Clinical and Experimental Obstetrics & Gynecology

*Clin. Exp. Obstet. Gynecol.* **2024**; 51(2): 35
https://doi.org/10.31083/j.ceog5102035

*Original Research*

# Effectiveness, Tolerability and Safety of a Compound Based on D-chiro-inositol + Myo-inositol, Melatonin, Folic Acid, and Vitamin D in Patients with Menstrual Cycle Disorders

Silvia P. González[1,*], María del Mar Rubio[2,†], Helena Losa[3,†]

[1]Obstetrics and Gynecology Department, HM Gabinete Velázquez, 28001 Madrid, Spain
[2]Obstetrics and Gynecology Department, Hospital Universitario de Guadalajara, 19002 Guadalajara, Spain
[3]Obstetrics and Gynecology Department, Hospital Álvaro Cunqueiro, 36312 Vigo, Spain
*Correspondence: spgonzalez@hmhospitales.com (Silvia P. González)
[†]These authors contributed equally.
Academic Editor: Michael H. Dahan
Submitted: 10 July 2023 Revised: 26 October 2023 Accepted: 2 November 2023 Published: 4 February 2024

**Abstract**

**Background**: Menstrual cycle disorders represent a prevalent cause for gynecological consultations. These disorders often encompass ovulatory dysfunction, accompanied by analytical and clinical anomalies linked to hyperandrogenism, collectively defining polycystic ovary syndrome (PCOS). However, a considerable subset of patients suffering from menstrual cycle disorders fails to meet the diagnostic criteria for any recognized PCOS phenotypes, leading to substantial debate in the field. This study aims to assess the impact of a commercially available combination of inositols, melatonin, folic acid, and vitamin D in patients experiencing menstrual disorders, characterized by oligo-anovulation (amenorrhea and abnormally long cycles), irrespective of their actual compliance with PCOS criteria. **Methods**: An observational, prospective, non-randomized study was devised to assess cycle regularity, satisfaction levels, and analytical alterations following the administration of the combination of inositols, melatonin, folic acid, and vitamin D (at baseline and at 6 months). Statistical analysis was executed using SPSS (version 22.0). **Results**: The assessed treatment demonstrated an enhancement in the regularity of menstrual cycles, accompanied by notable reductions in androstenedione and dehydroepiandrosterone (DHEA) levels, as well as basal insulin and the homeostatic model assessment for insulin resistance (HOMA), despite their initial values falling within the normal range. Furthermore, there was a substantial elevation in the serum levels of vitamin D ($p < 0.05$). Following 6 months of treatment, a high degree of patient satisfaction was observed, with no documented adverse effects within the selected sample. **Conclusions**: The combination of inositols, melatonin, folic acid, and vitamin D exhibits potential as an efficacious approach for managing menstrual disorders while maintaining a commendable safety profile. Additional investigations into the long-term efficacy and safety of this formulation are warranted, although initial results hold promise.

**Keywords:** myo-inositol; D-chiro-inositol; melatonin; folic acid; vitamin D; menstrual cycle

## 1. Introduction

The normal menstrual cycle was defined by the International Federation of Gynecology and Obstetrics (FIGO) in 2011 as one in which menstruation occurs between days 24 and 38 of the cycle, with a regularity of $\pm 7$ days from month to month. The menstrual period should last between 4 and 8 days, and should not significantly affect the woman's quality of life or lead to anemia, with menstrual blood loss ranging from 5 to 80 mL per cycle [1]. While this classification primarily focuses on menstruation, it is important to recognize that many cases involve ovulatory dysfunction.

In October 2022, an Expert Committee convened by FIGO aimed to elucidate the etiology and pathophysiology of ovulatory disorders. This effort acknowledged the existence of a continuous spectrum, ranging from ovulation (eumenorrhea) to complete anovulation (amenorrhea), encompassing all conceivable disovulatory cycle alterations, along with their respective causes. These alterations exert a significant impact on patients' fertility, extending beyond the mere alteration of bleeding patterns and the consequent impact on their quality of life [1].

