadotropin-independent after activation from the quiescent pool [(5)].

In women with PCOS, there has been evidence of increased LH pulse rate, amplitude, and LH/FSH ratio. The reactivation of the hypothalamic GnRH pulse generator, increased gonadotropin secretion, and consequent enhanced ovarian estrogen production are the first signs of PCOS in early puberty [(6)]. Not every aspect has an impact on everyone since PCOS is a complex network of interconnected neuroendocrine, hormonal, metabolic, genetic, and environmental variables [(7)].

By preventing estrogen's negative feedback to the brain and causing the pituitary to release gonadotropins, clomiphene citrate (CC) encourages follicle growth. Due to its antiestrogenic effects on cervical mucus and endometrial receptivity, it has been utilized as a typical first-line treatment for ovulation induction in women with PCOS inspite of its poor pregnancy rates [(8)].

Received: 01/12/2022
Accepted: 03/02/2023

The best researched insulin sensitizer in PCOS is metformin. Despite the fact that it does not fulfill the labeling criteria for this indication [9], it is often used by teenagers (15–19 years). In addition, the most recent worldwide evidence-based recommendations for the evaluation and treatment of PCOS state that "additional metformin use to the lifestyle of adolescents with diagnosed PCOS or symptoms of PCOS may be considered prior to making a diagnosis" [10]. Although impact estimates are based on low-quality data from small trials, metformin and oral contraceptives have similar positive effects on hirsutism, triglycerides, and high-density lipoprotein cholesterol [11].

Stereoisomers of inositol Hexahydroxycyclohexanes, such as inositol (MI) and D-chiroinositol (DCI), have the same chemical structure as glucose. They are two of the nine stereoisomeric inositols that make up the family and are extensively distributed in nature [12]. The inositol found in fruits and legumes, phosphatidyl MI, which is a precursor to inositol triphosphate (InsP3), is integrated into cell membranes. Insulin and FSH are only two hormones that use InsP3 as a second messenger. Insulin resistance is brought on by flaws in this signaling system, which also affect insulin signaling. In order to treat insulin resistance diseases such polycystic ovary syndrome, inositol is advised [13].

All symptoms, manifestations, and laboratory abnormalities of PCOS may be improved with inositol combination treatment (MI and DCI). The ovarian myo-inositol paradox should be resolved by prescribing the two myo-inositols concurrently, which should raise the necessary myo-inositol concentrations in the systemic circulation and the ovaries. Metabolic characteristics of PCOS are resolved by MI's correction of systemic insulin resistance. A healthy ovarian environment is created by sufficient DCI levels, which also reduce hyperandrogenism, enhance menstrual regularity, and encourage ovulation and conception [14]. At the moment, oral contraceptives are used to treat hyperandrogenism and control menstruation as part of the therapy of PCOS. Metformin is also used to regulate metabolism. Each of these therapeutic modalities has benefits and drawbacks. None of them address all clinical elements of the disease; instead, each focuses on a single pathophysiologic feature of PCOS. Despite the fact that metformin increases insulin sensitivity, it is not recommended as a first-line therapy for skin conditions or hyperandrogenic characteristics [15].

MATERIALS AND METHODS:

150 PCOS patients were split into three groups:

Group 1: Choline and Inositol (1000 mg) once daily + Clomiphene citrate.

Group 2: Metformin (500 mg) once daily + Clomiphene citrate.

Group 3: Clomiphene citrate alone.

Studied groups received medication for six months then assessment have been done for each patient. Body mass index, regularity of menstrual cycle, ultrasound finding, follicular size, sign of hyperandrogenism, LH & FSH level, and pregnancy rate were recorded.

Ethical approval: The study was approved by College of Medicine, University of Thi –Qar Ethical board. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

A case-control study was conducted at Bint Al-Huda Teaching Hospital, Al-Hussein Teaching Hospital' Gynecology Clinic and Infertility Center in Al-Nasiriyah, Iraq from March 2021 to December 2021. 150 women with PCOS were examined. The effectiveness of choline and inositol in the treatment of PCOS patients was assessed compared with metformin and controls.

