Japan Journal of Research

Original Article

Effect of Myo-Inositol in Combination with Alpha-Lipoic Acid and Cysteine (Celine™) Based Co-Treatment on Oocyte Quality in Women with Polycystic Ovarian Syndrome Undergoing Assisted Reproductive Technology

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Keywords

Myo-Inositol, Polycystic Ovarian Syndrome, Assisted Reproductive Technology, Oocyte quality, Embryo quality

Abbreviations

ALA: Alpha Lipoic Acid; ART: Assisted Reproductive Technology; FA: Folic Acid; ICSI: Intracytoplasmic Sperm Injection; IVF: In Vitro Fertilization; MI: Myo-Inositol; MII: Metaphase II; NAC: N-Acetylcysteine; RCT: Randomized Controlled Trial; PCOS: Polycystic Ovarian Syndrome

- Received Date: 16 Feb 2024
- Accepted Date: 29 Feb 2024
- Publication Date: 01 Mar 2024

Abstract

Background: *Myo-inositol (MI), alone or in combination, has gained attention as a potential adjuvant therapy in women undergoing assisted reproductive techniques (ART). The aim of this study was to evaluate the effects of MI in combination with alpha-lipoic (ALA) and N-acetylcysteine (NAC) on oocyte quality and ART outcomes in women with polycystic ovary syndrome (PCOS).*

Methods: *A total of 100 women with PCOS, aged 20-40 years and undergoing ART were randomly assigned to either the MI-ALA-NAC group (n=50) or the control group (n=50). The intervention group received daily oral supplementation of Celine™ (MI in combination with ALA and NAC) in addition to folic acid (FA) supplementation and standard ART treatment, while the control group received FA only in addition to standard treatment. The primary outcome measures included preovulatory follicle count, the number of mature oocytes retrieved, and embryo quality. The secondary outcomes were the number of gonadotropin vials used, ovarian stimulation duration, and pregnancy rate.*

Results: *The Celine group demonstrated a significantly greater number of large sized follicles, oocytes retrieved, mature oocytes and improved embryo quality ($p<0.05$). Additionally, the Celine group exhibited shorter stimulation duration, reduced gonadotropin dose required, and higher pregnancy rate ($p<0.005$).*

Conclusions: *MI in combination with ALA and NAC as an adjunct to ART among women with PCOS showed promising results in improving reproductive outcomes. Future studies should aim to expand our understanding of the long-term effects, and refine the clinical application of this MI co-treatment as an adjunct therapy in fertility clinics to improving the success rates and overall effectiveness of fertility treatments.*

Trial registration: *PACTR, PACTR202401759325189. Registered 16 January 2024 - Retrospectively registered, https://pactr.samrc.ac.za/Search.aspx*

Background

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 4-20% of women of reproductive age [1], and is often associated with multiple comorbidities including obesity, metabolic syndrome, inflammation, hyperandrogenism, insulin resistance and infertility [2–4]. In women with PCOS, fertility is compromised by oligo-/anovulation, reduced oocyte quality, and increased risk of miscarriage [5]. Impaired oocyte quality is defined by a lower proportion of metaphase II (MII) mature oocytes despite a high number of oocytes retrieved, which contributes to a lower fertilization rate and lower quality embryos leading to miscarriage [6].

Management of infertility associated with PCOS is often based on lifestyle modification, pharmacotherapy, surgical treatment and assisted reproductive technologies (ART), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) [3,7]. Over the years, pharmacologic interventions in women with PCOS have included clomiphene citrate [8], letrozole [9], gonadotropin [10], and insulin sensitizers such as metformin which improve ovulation, pregnancy and live birth rates [11,12].

In recent years, several studies have been conducted on myoinositol (MI), an over-the-counter B-complex vitamin supplement, to evaluate its effects on all aspects of PCOS and to contribute to the advances in ART. Due to its

Citation: Elfarjani J, Choueiry P. Effect of Myo-Inositol in Combination with Alpha-Lipoic Acid and Cysteine (Celine™) Based Co-Treatment on Oocyte Quality in Women with Polycystic Ovarian Syndrome Undergoing Assisted Reproductive Technology. Japan J Res. 2024;5(2):012

ability to mediate insulin action, MI has been shown to be essential for menstrual cycle normalization, proper oocyte maturation, and embryo development [13,14]. Specifically, improvements in the number of total and mature oocytes retrieved, follicle count, embryo quality, and fertilization and pregnancy rates have been observed following MI supplementation [15–17].

Several studies have also investigated the effects of MI combinations with agents such as melatonin [18], metformin [19], alpha-lipoic acid (ALA) [20], N-acetylcysteine (NAC) [21], and folic acid (FA) [17] on ART outcomes among women with PCOS and have shown promising results.