Recent advances in our understanding of the menstrual cycle, coupled with developments in assisted reproduction techniques, have led to the identification of hitherto unknown molecules implicated in the fertilization process, such as vitamin D and inositol.

Polycystic ovary syndrome (PCOS) stands out as the most common cause of subfertility, ovarian dysfunction, and menstrual irregularity, rendering it the most extensively studied condition in this context. However, owing to its phenotypic heterogeneity, the diagnosis of PCOS remains a complex and contentious issue [1]. Although the Rotterdam criteria of 2003, which involves clinical or biochemical hyperandrogenism, oligo- or amenorrhea, and polycystic ovarian morphology, are widely accepted for diagnosis, the ultrasound criterion is the only one that has achieved

unequivocal consensus. The objective determination of whether clinical or biochemical criteria are met remains less straightforward [2].

Moreover, this definition does not encompass a significant disorder that has recently been linked with PCOS: insulin resistance. It appears that hyperinsulinemia and insulin resistance in PCOS may instigate androgenization in women by decreasing hepatic sex hormone-binding globulin (SHBG) levels, thereby elevating free testosterone levels. Consequently, restoring ovarian response can alleviate hyperandrogenemia, reestablish menstrual cyclicity and ovulation, and enhance the chances of spontaneous pregnancy [2,3]. Among insulin sensitizers, metformin has been the most frequently used, but its gastrointestinal side effects, including bloating, nausea, and diarrhea, have prompted the development of alternative, better-tolerated therapeutic options, with improved patient compliance and subsequent efficacy [2,3].

Individually, melatonin, vitamin D, B-complex vitamins (particularly vitamin B6, B9 or folic acid, and B12), and inositol (including myo-inositol (MYO) and D-chiro-inositol) have shown efficacy in restoring menstrual cycles and improving fertility, with a particular emphasis on PCOS patients [4–7]. In clinical practice, we encounter numerous patients with cycle disorders resulting from ovulatory dysfunction, who often do not strictly meet the criteria for PCOS, or whom a precise diagnosis cannot be established due to the absence of hormonal determination and/or high-resolution ultrasound. As such, the objective of this study was to assess the effectiveness of a compound based on these substances to regulate the menstrual cycle and improve hormonal profiles in patients selected based on their menstrual cycle disorders.

## 2. Materials and Methods

A prospective observational, non-randomized study was meticulously structured, targeting women of reproductive age, aged 18 years or older, who sought medical consultation due to prolonged menstrual cycle duration, as defined by the FIGO criteria (i.e., cycles exceeding 38 days).

Excluded from the study were perimenopausal and immediately postmenarcheal women, irrespective of their adherence to the Rotterdam criteria for PCOS. Furthermore, women undergoing concurrent pharmacological or phytotherapeutic treatments known to potentially disrupt the hormonal systems under investigation, including estrogens, selective estrogen receptor modulators, gonadotropin-releasing hormone (GnRH) analogs, levothyroxine, among others, were also excluded. Patients with a history of prior therapies for menstrual disorders, which might exert residual effects (with a mandated 2-month washout period), as well as those possessing formal contraindications for the administered intervention, were carefully excluded as per the investigator's judgment.

A total of 44 patients were recruited, and there were no dropouts during the 6-month treatment period. The patients received a commercially available standardized combination comprising MYO (4 g), D-chiroinositol (100 mg), melatonin (1.8 mg), folic acid (400 mcg), and vitamin D (600 IU) on a daily basis. This compound is marketed in Spain by the *SeidLab* laboratory, under the trade name Seidivid Plus®. The monthly treatment would cost approximately between 30 and 40 euros.

