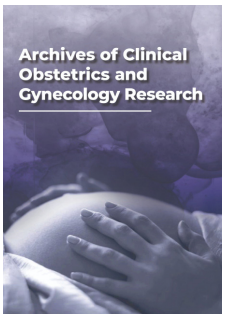
Archives of Clinical Obstetrics and Gynecology Research

Original Article



Effect of Myoinositol in Combination with Alpha-Lipoic Acid and N-acetylcysteine (Celine®) on Ovulation and Pregnancy Rates in Clomiphene-Resistant Women with Polycystic Ovarian Syndrome: A Prospective Chart Review

Jehan Elfarjani MD[1] **and Patrick Choueiry** MD[2]

[1]*Teaching Assistance Reproductive Technology Hospital, Benghazi, Libya*
[2]*Surveal Medical Department, Lebanon*

Correspondence
Patrick Choueiry
Surveal Pharma, Beirut, Lebanon

- Received Date: 15 April 2025
- Accepted Date: 05 May 2025
- Publication Date: 08 May 2025

Keywords: Polycystic Ovary Syndrome, Clomiphene Citrate Resistance, Celine®, Myo-inositol, Ovulation, Pregnancy Rate.

Abstract

Introduction: *Polycystic ovarian syndrome (PCOS) is often accompanied by anovulatory infertility in women and contributes to lower pregnancy rates and an increased risk of miscarriage. While clomiphene citrate (CC) is the first line treatment for ovulation induction, CC resistance develops in 15 to 40% of women with PCOS. Emerging studies suggest that insulin-sensitizing agents such as myo-inositol (MI), N-acetyl-cysteine (NAC), and α-Lipoic acid (ALA) can improve ovulation and pregnancy rates.*

Objectives: *This prospective chart review aimed to evaluate the efficacy of Celine®, an insulin-sensitizing agent containing MI, NAC, and ALA, in improving ovulation and pregnancy rates in CC-resistant women with PCOS.*

Methods: *Data were extracted from the medical records of one hundred women with CC-resistant polycystic ovarian syndrome who were initiated on Celine®. Of the main population, 63 women who remained anovulatory after two menstrual cycles were subsequently prescribed CC in addition to Celine®. Cumulative ovulation and pregnancy rates were calculated based on all ovulations/clinical pregnancies achieved after the first Celine® cycle (n=100) and after the second cycle of Celine® + CC (n=63).*

Results: *Spontaneous ovulation occurred in 37% with Celine® alone and 45% with Celine® + CC, yielding a cumulative ovulation rate of 82%. Clinical pregnancy rates were 18% and 17%, respectively, with a cumulative rate of 43%.*

Conclusions: *The addition of Celine®, alone or in combination with CC, to the treatment of PCOS in women with CC resistance improved ovulation and pregnancy rates, highlighting its potential role in enhancing reproductive outcomes.*

Background

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting 4-21% of women in reproductive age [1–3], and is often accompanied by numerous metabolic and reproductive implications including obesity, metabolic syndrome, hyperandrogenism, insulin resistance, hyperinsulinemia, and infertility [5–8] . PCOS accounts for 80% of anovulatory infertility in women [1] and contributes to lower pregnancy rates and an increased risk of miscarriage [9]. Insulin resistance and associated hyperinsulinemia are considered the main contributors to PCOS-related reproductive dysfunction, by disrupting normal folliculogenesis and inhibiting follicular maturation, ultimately resulting in chronic anovulation [10,11].

Currently, clomiphene citrate (CC) is the first-line medication for medical ovulation induction in anovulatory women with PCOS [12] with up to 80% ovulation rate, and a cumulative pregnancy rate between 60 and 70% in six cycles [13–15]. An initial dose of 50 mg/day starting about day two to five of the menstrual cycle for five days is usually recommended [16]. However, resistance to CC may develop in 15-40% of women with PCOS and presents as failure to ovulate after receiving up to 150 mg/day for five days up to at least three cycles [13].

