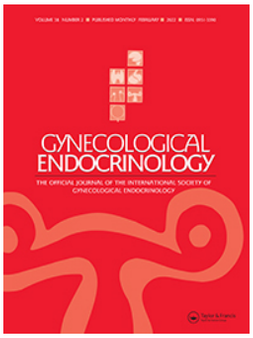

Taylor & Francis
Taylor & Francis Group

Gynecological Endocrinology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

Myoinositol *versus* metformin pretreatment in GnRH-antagonist cycle for women with PCOS undergoing IVF: a double-blinded randomized controlled study

Keerthana Rajasekaran, Neena Malhotra, Reeta Mahey, Rajesh Khadgawat & Mani Kalaivani

To cite this article: Keerthana Rajasekaran, Neena Malhotra, Reeta Mahey, Rajesh Khadgawat & Mani Kalaivani (2022) Myoinositol *versus* metformin pretreatment in GnRH-antagonist cycle for women with PCOS undergoing IVF: a double-blinded randomized controlled study, Gynecological Endocrinology, 38:2, 140-147, DOI: 10.1080/09513590.2021.1981282

To link to this article: https://doi.org/10.1080/09513590.2021.1981282

Published online: 30 Sep 2021.

GYNECOLOGICAL ENDOCRINOLOGY
2022, VOL. 38, NO. 2, 140–147
https://doi.org/10.1080/09513590.2021.1981282

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE
POLYCYSTIC OVARY SYNDROME

Myoinositol *versus* metformin pretreatment in GnRH-antagonist cycle for women with PCOS undergoing IVF: a double-blinded randomized controlled study

Keerthana Rajasekaran[a], Neena Malhotra[a], Reeta Mahey[a], Rajesh Khadgawat[b] and Mani Kalaivani[c]

[a]Department of Obstetrics & Gynaecology, All India Institute of Medical Sciences (AIIMS), New Delhi, India; [b]Department of Endocrinology, All India Institute of Medical Sciences (AIIMS), New Delhi, India; [c]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Objective: To study the effects of myoinositol (Myo) in comparison to metformin (Met), in reducing the risk of OHSS and improving ART outcome in PCOS women undergoing IVF.

Design: Double-blinded randomized controlled trial (CTRI/2018/05/014196).

Setting: ART Clinic, AIIMS, New Delhi patients: 102 infertile PCOS women undergoing IVF cycles were enrolled after evaluating for eligibility and allotted as 50 in group 1 (Myo) and 52 in group 2 (Met) after randomization.

Interventions: Recruited patients received Myo 2 g twice daily (group 1) and Met 850 mg twice daily (group 2). Pre- and post-treatment clinical (menstrual pattern, BMI), hormonal profile (LH, FSH, testosterone, prolactin [PRL], and AMH), biochemical parameters (HOMA IR, fasting glucose, and insulin), ovarian with antral follicle count (AFC) and side effect profile were assessed. After 3 months of therapy, patients were recruited for IVF cycle by antagonist protocol was involving controlled ovarian stimulation, cycle monitoring, oocyte recovery, insemination of oocytes and follow up with fertilization, cleavage, transfer of good grade cleavage embryos, or blastocysts pregnancy outcomes and OHSS incidence and medications was continued until the day of OPU.

Main outcome measures: Primary outcome was OHSS and clinical pregnancy rate including spontaneous, IVF, and cumulative pregnancy rate including FET. Secondary outcome was ART outcomes and the change in biochemistry and hormonal profile between groups and inter group after medications at 12 weeks.