Before the initiation of the treatment regimen, all participants meticulously maintained a menstrual calendar, documenting the duration, frequency, and intensity of their menstrual cycles. Additionally, they provided subjective assessments of satisfaction, using a 7-point Likert scale [7] at the conclusion of the study. Pertinent analytical parameters were quantified and subsequently juxtaposed to evaluate both the clinical and analytical effects of the intervention following the 6-month study period.

For statistical analyses, the SPSS package version 22.0 (SPSS Inc., Chicago, IL, USA) was employed. Differences in proportions or means were assessed using the Chi-square test and the *t*-student test. Statistical significance was defined at a threshold of $p < 0.05$.

## 3. Results

Out of the initial 50 patients enrolled in the study, a total of 44 successfully completed it. The study encompassed a comprehensive assessment of anthropometric, biochemical, endocrine, and metabolic parameters among the participating patients. These parameters are presented in Table 1 below.

The mean age of the patients was 29 years (standard deviation (SD) = 7.1 years). Their average weight measured at 61 $\pm$ 10 kg, with an average height of 160 $\pm$ 12 cm. The average duration of their menstrual cycles was 51 days, ranging from 39 to 63 days (Table 1), and 45.5% of the sample reported experiencing dysmenorrhea. Following 6 months of treatment, the average duration of menstrual cycles decreased to 39 $\pm$ 10.6 days ($p < 0.05$) (Table 1). Symptoms indicative of hyperandrogenism, such as hirsutism and acne, were present in 24.5% and 26.4% of the patients, respectively. Moreover, 90.9% of the sample were nulliparous, and 81.8% had previously used hormonal oral contraceptives (data not shown).

The degrees of satisfaction with the effects of the treatment received were determined through the use of a Likert scale, which showed that merely 9% of the sample reported not perceiving any effects from the treatment, while the remaining participants expressed varying degrees of satisfaction. Importantly enough, 63% of the sample recognized a high degree of satisfaction with the effects of the treatment received, 25% moderate satisfaction, and lastly 2% showed light satisfaction with the treatment received. As noted above, only 9% acknowledged that they did not per-

**Table 1. Baseline and post-treatment values for anthropometric, biochemical, endocrine, and metabolic parameters of the patients.**

