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Comparison of the effect of two combinations of myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial

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ABSTRACT

The purpose of this study was to evaluate the effect of two doses of D-chiro-inositol (DCI) in combination with Myo-inositol (MYO) in women with PCOS undergoing ICSI. This was a multicenter controlled, randomized, double-blind parallel group study with two MYO-DCI formulations for 12 weeks. The study group (SG) was administered 550 mg of MYO + 150 mg of DCI twice daily; the control group (CG) was administered 550 mg of MYO + 13.8 mg of DCI twice daily. The participants comprised 60 women with PCOS undergoing ICSI. At baseline, no differences were found between the two groups regarding age, BMI, HOMA-IR or testosterone levels. The pregnancy and live birth rates were significantly higher in the SG than in the CG (65.5 vs. 25.9 and 55.2 vs. 14.8, respectively) [risk ratio (RR) = 0.4; 95%CI (0.2, 0.79); $p = .003$ and RR = 0.27; 95%CI (0.10, 0.70); $p = .002$ respectively]. The risk of ovarian hyperstimulation syndrome (OHSS) was lower in the SG (3.44 vs. 18.5%, $p = .07$). The combination of MYO-DCI at high doses of DCI improves the pregnancy rates and reduces the risk of OHSS in women with PCOS undergoing ICSI.

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Introduction

Polycystic ovary syndrome (PCOS) is a complex disease that involves reproductive and metabolic problems [1]. For women with PCOS undergoing fertility treatments, reproductive improvements have been reported using drugs such as metformin or inositol in different forms, combinations or doses [2,3].

Inositol has two major stereoisomers: myo-inositol (MYO) and D-chiro-inositol (DCI). MYO supplements have been observed to improve the metabolic profile and hyperandrogenism of women with PCOS [4,5], in addition to increasing the clinical pregnancy rate in infertile women undergoing ovulation induction for ICSI or IVF-ET, probably improving the quality of embryos and reducing the number of unsuitable oocytes [6]. However, a recent systematic review showed that MYO supplementation is not sufficient to improve oocyte maturation, embryo quality or the pregnancy rate [7].

Regarding DCI, the existence of tissue-specific ratios, namely, in the ovary, has prompted researchers to recently develop a treatment based on both molecules in the proportion of 40 (MI) to 1 (DCI) [8]. This ratio has been effective in improving endocrine and metabolic parameters in obese PCOS women [9,10]. In a mouse model, a higher DCI dose was ineffective or even had a negative effect on clinical-pathological outcomes [11]. However, based on available data, the specific MI:DCI ratio to be administered to PCOS patients could not be established [12]. Therefore, the role of DCI supplementation also remains controversial or unknown, and future studies of the appropriate dose and duration are vital to clarify the role of DCI in the management of PCOS.

The aim of this study was to evaluate the effect of two DCI doses in combination with MYO in women with PCOS undergoing ICSI.

Materials and methods

Study design

This study was a double-blind, multicenter randomized clinical trial (RCT) with quadruple masking (Participant, Care Provider, Investigator and Outcomes Assessor). This study was conducted at five sites in Spain from February 2016 to April 2017 and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines; it is registered at clinicaltrials.gov with the identifier NCT03201601.

For a superiority trial to test that the pregnancy rate is higher under experimental treatment, with double the pregnancy rate than under normal treatment, assuming a 30% pregnancy rate under control treatment with a statistical power of 80% and a significance level of 5%, the sample per group needed was 30 patients per group.

Randomization system

The volunteers were randomly assigned to one of two groups according to a randomization scheme generated by a computer

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program (SIGESMU®). To maintain blinding, the investigator received a treatment allocation number for each subject from the IRT system.

Subjects

Inclusion criteria: women aged between 18 and 40 years with PCOS according to the Rotterdam criteria [13] with a body mass index (BMI) <30 who were undergoing ICSI and signed the informed consent document. All participants were required to have a normal uterine cavity. Before randomization, the patients were offered the possibility of doing inseminations or ICSI.