Statistical analysis

Statistical significance software package (SPSS) version 23 was used. The threshold of statistical significance, $P \leq 0.05$. ANOVA test was used for analysis of basic demographic characteristics.

RESULTS

The age range of participants was 15-45 years old, with a mean age of 31.1 ± 6.2 years. Interestingly, group 2 (comprising of those taking metformin and clomiphene citrate) had a significantly lower mean age in comparison with the other groups (p=0.01). The baseline BMI observed across all participants was 32.5 ± 5.5 kg/m^2, ranging from 20.7- 45.8 kg/m^2.

Surprisingly, the mean BMI of group 2 was significantly lower than the other groups (p=0.001). Infertility persisted for an average of 3.2 ± 2.8 years, regardless of the groups being observed (p = 0.25). Out of the total participants, 91.3% were found positive for ultrasound, displaying a follicle size averaging at 12.9 mm. No considerable difference in follicle size was noted among the three groups in the study (p=0.37). Analyzing the participant groups, there was no noteworthy variance in mean LH (p=0.44). Meanwhile, FSH was substantially greater in the group receiving both metformin and clomiphene citrate, unlike the other two groups (p=0.001) (Table 1).

Table (1): Baseline demographic characteristic of participants

Parameters	Choline &Inositol +CC	Metformin +CC	CC	*P-value*
Age (year)	31.78±6.40	28.94±5.88	32.54± 6.10	0.01
BMI (Kg/m²)	34.39±5.53	30.12±5.23	33.06± 5.12	0.001
Duration of infertility (year)	3.40±2.63	2.70±3.22	3.60± 0.67	0.25
Follicular size (mm)	12.60±1.62	12.96±1.14	12.92± 1.36	0.37
LH (mIU/L)	6.96±1.10	6.66±1.20	7.08± 1.49	0.44
FSH (mIU/l)	3.54±0.13	4.82±1.57	3.65± 0.32	0.001

- **ANOVA test**

The majority of participants (92) had irregular periods, as indicated in table (2). Nevertheless, there was no discernible difference in the frequency of cycles across the research groups (Chi-square was 4.2 and P was 0.32). The majority of participants had sign of hyperandrogenism (128 participants) like hirsutism. There was a significant higher sign of hyperandrogenism count among participants with group 1 (Choline & inositol + CC) and group 2 (Metformin + CC).

Table (2): Distribution of baseline cycle

Choline &Inositol + CC			Metformin +CC	CC	Total
	Amenorrhea	Count 16	9	17	42
		%	21.4%	40.	100.0
Cycle Irr		Count 29	36	27	92
		%	39.1%	29.	100.0
	Regular	Count 5	5	6	16
		%	31.3%	37.	100.0
Total		Count 50	50	50	15
		%	33.3%	33.	100.0

Chi-Square = 4.2, *P*=0.32.ANOVA test

2- Follow up after treatment (6 months)

6 months after treatment follow-up, table (3) provided an explanation of the substantial changes that occurred following therapy for six months. The mean BMI was reduced by an average of 1. 9 ± 4.2 kg/m², and this reduction was significant across all three groups (p=0.001). The mean change in follicular size was 2.9 mm, and it substantially increased after the start of therapy (p=0.001). The follow up of LH distribution across groups did not differ significantly (*p*=0.5), while FSH distribution showed significant higher level across metformin + CC group in comparison with other two groups (*p*=0.04).

Table (3): Follow up after treatment (6 months)

Parameters	Choline & Inositol +CC	Metformin + CC	CC	*P-value*
BMI (Kg/m²)	33.00 ±5.30	27.30 ±4.50	31.30 ±6.70	0.001
Follicular size (mm)	15.92 ±2.20	16.24 ±2.84	15.02 ±2.66	0.001
LH (mIU/L)	7.74±1.55	7.34±1.78	7.80±1.76	0.5
FSH (mIU/L)	7.34±1.25	8.18±1.99	6.30±1.73	0.04

- **ANOVA test**

Regular cycles were substantially more prevalent in the metformin + CC group compared to the other two groups in terms of menstrual cycle (p=0.001).according to table (4).