Despite the individually documented beneficial role of MI co-treatment with ALA, NAC, and FA in improving reproductive outcomes in women with PCOS, their synergistic effects in a specific combination have not been extensively studied. While only one study has reported a potentially beneficial effect of MI-ALA-NAC-FA on oocyte and embryo morphology in non-PCOS women undergoing IVF [22], there is a notable gap in the literature regarding their combined use in PCOS patients. Therefore, a randomized controlled trial (RCT) was conducted to determine whether this combined treatment, as an adjunct to ovarian stimulation, can improve IVF/ICSI outcomes in women with PCOS. To address this, we evaluated the effect of MI-ALA-NAC (Celine™) administration on oocyte yield, maturation, fertilization, and embryo quality. We also analyzed the duration of ovarian stimulation, number of gonadotropin vials used, and pregnancy rates following IVF/ICSI.

Methods

Study design

This study was a prospective, comparative, randomized, controlled trial conducted between January and June 2019 in women with PCOS undergoing ART at the Teaching Assistance Reproductive Technology Hospital in Benghazi, Libya.

Study population

Participants were women aged 20-40 years at the time of enrollment, diagnosed with PCOS (according to the Rotterdam criteria, represented by oligomenorrhea, hyperandrogenism or hyperandrogenemia, and typical ovarian features on ultrasound), and undergoing IVF/ICSI treatment. Normal uterine cavity as assessed by hysteroscopy or hysterosalpingography and normal prolactin and thyroid-stimulating hormone levels were required.

Women with male factor infertility, such as azoospermia, or other medical conditions causing ovulatory dysfunction, such as hyperprolactinemia, hypothyroidism, or adrenal hyperplasia, were excluded.

Randomization

Participants were randomized 1:1 to the control or intervention group. Women randomized to the intervention group (n=50) received a combination of MI-ALA-NAC (Celine™) twice daily in addition to 400µg FA. Those randomized to the control group (n=50) received 400µg FA alone.

Interventions

Participants who met the inclusion and exclusion criteria were provided with detailed information about the study protocol. Baseline information, including type of infertility and age, was collected. Participants were randomized to the two study groups and provided with the appropriate supplements. Daily supplementation began 6 weeks prior to stimulation and continued during ovarian stimulation until the day of final oocyte maturation. Women then underwent controlled ovarian stimulation using a long luteal-phase GnRH agonist protocol.

The total number of oocytes retrieved and the number of MII oocytes retrieved in the IVF cycle were recorded. The quality of the transferred embryos was assessed by the head of embryology department, who was blinded to the allocation group, using the embryo grading system.

Primary and secondary outcomes

The primary outcome measures were oocyte parameters, including preovulatory follicle count, which reflects the number of preovulatory follicles >17mm in size, total number of oocytes retrieved, which typically ranges from 6 to 15; oocyte quality, defined by the number of MII oocytes retrieved; and the number and quality of embryos transferred, based on the number of morphologically Grade 1 embryos.

Secondary outcomes included duration of ovarian stimulation, number of gonadotropin vials used reflecting total gonadotropin dose, and pregnancy based on ultrasound.

Statistical analysis

Baseline data and outcome data were summarized separately. For all categorical variables, descriptive statistics were generated and tested using either Fisher's exact or chi-square tests. A significance level of 0.05 was used for all hypothesis testing. All statistical analyses were performed using Stata v17.0 software.

Results

One hundred women were randomized, 50 to the Celine™ group and 50 to the control group. Of the randomized subjects, 9 were excluded (2 in the Celine™ group versus 7 in the control group) either because of poor response or hyperstimulation. The characteristics of the participants are summarized in Table 1. There were no differences in age or type of fertility between the groups.

Table 1. *Baseline characteristics of women included in the study (n=100).*

Baseline characteristics	**n (%)**	
Age category		
20 - 25	15 (15)	
26 - 30	26 (26)	
31 - 35	32 (32)	
36 - 40	27 (27)	
Type of infertility		
Primary infertility	77 (77)	
Secondary infertility	23 (23)	
	Celine™ Group	**Control group**
	n (%)	**n (%)**
Participation		
Completed the program	48 (96)	43 (86)
Cancelled	2 (4)	7 (14)
Reason of cancellation		
Poor response	1 (50)	4 (57)
Hyperstimulation	1 (50)	3 (43)