Exclusion criteria: Contraindications for ICSI, adrenal hyperplasia, hyperprolactinemia, thyroid disease, severe endometriosis, poor responder and severe male factor.

Methods

Sixty subjects were randomized to receive oral soft gelatin capsules of 550 mg of MYO + 150 mg of DCI twice daily (3.6: 1) [Study group (SG)] or 550 mg of MYO + 13.8 mg of DCI twice daily (40:1) [Control group (CG)] over 12 weeks until the day of ovarian puncture. Intake of other vitamins or antioxidants was not permitted during the study except for folic acid (400 mcg/day), which was provided to all the patients.

Initial ovulation stimulation was performed homogeneously in all participating centers using a GnRH antagonist cycle and an initial dose of 150 units of FSH for 5 days. After the initial stimulation, each patient was treated individually according to her response. Triggering was performed with 0.25 mg of hCG in all cases except when the risk of ovarian hyperstimulation syndrome (OHSS) was suspected. Follicular puncture was scheduled approximately 36–37 h after triggering. Embryo transfer (ET) was carried out individually according to the characteristics of each volunteer and her response, although in no case was more than three embryos transferred. In all ET cases, treatment with micronized natural progesterone for luteal phase support was prescribed.

Outcomes

The primary outcome was the pregnancy rate, and the secondary outcomes were oocyte maturation, embryo quality, testosterone levels and insulin sensitivity.

Pregnancy was defined as a positive test at 2 weeks from ET. Oocyte maturation was defined by the percentage of metaphase II (MII) oocytes. Embryos were assessed according to ESHRE criteria [14]. Participants who conceived were followed at the clinical site for ultrasound evidence of a viable intrauterine pregnancy and were referred for obstetrical care.

Ethical approval

The study was approved at each clinical site. Patients signed an informed consent document informing them about the procedure and possible risks of the study. ICSI was performed in all cases; in the circumstances of normal sperm, the patients were informed of possible higher fetal anomalies in ICSI vs IVF.

Statistical methodology

Bivariate statistical tests for the personal variables were performed to determine the homogeneity of the women's characteristics between the treatment groups. Frequencies, percentages and chi-square tests were performed on qualitative variables. For quantitative variables, the mean, standard deviation (SD) and 95% confidence intervals were obtained, and the asymptotic *t*-test or bootstrap technique for the *t*-test was performed to compare groups. Additionally, statistical multivariate modeling was applied to check differences between groups regarding the evolution of parameters, which used multivariate linear mixed regression models and intra-subject random effect and was fitted with the patients' characteristics.

The main outcome success of pregnancy was also described with the odds of pregnancy per group and corresponding OR and confidence interval.

Intention to treat analysis is the comparison of the treatment groups including all patients as originally allocated after randomization. We mainly present the per-protocol analysis for primary and secondary outcomes. However, to compare results, avoid possible bias in the primary outcome and increase the credibility of the results, an intention to treat analysis was also presented using R project 3.3.

Results

At baseline, no differences were found between the two groups (see Table 1). Four patients were removed from the study due to the risk of OHSS (one in the SG and three in the CG). Another

Table 1. Patients' characteristics at baseline.

	Study group ($N = 30$)		Control group ($N = 30$)	
Quantitative patients' characteristics at baseline				
	Mean (SD)	95%CI (LL, UL)	Mean (SD)	95%CI (LL, UL)
Age (years)	31.67 (0.86)	(29.91–33.42)	31.74 (0.89)	(29.91–33.57)
Weight (kg)	67.31 (2.33)	(62.53–72.09)	67.11 (2.09)	(62.82–71.4)
Height (cm)	162.67 (1.32)	(159.97–165.37)	164.11 (1.06)	(161.93–166.29)
BMI	25.51 (0.86)	(23.73–27.28)	24.88 (0.69)	(23.45–26.3)
Time of sterility (years)	3.35 (0.36)	(2.69–4)	2.57 (0.24)	(2.13–3.04)
Qualitative patients' characteristics at baseline *N* (%)				
Regular activity	10 (33.33%)		6 (20%)	
Alcohol consumption	9 (30%)		6 (20%)	
Smoking	7 (23.33%)		7 (23.33%)	
No previous pregnancy	28 (93.33%)		23 (76.66%)	
Familiar diabetes	7 (23.33%)		8 (26.66%)	

p Values = not significant in all cases.
BMI: body mass index; CI: confidence interval; HL: high limit; LL: low limit.