Table (4): Regularity of menstrual cycle after treatment

		Metformin + CC	CC	Total
Amenorrhea	Count	0	2	2
	Percentage	0.0%	100.0%	
Irregular	Count 19	3	21	43
	Percentage	7.0%	48.8%	
Regular	Count 31	47	27	105
	Percentage	44.8%	25.7%	

Chi-Square = 23.9, *P* =0.001.ANOVA test.

Although, pregnancy occurred more frequently among women who received choline and inositol + CC or metformin + CC in comparison with group-3 (Clomiphene citrate), no significant difference among the three groups was observed (*p*=0.19), as shown in figure (1).

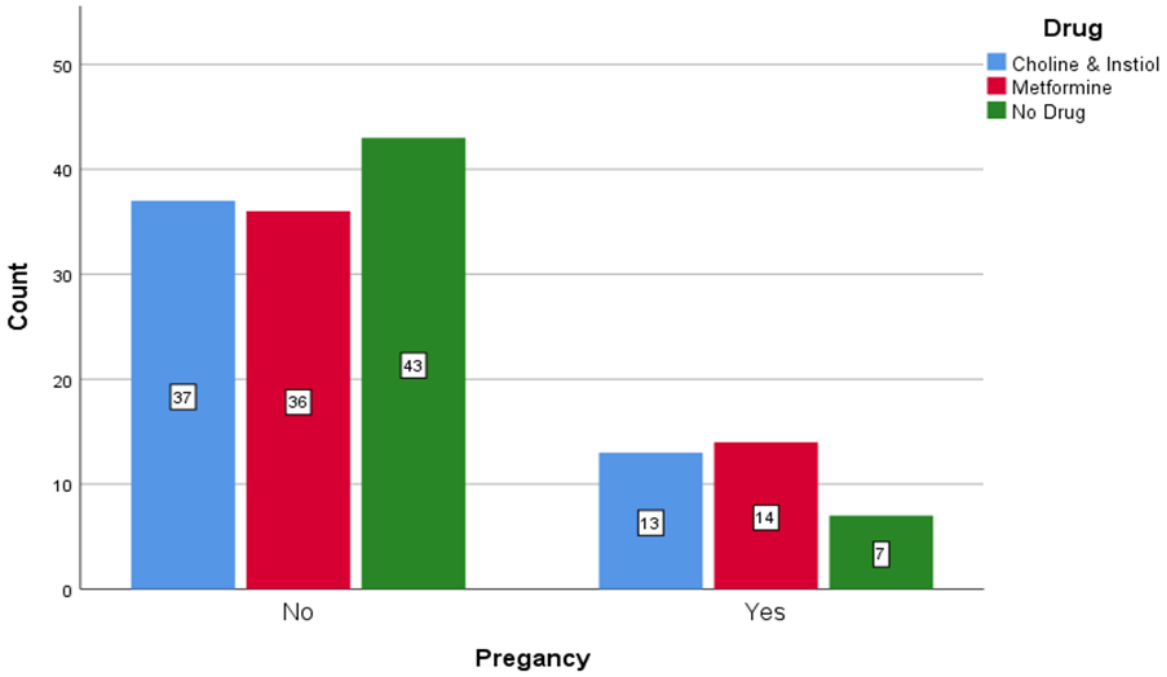

Figure (1): Pregnancy rate after treatment

DISCUSSION

A variety of treatment options are currently available to treat polycystic ovary syndrome (PCOS). To properly manage PCOS in all patients, lifestyle counseling is essential. In hirsutism, alopecia, and acne, these antiandrogenic progestins should be chosen. To control body weight, insulin resistance, and metabolic abnormalities, metformin should be used in overweight/obese adult PCOS women and should also be considered in adolescent PCOS patients. Metformin may also help you lose weight [1, 15].

The mean BMI of all subjects at baseline was 32.5 ± 5.5 kg/m^2, which is related to the fact that PCOS is defined as weight gain. The pathophysiology of anovulation in PCOS is closely related to obesity. Overweight and visceral obesity promote insulin resistance and compensatory hyperinsulinemia [16].