Other several insulin sensitizing agents and different therapeutical protocols have been used to increase ovulation rates in infertile women with anovulatory PCOS [17]. Recently, myoinositol (MI), a natural insulin sensitizer, alone or in combination, has gained increasing interest as a potential therapeutic option for increasing insulin sensitivity, decreasing

Abbreviations: ALA: Alpha Lipoic Acid; ART: Assisted Reproductive Technology; CC: Clomiphene Citrate; HCG: Human Chorionic Gonadotropin; MI: Myo-Inositol; NAC: N-Acetylcysteine; PCOS: Polycystic Ovarian Syndrome

Citation: Elfarjani J, Choueiry P. Effect of Myoinositol in Combination with Alpha-Lipoic Acid and N-acetylcysteine (Celine®) on Ovulation and Pregnancy Rates in Clomiphene-Resistant Women with Polycystic Ovarian Syndrome: A Prospective Chart Review. Arch Clin Obs Gyn Res. 2025;4(1):25-04

hyperandrogenism, and improving ovarian function in women with PCOS, specifically those seeking assisted reproductive technologies (ART) [18,19]. In addition to MI, other components with insulin-sensitizing and antioxidant properties, including alpha-lipoic acid (ALA) and N-acetylcysteine (NAC) have been demonstrated to improve metabolic parameters in PCOS [20–22] and restore ovulation in women with PCOS [23].

More recently, a novel therapeutic strategy of MI, ALA, and NAC in combination (Celine®) has been studied, as it appears to have a synergistic efficacy. Treatment with Celine® resulted in a shortened duration of ovulation stimulation and an increase in pregnancy rate among women with PCOS undergoing ART [24]. This study aims to evaluate the effectiveness of Celine® in improving ovulation and pregnancy rates in anovulatory women with CC-resistant PCOS. By demonstrating its role as a monotherapy and in combination with CC, we aim to determine whether Celine® is a beneficial nutraceutical in CC-resistant PCOS management.

Materials and methods

Study design and population

This prospective chart review was conducted on women with CC-resistant PCOS, attending the clinic at the Teaching Assistance Reproductive Technology Hospital, Benghazi - Libya, between January and June 2019. All women over 18 and under 37 years of age with CC-resistant PCOS who were initiated on Celine® (Surveal Pharma) were included in the study. PCOS was diagnosed based on the Rotterdam criteria represented by oligomenorrhea, hyperandrogenism, or hyperandrogenemia, and typical features of ovaries on ultrasound scans [25]. Clomiphene resistance was defined as failure to ovulate after receiving 150 mg of CC daily for five days per cycle, for at least three cycles [15].

The main study population consisted of all participants who received two tablets of Celine® twice daily for two menstrual cycles or 8 weeks. Data were extracted from the medical records of the main population at a baseline time point corresponding to the start of Celine® and at the end of the Celine® cycle. Within the main population, a subgroup of women remained anovulatory after after two menstrual cycles on Celine® alone and subsequently received another cycle of Celine® (two tablets twice daily) + CC (at a dose of 50 mg twice daily for five days, starting on day 3 of the menstrual cycle). Data were extracted again for this subgroup at the end of the second cycle of Celine® + CC.

Primary and secondary outcomes

Spontaneous ovulation was recorded after two menstrual cycles on Celine® alone for the main population, and then after a second cycle of Celine® in addition to CC for the subgroup of women who did not ovulate spontaneously after two months of supplementation with Celine® alone. Ovulation was defined as the presence of at least one follicle measuring ≥ 18mm in diameter and confirmed by a timed serum progesterone increase. The primary outcome measure was cumulative ovulation rate. The secondary outcome was clinical pregnancy, defined as the pregnancy that lasted six weeks (or 42 days) after the onset of the last menstrual period and confirmed by human chorionic gonadotropin (hCG) assay [26].

Statistical analysis

The clinical data were described using frequencies and percentages. Analysis was performed using STATA 17. The ovulation/pregnancy rate was calculated as the number of ovulatory cases/clinical pregnancies, which have been achieved, divided by the total number of women in the main population receiving Celine® alone or in the subgroup receiving Celine® + CC.

The cumulative ovulation/pregnancy rate was calculated by taking into account all ovulatory cases/clinical pregnancies achieved following the two supplementation cycles (Celine® alone and Celine® + CC).

Ethical considerations

The study was an observational analysis of pre-existing medical records and did not involve direct contact with participants. Each participant was assigned a unique, anonymized identification number to ensure the confidentiality and privacy of the data collected. However, approval to write and publish this manuscript was obtained from the ethical department at Teaching Assistance Reproductive Technology Hospital, Benghazi – Libya.