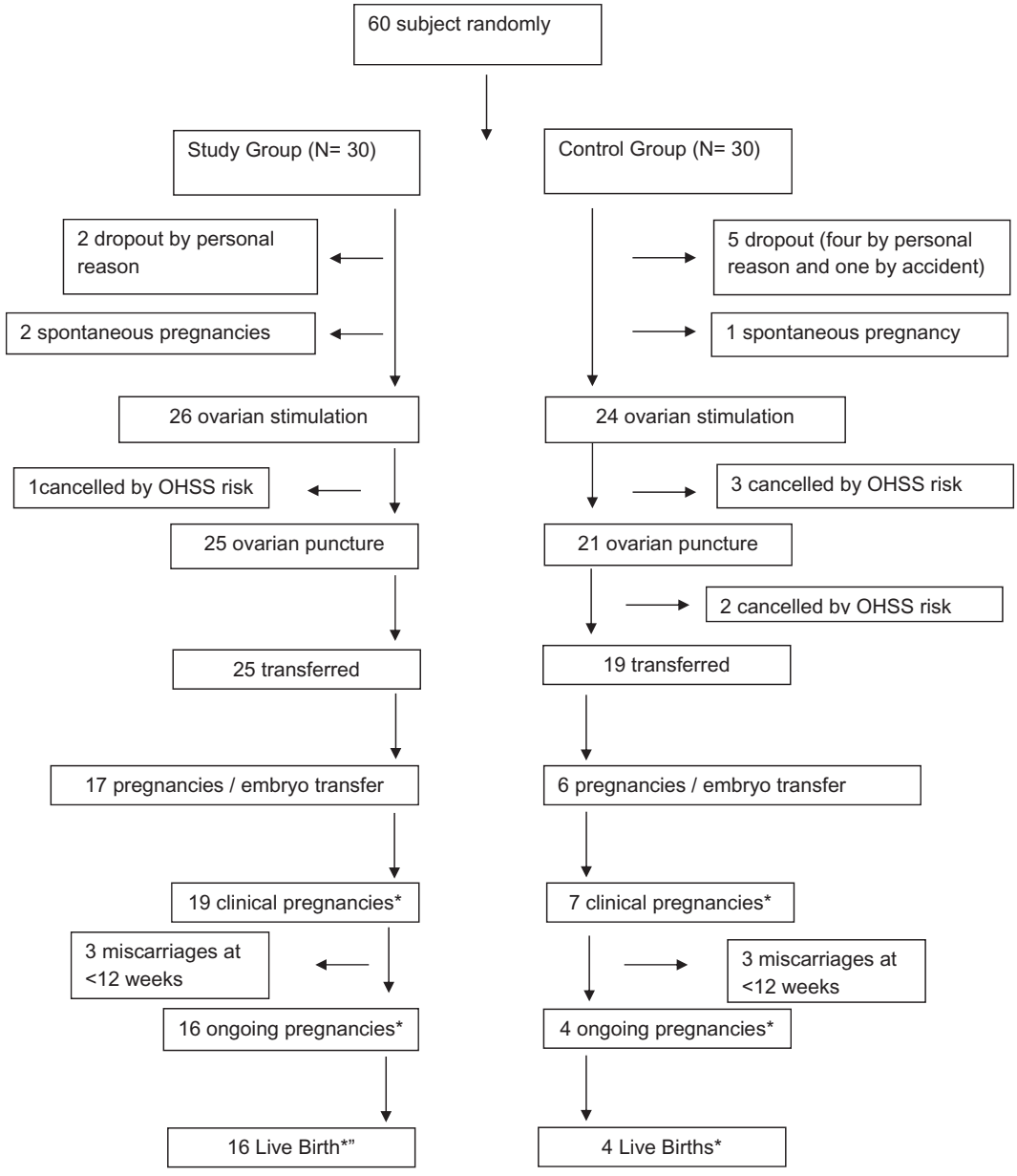

Figure 1. Flow chart of the subjects included in the study.