| Parameter | Normal range | Basal visit | Final visit (6 months) | *p*-value |
|---|---|---|---|---|
| Age (years) | | 29 ± 7.1 | | |
| BMI (kg/m$^2$) | | 23.8 ± 2.6 | 23.4 ± 2.9 | 0.62 |
| Average cycle length (days)* | | 51 ± 12.2 | 39 ± 10.6 | 0.04 |
| Hb (g/dL) | 12–15.6 | 12.8 ± 1.9 | 12.9 ± 0.7 | 0.71 |
| APTT (sec) | 26–36 | 27.62 ± 1.8 | 30.9 ± 1.4 | 0.57 |
| Vitamin D (nmol/L)* | 30–100 | 18.45 ± 3.4 | 36.5 ± 2.1 | 0.01 |
| Glucose (mg/dL) | 74–106 | 83.66 ± 6.2 | 78.5 ± 4.9 | 0.18 |
| Urea (mg/dL) | 19–49 | 28.33 ± 9.1 | 27.5 ± 7.0 | 0.84 |
| Creatinine (mg/dL) | 0.50–1.10 | 0.63 ± 0.4 | 0.65 ± 0.4 | 0.74 |
| AST (U/L) | <34 | 30 ± 10.3 | 28 ± 9.2 | 0.32 |
| ALT (U/L) | 10–49 | 27.6 ± 12.3 | 21 ± 14.1 | 0.40 |
| Cholesterol (mg/dL) | <200 | 178.3 ± 14.8 | 185 ± 10.9 | 0.08 |
| Triglycerides (mg/dL) | <150 | 97 ± 20.1 | 103.5 ± 13.4 | 0.21 |
| HDL (mg/dL) | >50 | 54 ± 9.2 | 58 ± 6.3 | 0.47 |
| LDL (mg/dL) | <160 | 121 ± 13.4 | 125.4 ± 17 | 0.36 |
| FSH (mIU/mL) | 2.5–10.2 | 7.5 ± 2.9 | 6.5 ± 3.6 | 0.09 |
| LH (mIU/mL) | 1.9–12.5 | 9.3 ± 3.0 | 8.2 ± 4.2 | 0.12 |
| Estradiol (pg/mL) | 20–144 | 47.16 ± 4.1 | 55.35 ± 7.9 | 0.30 |
| Progesterone (ng/mL) | 0.15–1.4 | 0.87 ± 0.2 | 0.75 ± 0.3 | 0.28 |
| Prolactin (ng/mL) | 2.8–29.1 | 23.26 ± 5.8 | 19.9 ± 1.2 | 0.09 |
| Total testosterone (ng/mL) | 0.12–0.59 | 0.4 ± 0.2 | 0.3 ± 0.1 | 0.64 |
| Free testosterone (pg/mL) | 0.1–4.1 | 1.64 ± 0.9 | 1.11 ± 0.2 | 0.55 |
| Androstendione (ng/dL)* | 30–350 | 452.6 ± 20.1 | 306.5 ± 9.8 | 0.03 |
| Hydroxyprogesterone (nmol/L) | 0.1–0.8 | 1.14 ± 0.5 | 0.91 ± 0.7 | 0.10 |
| DHEAS (µg/dL) | 35–430 | 303 ± 50 | 301 ± 41.0 | 0.21 |
| Basal insulin (U/mL)* | 3–25 | 6.23 ± 8.0 | 4.65 ± 4.1 | 0.01 |
| SHBG (nmol/L)* | 18–114 | 75.6 ± 32.6 | 101 ± 41.2 | 0.01 |
| HOMA* | <3.8 | 2.45 ± 0.7 | 1.99 ± 0.5 | 0.03 |
| DHEA (ng/mL)* | 1.32–19.95 | 10.78 ± 5.7 | 6 ± 3.6 | 0.01 |
| TSH (mIU/L) | 0.550–4.780 | 1.5 ± 0.6 | 0.91 ± 0.6 | 0.07 |
| Free T4 (ng/dL) | 0.89–1.76 | 1.41 ± 0.8 | 1.09 ± 0.7 | 0.18 |

BMI, body mass index; Hb, hemoglobin; ATTP, activated partial thromboplastin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FSH, follicle stimulating hormone; LH, luteinizing hormone; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-bindingglobulin; HOMA, homeostatic model assessment for insulin resistance; DHEA, dehydroepiandrosterone; TSH, thyroid stimulating hormone; T4, thyroxine. Glucose fasting, hormonal profile determined on day 3 of menstrual cycle.

Data are reported as means + SD (standard deviations).

*$p < 0.05$, compared with the level at the baseline.

ceive improvement with treatment, nor was there any worsening of the symptoms that led to his entry into the study, which can be proven by the described results in Fig. 1.

No notable adverse reactions were observed during the course of the study.

Overall, the sample displayed a deficiency in vitamin D at baseline, with a mean baseline value of 18 nmol/L. However, this deficiency was effectively addressed as it doubled, normalizing to 36 nmol/L after 6 months, a statistically significant improvement ($p = 0.01$).

The treatment had no discernible impact on renal function, as evidenced by stable levels of urea (28 *vs.* 27 mg/dL, $p = 0.84$) and creatinine (0.6 *vs.* 0.6 mg/dL, $p = 0.74$). Similarly, liver function remained unaltered, measured by transaminase levels (in normal limits). Although there was a slight trend toward a deterioration in the lipid profile, this difference did not attain statistical significance.