Table 2. *The effect of Celine™ supplementation on primary outcomes.*

	Celine™ Group	Control group	
Primary outcomes	**n (%)**	**n (%)**	**P-value**
Preovulatory follicle count	**n=50**	**n=50**	
< 1	1 (2)	4 (8)	0.014
1 – 4	1 (2)	3 (6)	
5 – 8	11 (22)	11 (22)	
9 – 12	21 (42)	14 (28)	
13 – 16	14 (28)	6 (12)	
17 - 20	2 (4)	11 (22)	
> 20	0 (0)	1 (2)	
Oocytes retrieved	**n=48**	**n=43**	
< 1	1 (2)	1 (2)	0.003
1 – 5	10 (21)	21 (48)	
6 – 10	29 (60)	16 (38)	
11 – 15	8 (17)	2 (5)	
16 – 20	0 (0)	3 (7)	
Mature oocytes (MII) retrieved	**n=48**	**n=43**	
< 1	1 (2)	4 (9)	0.025
1 – 2	6 (12)	17 (39)	
3 – 4	15 (31)	8 (19)	
5 – 6	16 (33)	8 (19)	
7 – 8	5 (11)	3 (7)	
9 – 10	5 (11)	3 (7)	
Grade 1 embryos	**n=48**	**n=43**	
0	4 (8)	16 (38)	< 0.001
1	0 (0)	9 (21)	
2	14 (29)	7 (16)	
3	13 (28)	9 (21)	
4	8 (17)	1 (2)	
5	6 (12)	0 (0)	
6	3 (6)	0 (0)	
7	0 (0)	1 (2)	
Embryo transfers	**n=48**	**n=43**	
0	4 (8)	8 (19)	0.025
1	1 (2)	5 (12)	
2	15 (31)	16 (37)	
3	28 (59)	13 (30)	
4	0 (0)	1 (2)	

Primary outcomes

Fertility outcomes including oocyte yield, maturation and embryo quality are shown in Table 2.

There was a significant increase in preovulatory follicle count in the Celine™ intervention group compared to the control group (p=0.014). As for the number of oocytes retrieved, 77% of women receiving Celine™ supplementation were within the normal range (between 6 and 15) compared to only 42% of the control group (p=0.003). The number of MII oocytes was also significantly higher in the Celine™ group than in the control group (p=0.025).

Regarding embryo quality, the number of Grade 1 embryos was higher in the Celine™ group compared to the control group (p<0.001). In addition, 58% of women in the Celine™ group had 3 embryos transferred compared to 30% in the control group (p=0.025).

Secondary outcomes

The duration of ovarian stimulation, the number of gonadotropin vials received, and the pregnancy rates in both groups are shown in Table 3. There was a significant difference in the duration of ovarian stimulation between the two groups. More women in the Celine™ group (64%) had a normal duration of stimulation (9-11 days) compared to 44% in the control group (p=0.006).

There was also a significant difference in favor of the Celine™ group in the number of gonadotropin vials used, with 80% of participants in the Celine™ group receiving 25 vials or less compared to 40% of women in the control group (p<0.001).

Pregnancies were reported in 12 women in the Celine™ group and 2 women who received folic acid supplementation only. The pregnancy rate was significantly improved in the Celine™ group (24%) compared to the control group (4%, p=0.004).

Discussion

To our knowledge, this was the first study to evaluate the synergistic effect of MI, ALA, and NAC combination therapy on ART outcomes in women diagnosed with PCOS. Our results showed that this unique combination significantly increased the preovulatory follicle count, the number of oocytes retrieved, and the number of mature oocytes and Grade 1 embryos. Treatment of PCOS patients with MI co-treatment resulted in a reduction in the total dose of gonadotropins, a shortened duration of ovulation simulation and an improvement in pregnancy rate.

Table 3. *The effect of Celine™ supplementation on secondary outcomes.*

	Celine™ Group (n=50)	Control group (n=50)	
Secondary outcomes	**n (%)**	**n (%)**	**P-value**
Gonadotropin vials received			
< 15	7 (14)	6 (12)	< 0.001
15 – 25	33 (66)	14 (28)	
26 – 35	9 (18)	20 (40)	
36 – 45	1 (2)	10 (20)	
Ovarian stimulation duration (days)			
6 - 8	12 (24)	7 (14)	0.006
9 - 11	32 (64)	22 (44)	
12 - 14	6 (12)	17 (34)	
> 14	0 (0)	4 (8)	
Pregnancy test			
Positive	12 (24)	2 (4)	0.004
Negative	38 (76)	48 (96)	

Our results were consistent with previous studies showing that MI supplementation significantly increased the number of large follicles (>17 mm) and decreased the number of small follicles in women with PCOS [15,23]. However, the effect of MI supplementation on the total number of oocytes retrieved in different studies has yielded inconsistent results. While our findings confirmed previous studies [24,22,23] reporting a significant increase in the total number of oocytes with MI, others have failed to observe a significant effect [16,25,26]. The discrepancies among these studies may be due to differences in study design, sample size, MI dosage, and treatment duration. In addition, differences in the characteristics of the study populations, including age and specific infertility diagnoses, may also contribute to the conflicting results.