two patients in the CG also did not undergo ET due to the risk of OHSS. For these patients, triggering was performed with leuprolide 0.2 mg and all embryos were frozen. When ET was not achieved due to the OSSH risk, HOMA-IR and testosterone tests were performed at the time of ovarian puncture. Globally, the percentage of exclusions due to the risk of OSSH was lower in the SG (3.84% vs. 20.83%, $p = .065$) (see Figure 1).

Regarding compliance, all the patients returned the container to verify that they had complied with the intake of the medication. No participant showed side effects with any of the two combinations studied.

At the end of the ICSI cycle, the duration of ovarian stimulation ($SG = 10.48 \pm 1.39$ vs. $CG = 10.38 \pm 0.86$) and units of FSH used per cycle ($SG = 1219.23 \pm 102$ vs. $CG = 1137.5 \pm 68$) were similar in both groups. Likewise, total testosterone, glucose and insulin levels, HOMA-IR, number of MII oocytes and percentage of good-quality embryos were also similar in both groups (Table 2).

Forty-four patients underwent ET (25 in the *SG* and 19 in the *CG*). No differences in the average number of embryos transferred or percentage of women with more than one embryo transferred were found. However, the pregnancy rate was significantly higher in the *SG* than in the *CG* (65.5% vs. 25.9%, $p = .003$). Additionally, pregnancies after ET were higher in the SG (68% vs. 31.6%, $p = .017$). The global data of each pregnancy rate are shown in Table 3.

Concerning the testosterone levels, a significant difference was found from the baseline to end of the study. However, the difference was similar in both the groups (Dif = −0.13; 95% (−0.17, −0.08); p values $< .001$). Similarly, a decrease from the baseline to the end of the study in HOMA-IR was observed in both the groups (Dif = −0.70; 95%CI (−1.23, −0.16); $p = .011$).

Table 2. Summary results for reproductive and analytic outcomes.

	Study group		Control group		
	95%CI		95%CI		
	Mean (SD)	(LL–UL)	Mean (SD)	(LL–UL)	*p* Value
Number of oocytes	13.46 (1.01)	(11.38–15.54)	13.76 (1.48)	(10.67–16.85)	.864
No mature oocytes	3 (0.49)	(1.98–4.02)	3.1 (0.55)	(1.98–4.25)	.898
Mature oocytes	10.46 (0.88)	(8.65–12.28)	10.67 (1.57)	(7.4–13.94)	.910
Ratio mature oocytes/N. oocytes	0.77 (0.04)	(0.7–0.84)	0.74 (0.05)	(0.63–0.84)	.575
Number of embryos	6.88 (0.77)	(5.65–8.2)	7.19 (1.41)	(4.52–9.89)	.858
Embryos type A	3.08 (0.71)	(2–4.27)	3.86 (1.22)	(1.76–6.38)	.571
Embryos type B	1.5 (0.31)	(1–2.04)	1.35 (0.44)	(0.75–2.1)	.467
Embryos type C	1.81 (0.38)	(1.15–2.49)	1.6 (0.38)	(0.85–2.55)	.754
Insulin at baseline	11.75 (1.31)	(9.5–14.55)	11.53 (2.12)	(8.28–15.38)	.929
Insulin at end	9.04 (0.95)	(7.22–11.16)	9.05 (1.13)	(7.19–11.07)	.993
Difference in insulin	2.8 (1.04)	(1.15–4.83)	2.97 (2.19)	(−0.64–7.41)	.951
Testosterone at baseline	0.57 (0.04)	(0.48–0.66)	0.56 (0.05)	(0.45–0.67)	.911
Testosterone at end	0.41 (0.04)	(0.34–0.49)	0.46 (0.05)	(0.36–0.56)	.430
Difference of testosterone	0.14 (0.03)	(0.07–0.21)	0.12 (0.03)	(0.05–0.18)	.607
Glucose at baseline	90.82 (1.77)	(87.2–94.43)	91.85 (2.48)	(87.81–96.88)	.757
Glucose at the end	85.96 (1.1)	(83.7–88.22)	86.62 (1.51)	(83.49–89.76)	.720
Difference in glucose	4.61 (1.96)	(0.59–8.64)	5.77 (2.55)	(1.58–11.28)	.727
HOMA at baseline	2.64 (1.66)	(2.02–3.26)	2.65 (2.6)	(1.62–3.69)	.288
HOMA at the end	1.94 (1.1)	(1.51–2.37)	1.96 (1.23)	(1.43–2.49)	.719
Difference in HOMA	0.72 (1.31)	(0.21–1.24)	0.82 (2.52)	(−0.27–1.91)	.408