Results: Incidence of OHSS (Myo 5 (10.0) ($n = 50$), Met 10 (20.0) ($n = 50$) p .07) was not statistically different between groups. Clinical pregnancy rate (Myo 18 (36.0) ($n = 50$), Met 9 (18.0) ($n = 50$) p .04) cumulative pregnancy rate including FET (Myo 16 (43.2) ($n = 37$) *vs.* Met 10) 22.7) ($n = 44$) p .05) and spontaneous conception (prior to IVF) Myo 13 (26.0) ($n = 50$), Met 6 (12.0) ($n = 50$) p .07) was significantly high in Myo group. No between group difference in ovarian stimulation outcomes including duration and dosage of gonadotropins, E2, P4 levels, number of follicles >14 mm on day of trigger. Number of oocytes retrieved and grade of maturity were similar between groups. Fertilization, cleavage and number of good grade embryos were significantly higher in Myo group. However, implantation rate and number of embryos for freezing were similar between groups. Myo had improvement in fasting insulin, HOMA, Sr.AMH, and SHBG suggesting decreased insulin resistance

Conclusions: Myo is equally beneficial as Met in reducing the risk of OHSS and has better ART outcome in PCOS women undergoing antagonist cycles.

ARTICLE HISTORY
Received 29 March 2021
Revised 9 August 2021
Accepted 13 September 2021
Published online 30 September 2021

KEYWORDS
PCOS; myoinositol; metformin; OHSS; IVF

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting 6−10% of women in reproductive age group [1,2]. A complex syndrome with heterogenous phenotypes, ovarian dysfunction, and hyperandrogenemia with polycystic ovaries on ultrasound is the diagnostic hallmarks of PCOS [3]. Chronic anovulation is the key reason for menstrual irregularities and infertility in women with PCOS in reproductive years [4]. Even though the etiology is multifactorial, the fundamental pathology is hyperinsulinemia and hyperandrogenemia that explains the reproductive symptoms and metabolic consequences in later life. Insulin plays a direct role in the pathogenesis of hyperandrogenism in PCOS acting synergistically with luteinizing hormone (LH) to enhance androgen production in theca cells [3], leading to increase in local intra-follicular androgens, follicular atresia, and anovulation.

Insulin sensitizers are therefore advocated to improve the insulin levels and sensitivity even at the ovarian levels and improve fertility outcomes, including lowered risk of OHSS [5]. Metformin (Met), an oral biguanide is the most commonly used insulin sensitizer that has been suggested to improve ovulation, clinical pregnancy rates in PCOS women with subfertility [6]. Met given to women with PCOS prior to IVF cycles [7] proved useful in reducing OHSS and improving pregnancy outcome. Inositols are sugar alcohol and two forms, Myoinositol (Myo) and D-chiroinositol available as nutritional supplements are known to improve insulin resistance. Acting through calcium signaling pathways inositols, in PCOS improve oocyte

CONTACT Neena Malhotra malhotraneena@yahoo.com Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India

maturation and quality with improved fertilization rate during IVF cycles [8]. Studies comparing Myo have proven benefit over placebo [9] as regards restoration of ovulation and improved oocyte quality [10]. Comparing use of Met to Myo for 8–12 weeks prior in women undergoing IVF cycles [11] suggested equal benefits as regards improving oocyte quality by reducing oxidative stress at ovarian level. However, in a recent meta-analysis, involving 11 studies with Myo pretreatment in PCOS undergoing IVF cycles there was uncertainty, with low-quality evidence on its benefits in improving outcome including live birth or clinical pregnancy [12]. Further, there was no study that considered adverse outcome including OHSS with the use of inositol. Therefore, with limited data from this meta-analysis, we conducted an adequately powered single center, double-blind randomized study (CTRI/2018/05/014196) to compare the effects of Myo to Met as regards adverse incidence including OHSS and other ART cycle outcome when given at least 12 weeks prior to cycle.

Materials and methods

A prospective double-blind randomized study was conducted at the infertility and ART center of AIIMS New Delhi, recruiting women from May 2018 to March 2020. The study was approved by the Institutional review board (IRB) (IEC-565/08.12.2016, RT-19/16.02.2017) and all participating women provided written informed consent before enrolling into the study. The inclusion criteria for participating in the study were women with PCOS, as defined by the Rotterdam's criteria, aged between 21 and 38 years and undergoing their first IVF cycle. Women with conditions unfavorable for implantation (fibroids distorting cavity and thin endometrium), prior ovarian drilling, known diabetes mellitus or previously on hypoglycemic agents and disturbed renal or liver function tests were excluded from the study.