Results

A total of 100 women with CC-resistant PCOS who were initiated and maintained on Celine® for two menstrual cycles were included in the study. In the main population, 63 women remained anovulatory on Celine® after two menstrual cycles and subsequently received Celine® + CC.

Table 1 summarizes the ovulation and pregnancy rates among the study participants. Spontaneous ovulation occurred in 37 out of 100 women in the main population who were initiated on Celine®. Of the 63 participants who remained anovulatory and were subsequently treated with Celine® + CC, 45 achieved spontaneous ovulation, while 18 remained anovulatory. The ovulation rate was 37% in the main population receiving Celine® and 71% in the subgroup receiving Celine® + CC, resulting in a cumulative ovulation rate of 82%.

In the main study population, 18 of the 37 women who ovulated became pregnant, for a pregnancy rate of 49%. In the Celine® + CC subgroup, 17 clinical pregnancies were achieved with a pregnancy rate of 38% resulting in a cumulative clinical pregnancy rate of 43%.

Table 1. *Spontaneous ovulation and clinical pregnancy rates in the main population of women with clomiphene citrate-resistant polycystic ovarian syndrome treated with Celine® alone and in the subgroup of women subsequently treated with Celine® + Clomiphene Citrate.*

	Main population who received Celine® alone	**Subgroup who subsequently received Celine® + CC**
Outcome	**n (%)**	**n (%)**
Spontaneous Ovulation	***n =100***	***n =63***
Yes	37 (37)	45 (71)
No	63 (63)	18 (29)
Clinical Pregnancy	***n =37***	***n =45***
Yes	18 (49)	17 (38)
No	19 (51)	28 (62)

CC: Clomiphene Citrate.

Discussion

This study evaluated the real-world effectiveness of Celine® in improving ovulation and pregnancy rates in CC-resistant women with PCOS. Our findings showed that Celine® supplementation alone helped induce ovulation in 37% of women, while the combination of Celine® + CC further improved ovulation, resulting in an 82% cumulative rate. We also confirmed clinical pregnancy in 18% and 17% in women within the study population and Celine® + CC subgroup, respectively, with the cumulative pregnancy rate reaching 43%.

The improved ovulation rate observed here aligns with previous studies assessing the efficacy of insulin-sensitizing agents in restoring ovulation in PCOS patients. Studies on MI demonstrated its effect in improving metabolic and reproductive functions associated with PCOS [18,19,27] and indicated that PCOS women treated with MI were two times more likely to ovulate compared to placebo [28]. While ALA and NAC were also linked to improved insulin resistance and oxidative stress, leading to enhanced ovulatory function [22,23,29], according to a recent systematic review and meta-analysis, NAC may complement the ovulation-inducing effects of CC, MI, and ALA [21], especially in women with PCOS who are CC-resistant [30,31].

In the present study, 43% of CC-resistant women achieved clinical pregnancy after Celine® administration, alone or with CC. Numerous previous studies have demonstrated the effects of MI, NAC, and ALA in monotherapy on pregnancy rate. Previous findings indicate that MI supplementation led to significant improvements in pregnancy rate [32,33]. Moreover, a high implantation rate and cumulative pregnancy rate were observed among non-PCOS women treated with a MI + ALA combination [34].

While studies suggest a potential benefit of NAC in improving pregnancy rate [29] specifically in women with CC-resistant PCOS [30,31], the addition of NAC to CC treatment did not show significant improvement of pregnancy in patients with PCOS-related infertility [35]. The cumulative pregnancy rate observed in this study reflects the overall improvement of ovulation and subsequent fertility restoration following the combined therapeutic approach.

Despite the individually documented beneficial role of MI, ALA, NAC, in improving ovulation and pregnancy rates in women with PCOS, their synergistic effects have not been extensively investigated. A previous study on Celine® highlighted its efficacy in improving parameters such as ovarian function, oocyte quality, embryo development, and pregnancy rate in women with PCOS undergoing ART [24]. Overall, these findings support the efficacy of Celine®, alone or in combination with CC, as a nutraceutical with promising implications for ovulation induction and improved reproductive outcomes.