CI: confidence interval; LL: low limit; HL: high limit; HOMA: homeostasis medical assessment.

Table 3. Pregnancy outcomes.

		Number of cases per treatment group								
		SG	CG	Risk ratio	95%CI		OR(A/B)	95%CI		*p* Value
					Lower limit	Upper limit		Lower limit	Upper limit	
Pregancy rate	No	10	20	0.40	0.20	0.79	5.25	1.51	20.33	.003
	Yes	19	7							
Miscarriage rate	No	16	4	2.71	0.71	10.42	0.27	0.02	2.76	.146
	Yes	3	3							
Clinical pregnancy rate	No	10	20	0.40	0.20	0.79	5.25	1.51	20.33	.003
	Yes	19	7							
Ongoing pregnancy rate	No	13	23	0.27	0.10	0.70	6.81	1.72	34.12	.002
	Yes	16	4							
Pregnancy rate by stimulation cycle	No	9	18	0.40	0.19	0.84	5.44	1.38	24.35	.005
	Yes	17	6							
Pregnancy by embryo transfer	No	8	13	0.46	0.23	0.95	4.43	1.09	20.30	.017
	Yes	17	6							
Pregnancy per ITT analysis[a]	No	14	23	0.38	0.17	0.82	4.65	1.48	14.61	.007
	Yes	17	6							
Live-birth rate	No	13	23	0.27	0.10	0.70	6.81	1.72	34.12	.002
	Yes	16	4							

SG: study group; CG: control group; CI: confidence interval; OR: odds ratio.
[a]For the ITT analysis the 60 women sample size were used, for the posterior exclusions, dropouts, canceled and spontaneous pregnancies, the worst result, no-occurrence, was assumed.

Discussion

The primary findings of this study show that high doses of DCI combined with MYO increase the percentage of pregnancy rates in women with PCOS undergoing ICSI. To our knowledge, this is the first RCT investigating the effect of different doses of DCI concerning reproductive outcomes.

Studies carried out over the 30-year history of ART coincide in highlighting the importance of the quality of embryos/oocytes as the main predictors of positive results, and it seems that both MYO and DCI can improve the outcomes by diverse mechanisms: improving insulin sensibility, increasing ovulation or reducing oxidative stress of follicular fluid [10,15–22]. However, data obtained from a meta-analysis indicate a lack of evidence to justify that MYO supplementation is enough to improve the oocyte or embryo quality and pregnancy rates [7].

The main strength of this study is that the pregnancy rates are high with 150 mg of DCI twice daily and could involve DCI in early embryonic implantation and development. The main weakness of this study is the sample size, although the calculation of the sample size indicated *a priori* that 60 subjects were sufficient to draw conclusions.

There are precedents that indicate that inositol improves the metabolic parameters of women with PCOS [23–26]. In our study, significant improvement was found from the baseline to the end of the study both in the testosterone level and HOMA-IR, although the difference was similar in both the groups.