Each participant was counseled on the pretreatment drug intake and duration before IVF cycle, besides potential side effects. The block randomization with varying size was used to randomize the patients into the treatment groups and the sequentially numbered opaque sealed envelope (SNOSE) technique was used for allocation concealment. To avoid selection bias, 102 women were randomized into 50 (group 1) and 52 (group 2) in each group to receive Myo 2 g bid and Met 850 mg bid respectively, at least 12 weeks prior to IVF cycle. Allocation concealment was possible with the drugs dispensed in opaque plastic bottles bearing the code. Tablets containing only myo-inositol were not available and are dispensed as combinations with folic acid or D-chiro-inositol, therefore similar-looking tablets containing only myo-inositol 2 g were ordered from the pharmacy. Both patients and investigators being blinded to the allocation. The allocation code was broken once the patients initiated the treatment cycle.

Baseline information on menstrual cycle, body mass index (BMI), baseline blood hemogram, renal function test and liver function test done and was normal, baseline biochemistry (fasting blood glucose [FBG], post-prandial blood glucose (PPBG), fasting serum insulin, Homeostatic module assessment of insulin resistance (HOMA-IR,) lipid profile, hormonal profile (serum Follicle-stimulating hormone (FSH), Luteinizing Hormone (LH), anti-Mullerian hormone (AMH), prolactin (PRL), testosterone, and sex hormone-binding globulin (SHBG) and ovarian volume with antral follicle count (AFC) were obtained before start of medications. Hormone assays and ovarian ultrasound were done between days 2 and 5 of cycles. All the parameters were repeated after completion of the medications. Patient compliance and side effects were checked on regular basis. IVF cycle was initiated after 12 weeks of medications which were continued until the day of OPU.

Ovarian stimulation and ART cycle

All participating women were advised antagonist protocol. Gonadotropins were initiated as recombinant FSH (GONAL-f (FSH I.P. 1050 IU/1.75 ml (77 mcg/1.75 ml) subcutaneous, Merck Specialities Private Limited, Mumbai, India) from second day of the period or withdrawal bleed. Follicle monitoring was initiated after 5 d of stimulation and GnRH-antagonist, Cetrorelix 0.25 mg (Cetrotide, Cetrorelix acetate 0.25 mg/ml subcutaneous, Merck Specialities Private Limited, Mumbai, India) was initiated with the lead follicle of 12–13 mm and serum estradiol levels of at least 300 pgm/ml and continued until the day of trigger. Follicle growth was monitored by serial ultrasound and hormone assays. The doses of gonadotropins were titrated with follicular growth for optimal outcome. Starting dose of gonadotropins was not the same in all patients but variable. The starting dose was decided on the basis of age and BMI of the patients, besides their risks of OHSS based on AMH values. The starting dose varied from 112–225 IU of recombinant FSH, which was titrated after day 6 scan. Decision to lower or increase this was based on response to starting doses. Those who had a past experience of OHSS on prior stimulation even on IUI cycles were given doses lesser than those of same age and BMI without the risk. With at least two dominant follicle of 18 mm, ovulation trigger was given with recombinant hCG (Ovitrelle 250 micrograms/0.5 ml solution for injection in prefilled syringe, Choriogonadotropin alfa – Merck Specialities Private Limited, Mumbai, India) to 27 patients in Myo group and 23 patients in Met group. GnRH agonist trigger (Injection Lupride 2 g – LUPRIDE 0.5 ml (1 mg) INJ, Sun Pharmaceutical Industries Limited, Mumbai, India) was given to 11 patients in Myo group and 12 patients in Met group, depending on levels of serum estradiol or number of follicles beyond 14 mm with the aim to avert OHSS and freeze all policy. Ovum pick up was done 36 h after trigger and retrieved oocytes were scored for maturity and graded accordingly [13]. Conventional IVF or ICSI was done depending on the indication, and fertilization was checked and embryos graded accordingly [14]. The embryologists were blinded to the study protocol and the drugs given pretreatment. A freeze all policy was followed in those at risk, as per levels of E2 or number of oocytes (>25) at OPU or symptoms of OHSS. For the others, fresh embryo transfer was done at cleavage (day 3) or blastocyst stage and surplus embryos frozen. Patients were closely monitored after OPU and checked for onset of OHSS and graded accordingly [15]. Those who developed mild OHSS were managed on outpatient basis, reserving admission for moderate to severe OHSS and managed as per unit protocols [15]. Fresh transfers were deferred in women who developed OHSS or any other indication including raised P4 on the day of trigger (>1.5 ng/ml). Frozen embryo transfer (FET) was done in the subsequent cycle. All patients who received GnRh agonist trigger had freeze all cycle and FET was done.