Noteworthy alterations were observed in some hormone levels. The most significant reduction occurred in androstenedione levels, which decreased from 452 to 306 ng/mL after 6 months of treatment ($p = 0.03$). The decline

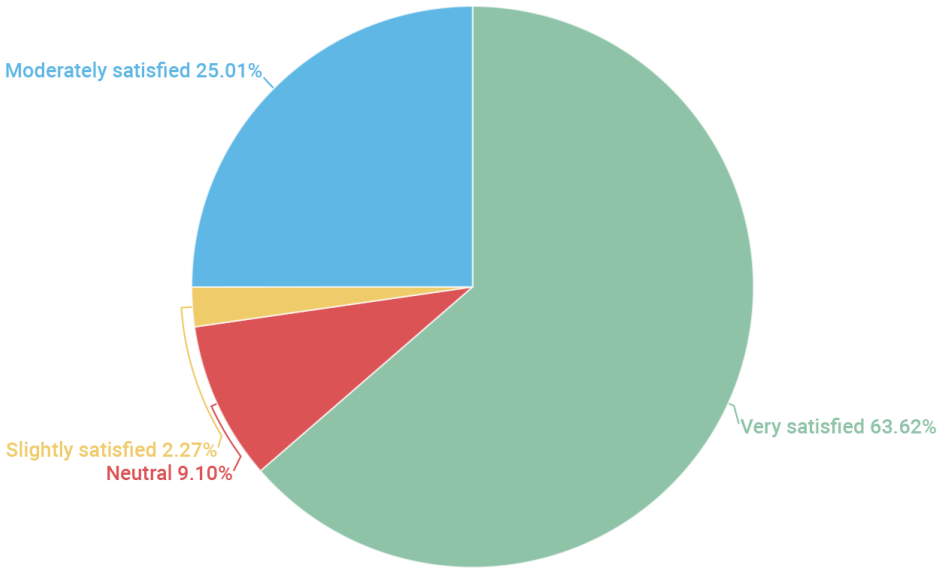


**Fig. 1. Graphic of satisfaction Rate.** The treatment's satisfaction rate, assessed using a 7-point Likert scale, revealed that no patients expressed dissatisfaction with the treatment.

in dehydroepiandrosterone (DHEA) was less pronounced, shifting from 10 to 6 ng/mL, also reaching statistical significance ($p$ = 0.01). SHBG exhibited a significant increase, rising from 75 nmol/L at baseline, to 101 nmol/L at 6 months ($p$ = 0.01). Thyroid function experienced minor, albeit non-significant, fluctuations (thyroid stimulating hormone (TSH) from 1.5 to 0.91 mIU/L, free thyroxine (T4) from 1.4 to 1.09 mIU/L). Additionally, follicle stimulating hormone (FSH) and luteinizing hormone (LH) showed slight, non-significant reductions (from 7.5 mIU/mL at baseline to 6.5 mIU/mL at 6 months and from 9.3 mIU/mL at baseline to 8.2 mIU/mL at 6 months, respectively).

Furthermore, despite initially falling within the normal range, basal insulin, and homeostatic model assessment (HOMA) significantly improved. Basal insulin levels decreased from 6.23 U/mL at baseline to 4.65 U/mL ($p$ = 0.01) at 6 months, while HOMA decreased from a baseline value of 2.45 to 1.99 ($p$ = 0.03) at 6 months.

## 4. Discussion

The advent of assisted reproduction techniques in recent decades has unveiled various substances that participate in the process of menstrual cycle regulation and fertilization. Among these substances are melatonin, vitamin D, the B-vitamin complex (particularly vitamins B6, B9 or folic acid, and B12), as well as inositol and MYO [4–7].

Melatonin appears to possess multiple roles across different stages of follicular development, oocyte maturation, and the luteal phase. It has been noted that the concentration of melatonin within the growing follicle could be a pivotal factor in preventing atresia [8–10].

Supplementation with vitamin D may stimulate the synthesis of anti-Müllerian hormone, potentially extending the maintenance of ovarian reserve. Furthermore, vitamin D might enhance fertility by modulating androgenic activity and influencing sensitivity to FSH, potentially contributing to follicular development [11,12]. In the current study, while fertility assessments were not conducted post-treatment, cycle regularization, as defined by FIGO, was predominantly achieved in most cases.