Regarding the effect of DCI on oocyte and embryo quality, studies that have analyzed its use have reported contradictory results. A study comparing both inositol forms observed that MYO supplementation rather than DCI could improve oocyte and embryo quality [21]. In other, an increased DCI dosage progressively worsened oocyte maturation [27]. However, Piomboni

et al. observed a higher number of MII oocytes with DCI [16], and Colazingari et al. showed that only the MYO-DCI-treated group (physiological ratio: 1.1 g + 27.6 mg) increased the embryo quality [28]. Interestingly, in the current study and in all the studies reviewed, no side effects were reported at any dose of MYO or DCI, resulting in a high degree of patient compliance.

Studies performed with the combination of MYO:DCI at a ratio 40:1 showed better results than the administration of DCI or MYO alone. The ratio 40:1 was based on the physiological blood ratio of the two molecules, although each tissue has its own ratio [11]. Thus, some authors pointed out that the ratio was not as important as the absolute concentration of either MYO or DCI. These authors suggest that the amount of DCI in studies using the 40:1 ratio was very low (13.8–27.6 mg/day) and might have been insufficient to achieve adequate levels of DCI as predicted by the studies showing a beneficial effect [12]. We agree with these authors that more studies should be performed to evaluate different ratios or dosages to determine the most efficient dose for each PCOS condition [7]. Therefore, we performed a study comparing the 40:1 ratio with other proposed MYO:DCI combinations containing higher dose of DCI, more in line with the dose used in the studies showing beneficial effects in PCOS. To determine the dose, we considered the results published by Isabella and Raffone in 2012 showing that a high dose of DCI might affect oocyte quality [27]. Although these results were contradictory to those posteriorly published by Piomboni et al. in 2014 [16], we decided to use 300 mg, which was also in line with the estimated daily conversion of MYO to DCI in a healthy person.

In our study, the improvement in the pregnancy rates observed in the SG was not accompanied by improvements in intermediate parameters, such as oocyte or embryo quality. It is true that the percentage of pregnancies in the control group was too low, without the need for justification. Taken together, these findings suggest that DCI might affect other variables of oocyte or embryo quality that go unnoticed in the classifications that are made in a generalized manner. In this sense, it would be valuable to know how supplementation with MYO or DCI affects other markers of oocyte quality.

Another hypothesis that justifies the percentage of pregnancies is higher with higher doses of DCI suggests that DCI could influence embryo implantation. There are no clinical studies that indicate whether inositol influences embryo implantation; thus, study to test this hypothesis is warranted.

Another relevant finding of this study is the difference in cancelations due to OHSS, a result that has not been previously published. However, OHSS was not previously defined as an objective of this study. Additionally, the criteria to define OHSS risk were not defined at the beginning of the study; therefore, they were left to the criteria of each participating center. Although it has been suggested that metformin can reduce OHSS [29,30], this was not corroborated in a Cochrane review [31]. Concerning inositol, there are only two studies, including one in an animal model in which vascular permeability as well as VEGF and COX-2 expression were reduced in animals treated with MYO [32]. An RCT in women with PCOS undergoing intrauterine insemination showed that supplementation with MYO prevented OHSS [18].

In our study, the CG OHSS rates were similar to those described for women with PCOS [33,34]. This finding reinforces the conclusions of a previous meta-analysis that showed MYO alone did not seem to influence the results of the stimulation cycle, but DCI supplementation could prevent it [3]. The result did not reach statistical significance ($p = .07$), probably due to the small sample size, which was not calculated *a priori* to assess this parameter. However, these data are relevant from a clinical point of view and should be contrasted in future studies.

In conclusion, the combination of MYO-DCI at high doses of DCI improves the pregnancy rate with respect to its physiological concentration. This same combination reduces the risk of OHSS. These results highlight the importance of DCI supplementation in women with PCOS undergoing ICSI.

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Disclosure statement

Díaz-Ropero MP, Maldonado-Lobón JA, Olivares M, Fonollá J are workers of Biosearch Life, a company that produces DCI from carob fruit. The remaining authors declare that they have no competing interests.

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