Outcomes

The primary outcome was percentage of women developing OHSS and pregnancy rate. Secondary outcome was ART outcomes including dosage of gonadotropins, quantity, and quality of oocytes, fertilization rate, cleavage rate, blastocyst rates,

percentage of good grade embryos, and implantation rates. Also, included in secondary analysis was the change in biochemistry and hormonal profile between groups and inter group after medications at 12 weeks.

Statistical analysis

In a study conducted by Tso et al. [7], a meta-analysis compiling the outcome of eight studies published in Cochrane database of systematic reviews 2014, the incidence of OHSS was lower in the Met group than in the placebo or no treatment group (OR 0.29; 95% CI 0.18–0.49, eight RCTs, 798 women, I2 = 11%, moderate-quality evidence). This suggests that for a woman with a 27% risk of OHSS without Met, the corresponding risk using Met would be between 8%. However, on reviewing the literature no other study could be retrieved comparing the rate of OHSS after Myo treatment in PCOS women.

Hence assuring 3% decrease in the incidence of OHSS in Myo group, when compared to Met group, with 10% non-inferiority margin the estimated sample size required will be 44 per group. With the assumed power and level of significance of 80 and 5%, respectively, the study included 50 patients per group considering a 5% loss to follow up

Statistical analysis was performed using Stata version 12.0 (College Station, TX).

Data were presented as number (%) or mean ± SD (min–max) as appropriate. Categorical baseline characteristics were compared using Chi-square test/Fisher's exact test and Continuous baseline characters were compared using Unpaired 't' test/Wilcoxon rank-sum test.

The primary outcomes were analyzed by both intension to treat as well as per protocol analysis. There were two women who were lost to follow up in the Met group, their outcomes were considered as worst, with OHSS, for intension to treat analysis. Both adjusted and unadjusted analysis for comparing the difference and proportion of OHSS between the groups were carried out using Z-test and linear regression analysis. The results were presented as difference in proportion (95% CI).

The secondary outcomes ovarian stimulation and ART outcomes were compared between groups using Wilcoxon rank-sum test or variables, which were not following normal distribution. The change in hormone profile at 3 months from baseline was compared using Signed rank test/paired 't' test in each group separately. The shift in the frequency at 3 months from baseline was tested using McNemar's test in each group separately. A p value of $<.05$ was considered statistically significant.

Results

A total of 231 infertile PCOS women undergoing IVF cycles were assessed for eligibility and 102 patients were recruited after meeting the inclusion criteria, 50 in group I and 52 in group II with 2 loss to follow-up and all the other patients were compliant to medications (Figure 1). Recruited patients were treated accordingly (Figure 2).

Demographic data

There was no significant difference in demographic characteristics between two groups of women (Table 1). Hormonal and baseline biochemical parameters were comparable between both groups, although Myo group had significantly higher LH, FSH, and AMH values which was a chance finding and the outcome was adjusted accordingly. Ultrasound features of PCOS were also equally matched (Table 4). Similar baseline characteristics demonstrate equal risk in OHSS. Post treatment with insulin sensitizers, Myo group had increased regularity in menstrual pattern (p .001) and improvement in fasting insulin (p .001), HOMA IR (p .001), S. AMH (p .001), and Sr SHBG (p .032) suggesting decreased insulin resistance, while there was no between group difference found in the other parameters (Table 4).

Stimulation and treatment outcome

As for primary outcome, the rate of OHSS was not different between groups (Table 2), with five cases of mild OHSS in Myo group and 10 cases of mild OHSS in Met group. No cases of moderate or severe OHSS were noticed in either group. The clinical and ongoing pregnancy rate after fresh transfer was significantly high in Myo group. Myo group also had more women who had spontaneous conception prior to treatment cycle (Table 2).