Furthermore, improvements in ovulation and pregnancy rates found in this study could be attributed not only to the insulin-sensitizing components of Celine®, but also to the addition of CC to the treatment of women who did not initially ovulate. The combination of these two approaches may have had a synergistic effect in improving CC sensitivity and ovarian function. A previous study on CC-resistant PCOS patients demonstrated that extended CC treatment was effective for increasing both ovulation and pregnancy rates [13].

In view of the potential benefits of Celine®, thorough and critical evaluation of its efficacy in the treatment of CC-resistant PCOS is essential. Further larger studies are needed to confirm these results and refine the clinical application of this combination therapy.

Strengths and limitations

This is, to our knowledge, the first study to assess the effect of Celine® supplementation, with or without CC, on ovulation and pregnancy rates in women with CC-resistant PCOS. Another strength of this study is the use of real-world data of a well-defined population of women with CC-resistant PCOS, which provides valuable insights into the potential effects of Celine® in this targeted population. However, this study is limited by its observational chart review design, which limits close monitoring of patients and accurate clinical assessments, and by the relatively small sample size, which limits the generalizability of the findings to a broader population. Furthermore, the absence of a control group and the lack of adjustment for potential confounding factors limit the ability to attribute improvements solely to Celine® supplementation. Future large-scale randomized controlled trials are needed to confirm these findings and establish more definitive conclusions.

Conclusion

In summary, our preliminary results indicate that Celine® may be an option to improve ovulation and pregnancy rates in women with PCOS. Large-scale randomized controlled trials are warranted to exclude potential confounders and provide stronger evidence to guide the clinical treatment of women with PCOS.

References

1. Deswal R, Narwal V, Dang A, Pundir CS. The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. J Hum Reprod Sci. 2020;13:261–71.
2. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016;106:6–15.
3. Belenkaia LV, Lazareva LM, Walker W, Lizneva DV, Suturina LV. Criteria, phenotypes and prevalence of polycystic ovary syndrome. Minerva Ginecol. 2019;71:211–23.
4. Che Y, Yu J, Li Y-S, Zhu Y-C, Tao T. Polycystic Ovary Syndrome: Challenges and Possible Solutions. J Clin Med. 2023;12:1500.
5. Leon LIR, Anastasopoulou C, Mayrin JV. Polycystic Ovarian Disease. StatPearls Internet [Internet]. StatPearls Publishing; 2022 [cited 2023 May 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459251/
6. Sadeghi HM, Adeli I, Calina D, Docea AO, Mousavi T, Daniali M, et al. Polycystic Ovary Syndrome: A Comprehensive Review of Pathogenesis, Management, and Drug Repurposing. Int J Mol Sci. 2022;23:583.
7. Liu Y-N, Qin Y, Wu B, Peng H, Li M, Luo H, et al. DNA methylation in polycystic ovary syndrome: Emerging evidence and challenges. Reprod Toxicol. 2022;111:11–9.
8. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010;8:41.
9. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016;22:687–708.
10. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic

review and meta-analysis of euglycaemic–hyperinsulinaemic clamp studies. Hum Reprod. 2016;31:2619–31.