The mean duration of infertility was 3.2 ± 2.8 years. The most frequent cause of anovulatory infertility and hyperandrogenism is PCOS. Infertility is common in PCOS patients with a prevalence of 74% [17, 18]. Hirsutism is a common clinical manifestation of androgen excess, with 85.3% of participants showing signs of hirsutism at baseline. On androgen-sensitive areas of the body, hirsutism is due to the conversion of weak light-colored vellus hairs to dense black terminal hairs [17].

- **Follow up period after treatment for six months**

Polycystic ovary syndrome is a complex disorder, and its relationship to obesity may also be complex [19]. Mean BMI decreased by 1.9 ± 4.2 kg/m^2 after treatment, representing a significant shift. Numerous studies have shown that weight loss in PCOS patients is associated with improved symptoms, especially PCOS symptoms, which typically improve with a 5% to 10% weight loss [20]. Although there was no significant difference in weight reduction between treatment groups, it should be noted that patients using metformin had a lower BMI. The first medication used to make insulin more sensitive in PCOS patients was metformin. Endocrine health is enhanced with metformin. According to a recent study, choline and inositol supplementation was successful in obese and non-obese women with PCOS after 12 weeks of supplementation. Choline and inositol, however, demonstrated the least amount of weight loss. Additionally, they came to the conclusion that obese and non-obese PCOS women can benefit from the combination of insulin sensitizers [21].

Inositol plus metformin was tested against metformin alone by **Agrawal *et al.*** [22]. The findings revealed that the addition of inositol improved menstrual cycles significantly in the former group. What's intriguing is that **Kim *et al.*** [23] published a study in 2020 analyzing the impact of metformin on polycystic ovary syndrome and discovered that the menstrual cycle enhancements from metformin alone or in tandem with lifestyle changes did not

vary much. There were no substantial deviations in pregnancy rate or body mass index. However, the study showed that implementing lifestyle changes helped reduce insulin resistance while also increasing serum levels of sex hormone-binding globulin in comparison with metformin. Aggressively counseling women with PCOS on lifestyle changes is recommended when metformin is not indicated [23].

In addition, the distribution of LH after follow-up was not significantly different between the treatment groups (p = 0.5). However, the distribution of FSH after follow-up showed significantly higher levels in the metformin group than in the other groups (p = 0.04). This suggests that metformin has a weaker effect on lowering FSH compared to choline and inositol. **Zacche *et al.*** [24] found that choline and inositol lowered LH but had no effect on FSH (the study only compared choline and inositol to placebo).

- **Pregnancy rate after treatment**

70% of PCOS sufferers have trouble becoming pregnant. Most likely, there wasn't an ovulation, it was sporadic, or there wasn't enough naturally occurring progesterone to sustain an early pregnancy. Drugs are therefore required to boost PCOS women's chances of conception [25].

Pregnancy rates were higher in the choline and inositol or metformin group compared to women not taking choline and inositol or metformin. However, this result was lower than a previous study by **Prabhakar *et al.*** [26] who found a clinical pregnancy rate of 42% for inositol plus metformin and 42% for inositol alone and 6 months for inositol alone. Researchers found that inositol can act as an insulin sensitizer to help improve metabolism in infertile women with PCOS. In PCOS patients, administration of metformin prior to clomiphene resulted in significantly increased ovulation and conception rates compared to placebo [27].

CONCLUSION

Follow up treatment (6 months), significantly decreased BMI, while significantly increased follicular size among the three studied groups. The regularity of menstrual cycle was significantly higher among metformin group in comparison with the other two groups. The follow-up of LH distribution did not differ significantly. Regarding FSH, there was significant higher level across metformin + CC group in comparison with the other two groups. Although, pregnancy occurred more frequently among women who received choline & inositol or metformin in comparison with no drug group, no significant difference between groups observed.

- **Acknowledgement:** Thanks for all the participants in this study and coworkers.
- **Conflict of interest:** No conflict of interest.
- **Consent to participate:** All participants gave written informed consent prior to participation in the study.
- **Source of funding:** None.

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