No between group difference was found in the ovarian stimulation outcomes including duration and dosage of gonadotropins, E2 and P4 levels, and number of follicles more than 14 mm on day of trigger (Table 3). The number of oocytes retrieved, grade of maturity were similar between both groups. The fertilization and cleavage rate were significantly higher as were the number of all and good grade embryos in the Myo group. However, the implantation rate, number of embryos for freezing was not different between groups (Table 3). Both drugs had no adverse reactions but Met group had comparatively higher incidence of abdominal discomfort and bloating sensation (Table 4).

Discussion

Insulin sensitizers have a major role in alleviating the disease physiology in women with PCOS [5]. In the backdrop of raised insulin levels and or insulin resistance, theca cells produce excess androgens causing increased folliculogenesis. Insulin resistance reduces the uptake of glucose at the follicular level that causes resultant increase in androgen levels thereby modifying folliculogenesis. Ovarian hyperstimulation syndrome (OHSS), is a feared complication, occurring in 11–13% of IVF cycles in PCOS as against approximately 0.6–1.4% in women with other indication [16]. Strategies to reduce OHSS include antagonist cycles, agonist trigger and freeze all embryos during cycle and insulin sensitizers prior and during cycle [17]. Insulin sensitizers including Met have been accepted as one of the strategies to reduce the risk of OHSS (Cochrane, Tso et al.). Met, an oral biguanide, acting by both direct and indirect mechanisms, can mediate ovarian response to gonadotropins, reducing the risk of OHSS [18] in agonist cycle. In a randomized trial, Met was successful in reducing the risk of OHSS when used during antagonist cycle [19]. However, in a recent randomized study, Met did not prove beneficial in reducing OHSS during antagonist cycles [20]. Inositol has been attempted prior to treatment cycles suggesting benefits, in improving ART outcomes, though in small non-randomized studies. However, a meta-analysis [21], could not confirm their benefits as these were small underpowered studies. In yet another recent meta-analysis [12], the reviewers concluded uncertainty on the benefits of inositol use in PCOS, thus creating need for further trials to address the role of inositol in reductions of adverse outcomes and cycle outcome when compared to Met.