11. Li Y, Chen C, Ma Y, Xiao J, Luo G, Li Y, et al. Multi-system reproductive metabolic disorder: significance for the pathogenesis and therapy of polycystic ovary syndrome (PCOS). Life Sci. 2019;228:167–75.
12. Melo AS, Ferriani RA, Navarro PA. Treatment of infertility in women with polycystic ovary syndrome: approach to clinical practice. Clinics. 2015;70:765–9.
13. Elkhateeb RR, Mahran AE, Kamel HH. Long-term use of clomiphene citrate in induction of ovulation in PCO patients with clomiphene citrate resistance. J Gynecol Obstet Hum Reprod. 2017;46:575–7.
14. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod Oxf Engl. 2008;23:462–77.
15. Brown J, Farquhar C. Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome - Brown, J - 2016 | Cochrane Library. [cited 2025 Feb 25]; Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002249.pub5/full
16. Mbi Feh MK, Patel P, Wadhwa R. Clomiphene. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Mar 5]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559292/
17. Sparić R, Andjić M, Rakić A, Bjekić-Macut J, Livadas S, Kontić-Vučinić O, et al. Insulin-sensitizing agents for infertility treatment in woman with polycystic ovary syndrome: a narrative review of current clinical practice. Hormones. 2024;23:49–58.
18. Sharon P M, P M, Manivannan A, Thangaraj P, B M L. The Effectiveness of Myo-Inositol in Women With Polycystic Ovary Syndrome: A Prospective Clinical Study. Cureus. 16:e53951.
19. Merviel P, James P, Bouée S, Le Guillou M, Rince C, Nachtergaele C, et al. Impact of myo-inositol treatment in women with polycystic ovary syndrome in assisted reproductive technologies. Reprod Health. 2021;18:13.
20. Liu J, Su H, Jin X, Wang L, Huang J. The effects of N-acetylcysteine supplement on metabolic parameters in women with polycystic ovary syndrome: a systematic review and meta-analysis. Front Nutr. 2023;10:1209614.
21. Viña I, Viña JR, Carranza M, Mariscal G. Efficacy of N-Acetylcysteine in Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. Nutrients. 2025;17:284.
22. Guarano A, Capozzi A, Cristodoro M, Di Simone N, Lello S. Alpha Lipoic Acid Efficacy in PCOS Treatment: What Is the Truth? Nutrients. 2023;15:3209.
23. Fruzzetti F, Fidecicchi T, Palla G, Gambacciani M. Long-term treatment with α-lipoic acid and myo-inositol positively affects clinical and metabolic features of polycystic ovary syndrome. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2020;36:152–5.
24. Elfarjani J, Choueiry P. Effect of Myo-Inositol in Combination with Alpha-Lipoic Acid and Cysteine (CelineTM) Based Co-Treatment on Oocyte Quality in Women with Polycystic Ovarian Syndrome Undergoing Assisted Reproductive Technology. Jpn J Res [Internet]. 2024 [cited 2025 Mar 6];5. Available from: https://www.sciencexcel.com/article/effect-of-myo-inositol-in-combination-with-alpha-lipoic-acid-and-cysteine-celinetm-based-co-treatment-on-oocyte-quality-in-women-with-polycystic-ovarian-syndrome-undergoing-assisted-reproductive-technology
25. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod Oxf Engl. 2004;19:41–7.
26. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril. 2003;79:577–84.
27. Agrawal A, Mahey R, Kachhawa G, Khadgawat R, Vanamail P, Kriplani A. Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2019;35:511–4.
28. Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H, et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG Int J Obstet Gynaecol. 2018;125:299–308.
29. Thakker D, Raval A, Patel I, Walia R. N-Acetylcysteine for Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. Obstet Gynecol Int. 2015;2015:817849.
30. Nemati M, Nemati S, Taheri A-M, Heidari B. Comparison of metformin and N-acetyl cysteine, as an adjuvant to clomiphene citrate, in clomiphene-resistant women with polycystic ovary syndrome. J Gynecol Obstet Hum Reprod. 2017;46:579–85.
31. Nasr A. Effect of N-acetyl-cysteine after ovarian drilling in clomiphene citrate-resistant PCOS women: a pilot study. Reprod Biomed Online. 2010;20:403–9.
32. Mamadjanova K, Mamadjanova S, Shamansurova Z. Evaluation of the myo-inositol effect in treating infertility among patients with polycystic ovary syndrome. Endocr Abstr [Internet]. Bioscientifica; 2024 [cited 2025 Mar 8]. Available from: https://www.endocrine-abstracts.org/ea/0104/ea0104p198
33. Zheng X, Lin D, Zhang Y, Lin Y, Song J, Li S, et al. Inositol supplement improves clinical pregnancy rate in infertile women undergoing ovulation induction for ICSI or IVF-ET. Medicine (Baltimore). 2017;96:e8842.
34. Canosa S, Paschero C, Carosso A, Leoncini S, Mercaldo N, Gennarelli G, et al. Effect of a Combination of Myo-Inositol, Alpha-Lipoic Acid, and Folic Acid on Oocyte Morphology and Embryo Morphokinetics in non-PCOS Overweight/Obese Patients Undergoing IVF: A Pilot, Prospective, Randomized Study. J Clin Med. 2020;9:2949.
35. Ghomian N, Khadem N, Moeindarbari S, Abdolrazagh A. Comparison of Pregnancy Rate in Patients With Polycystic Ovary Syndrome Treated With Clomiphene Alone and in Combination With N-acetyl Cysteine: A Randomized Clinical Trial. Int J Womens Health Reprod Sci. 2018;7:185–9.