In terms of oocyte maturation, our results are in align with previous researches [16,17,24,25, 27–29], demonstrating a significant increase in the number of mature oocytes with MI supplementation in women undergoing ART and reinforcing the consistency of MI's positive impact on oocyte maturation and subsequent quality. Improved oocyte quality can potentially contribute to higher fertilization rates, embryo implantation, and ultimately better clinical pregnancy outcomes.

Similar to the results of previous studies on MI [23,25,26,28,30], our study suggested that MI had an effect on embryo development, as evidenced by the improvement in the number of Grade 1 embryos in the Celine™ group. A study conducted in non-PCOS women receiving MI-ALA-NAC and FA also reported a significant increase in the proportion of high quality embryos [22]. In addition, consistent with previous studies [22,24,25,27,29,31], the use of MI was associated with an increase in embryo transfers, which ultimately resulted in higher pregnancy rates compared to the control group, although not all associations were significant. The higher number of embryo transfers is indicative of improved overall embryo quality and viability following MI-ALA-NAC supplementation. It is important to note that a higher embryo transfer rate does not necessarily guarantee a higher pregnancy rate. Several factors come into play, including uterine health and receptivity, the overall health of the women receiving the embryos, and the presence of other underlying fertility conditions.

Considering these collective findings and the differences in study design, participant characteristics, and MI combinations between studies, it is important to note that further research is warranted to fully understand the precise mechanisms by which the combination of MI-ALA-NAC affects embryo development and facilitates embryo transfer, and to determine its effect on pregnancy rates and live birth outcomes.

The results demonstrating a significant reduction in the required dose of gonadotropin and a reduction in the duration of ovulation stimulation with MI-ALA-NAC therapy is a promising finding that is consistent with the existing literature on MI [17,27,28,31,32]. For example, several studies [17,22,24,28,31–33] reported a similar reduction in the required gonadotropin dose in patients receiving MI supplementation during their IVF cycles. Others [17,28,31–34] have also documented a shortened duration of ovulation stimulation with MI therapy.

The consistent evidence from multiple studies, including our own, suggests that MI co-treatment holds promise in its potential to optimize ovarian sensitivity to gonadotropin [24,25,30], reduce the risk of ovarian hyperstimulation syndrome [17], and minimize the cost burden and the physical and emotional stress associated with prolonged fertility treatment protocols.

Overall, the results of the current RCT not only provide evidence for the efficacy of MI therapy, but also provide guidance for future research in this area given the novelty of combined treatment with MI, ALA, NAC, and FA in women with PCOS undergoing IVF/ICSI.

Strengths and limitations

The current study is, to our knowledge, the first RCT to evaluate the effect of MI, ALA and NAC supplementation on ART outcomes in women with PCOS. While our study contributes to the existing knowledge base in the field of fertility treatment for PCOS, it is important to acknowledge the limitations, such as the lack of adjustment for potential confounding factors. Despite randomization, there may still be unmeasured factors such as age, body mass index, and underlying medical conditions that could introduce bias and affect the results. Future studies that aim to collect comprehensive information on potential confounders using appropriate statistical analyses may help to improve the validity of the results.

Conclusion

In conclusion, our study provided evidence to support the potential benefits of MI, ALA and NAC combination in ART cycles in women with PCOS. The comparable results obtained in our study with previous research highlight the consistency of the effects of MI on parameters such as ovarian function, oocyte quality, embryo development and pregnancy rate. Furthermore, our findings provide valuable insights into the potential benefits of this novel co-treatment approach on oocyte yield and embryo quality in patients with PCOS and lay the groundwork for future larger RCTs in this area aimed at expanding our understanding of long-term effects and refining the clinical application of MI-ALA-NAC combination as adjunctive therapy in fertility clinics. Ultimately, these efforts may help improve the success rates and overall effectiveness of fertility treatments.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from study participants. The study received ethical approval from the Institutional Review Board of the Teaching Assistance Reproductive Technology Hospital in Benghazi, Libya.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Medical writing was supported by Surveal

Funding

None

Authors' contributions

The authors confirm contribution to the paper as follows: study conception and design: JE; data collection: JE; analysis and interpretation of results: JE, PC; draft manuscript preparation: PC. All authors reviewed the results and approved the final version of the manuscript.

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