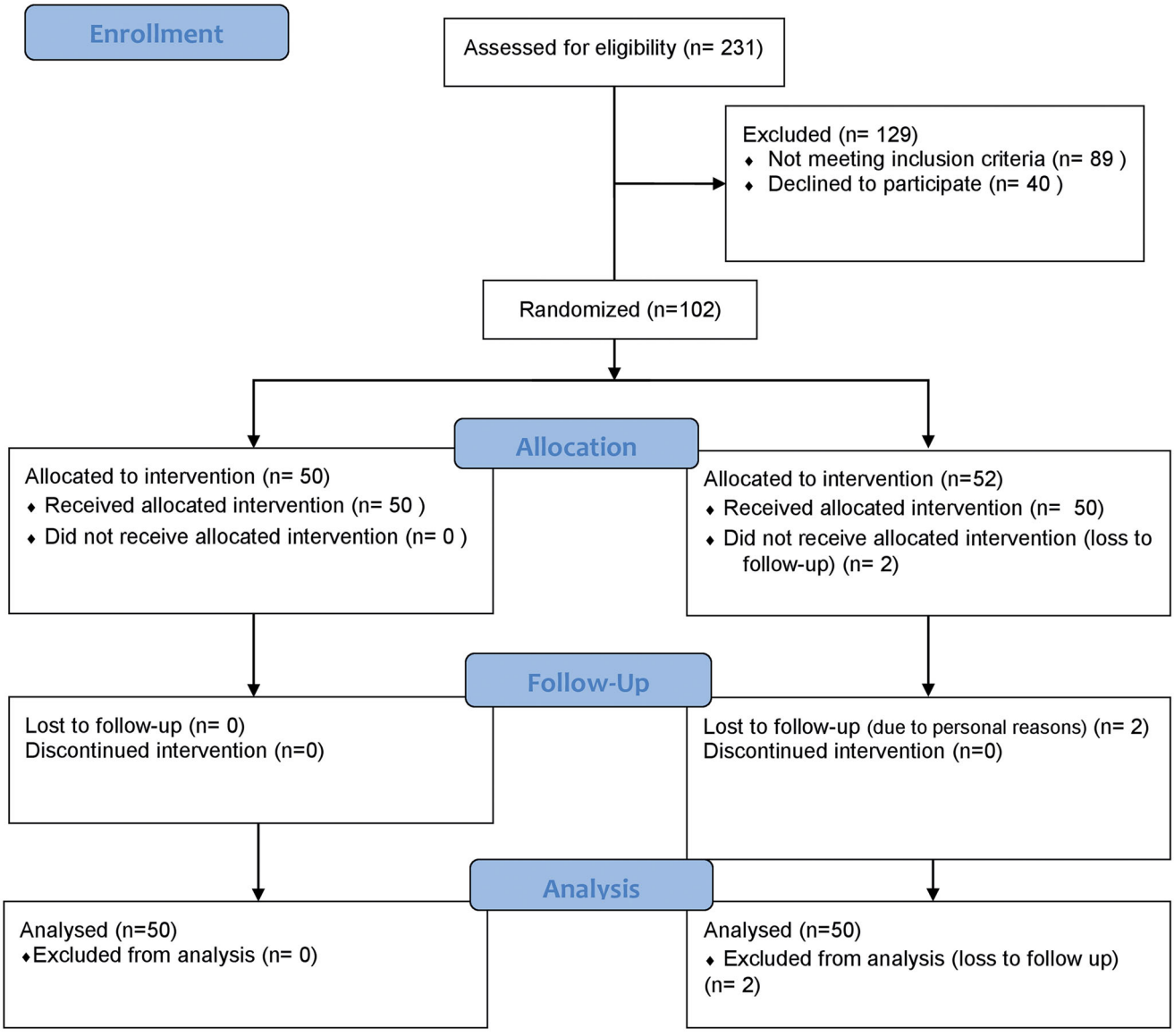

Figure 1. Consort diagram.

This study was therefore an attempt to compare Met and Myo in suggesting their benefits to reduce the risk of OHSS when given over a period of 12 weeks prior to IVF cycle. The rationale was that either drug would optimize the disturbed endocrine milieu and prove useful. While there was no significant difference in the primary outcome, fewer women in the myo-inositol suffered OHSS. Although none of the patients suffered moderate-severe OHSS, both being beneficial, the side-effects, in particular gastro-intestinal were significantly higher with Met as compared to Myo-inositol (Tables 1 and 4).

The cycle outcomes including dose and duration of gonadotropins, E2, and P4 levels, number of follicles on the day of trigger, were no different between groups, but the number of MII oocytes and fertilization and cleavage rates, number of good grade embryos were significantly higher with Myo-inositol when compared to Met use. While both drugs act to improve hyperinsulinemia and hyperandrogenemia, the action of Myo-inositol on the ovary is perhaps far reaching in terms of these benefits [22]. However, this did not translate to higher IVF pregnancy between the two drugs, but could be an answer to higher spontaneous pregnancy with Myo-inositol prior to cycle start. The clinical pregnancy and cumulative pregnancy rate between groups were no different; however, the cumulative live birth rate was non-significantly higher in the Myo-inositol group. This was because there were higher number of women who failed oocyte recovery in Met group due to poor response to ovarian stimulation compare to Myo-inositol. Further number deferred fresh transfer for mild OHSS and raised P4 on day of trigger was non-significantly higher with Met. In a previous study Jacob et al., Met was associated with lower pregnancy rate when compared to placebo, similar to our study with poor response pre-oocyte retrieval. The plausible explanation could be that Met in less efficient in improving the AMH levels compared to Myo which results in poor response to ovarian stimulation. The optimization of AMH levels particularly in those with high values may be an added advantage using Myoinositol.