Folate supplementation has been associated with significantly lower homocysteine concentrations in follicular fluid, with a negative correlation observed between homocysteine levels and oocyte maturity, or embryonic quality [13–15]. Hyperhomocysteinemia is a common occurrence in women with PCOS, exacerbated by metformin treatment aimed at improving insulin resistance. This effect may be mediated by metformin-induced folate depletion, and folate supplementation has been shown to prevent the rise in homocysteine levels in patients treated with metformin or experiencing weight loss [11].

Inositol is a member of the B-vitamin complex. The epimerization of the six hydroxyl groups in inositol results in the formation of more than nine stereoisomers, including MYO and D-chiro-inositol, both of which are used as insulin sensitizers [16]. Elevated levels of MYO in human follicular fluid play a crucial role in follicular maturation and the development of the oocytes' nucleus and cytoplasm, making it a valuable biomarker for oocyte quality. MYO administration has shown promise in restoring spontaneous ovarian activity and fertility, particularly in PCOS patients. MYO can also modify hormonal profiles, leading to decreased plasma insulin levels, improvements in the

glucose/insulin ratio, reductions in the HOMA index, LH levels, LH/FSH ratio, free and total testosterone, and prolactin, while increasing SHBG levels. Additionally, it has been observed to improve hirsutism and acne in 6-month therapies. Several studies have indicated that insulin sensitizers like metformin or MYO are first-line treatments for restoring normal menstrual cycles in women with PCOS [17–29]. Our study demonstrated improvements in these parameters, despite the small sample size.

As previously mentioned, there is a dearth of studies evaluating the efficacy of these substances in combination. The results of this study suggest that the synergistic efficacy of these substances may be equal or even superior to their individual effects in terms of cycle regularization, and the treatment was well-tolerated. This therapeutic option could represent as a viable alternative to classic metformin for patients with ovulatory dysfunction, irrespective of PCOS diagnosis. Its aim is to improve their menstrual cycles and reducing hyperandrogenism in PCOS patients [30,31]. However, it is important to note that robust, similar studies solely focused on cycle disturbances are lacking, preventing a direct comparison with our results.

The primary limitation of this study lies in its failure to differentiate between patients diagnosed with PCOS and those without this diagnosis. Although none of the patients met the ultrasound criterion for PCOS, upon detailed analysis, 29.5% met the criteria for PCOS phenotype B based on clinical and analytical hyperandrogenism. When the data was reanalyzed, after excluding these patients, the differences remained significant, except for HOMA and androstenedione levels. This suggests a potential effect of the compound in patients with ovulatory dysfunctions other than PCOS, or raises questions about the diagnostic criteria for PCOS in light of evolving pathophysiological knowledge since the criteria were established two decades ago. Further investigations will be essential to delve deeper into this matter.

## 5. Conclusions

The combination of inositols, melatonin, folic acid, and vitamin D has demonstrated its utility in the regularization of menstrual cycles, enhancement of the androgenic hormonal profile, and has exhibited highly satisfactory tolerability and safety profiles.

Further studies are warranted to conduct a more comprehensive assessment of the potential impact of this combination of active compounds on fertility and overall quality of life.

## Availability of Data and Materials

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

## Author Contributions

SPG designed the research study and performed the research and analyzed the data. MMR and HL provided help and advice on data presentation and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

This study was approved by the ethics committee HM Hospital (committee's reference number 21.05.1849-GHM). The written informed consent was obtained from participants.


## Acknowledgment

Not applicable.

## Funding

The funds necessary for the publication of the manuscript have been provided by SEID pharma company.


## Conflict of Interest

This project was supported financially by SEID pharma company however the analysis, interpretation of data, and writing the manuscript have all been done by the authors. Their judgment on the interpretation of data and writing was not affected by this financial relationship and SEID pharma company had no control on them.

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