The improvements in the hormone levels from baseline until 3 months were significant with both drugs for serum SHBG, LH, and AMH, but was significantly higher with myo-inositol as regards serum AMH and testosterone when compared between both (Table 2). The improvement in AFC and ovarian volume from baseline until 3 months was also significant in both groups

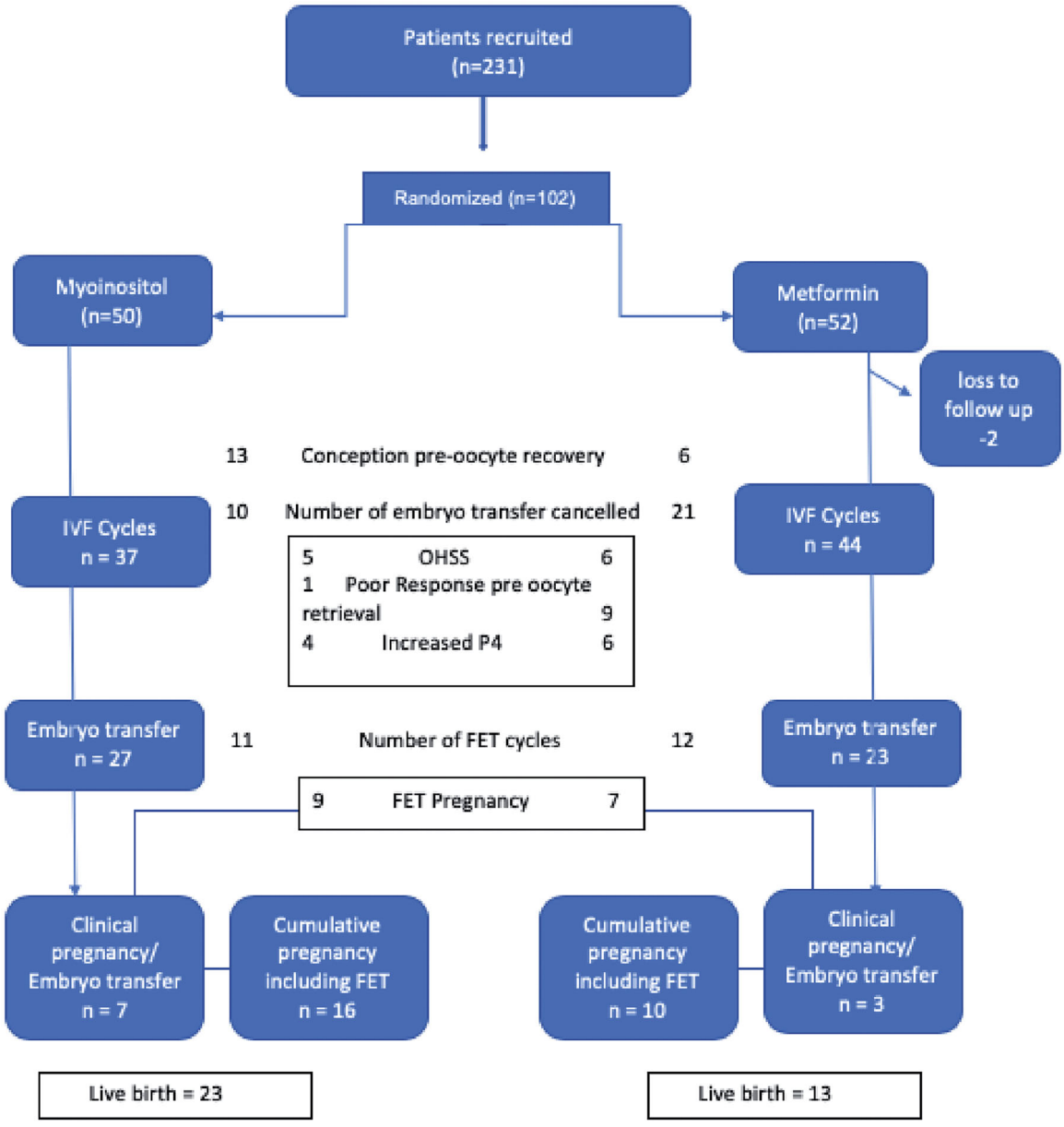

Figure 2. Recruitment and treatment pathway.

Table 1. Demographic data.

Parameters	Myoinositol ($n = 50$)	Metformin ($n = 50$)	p Value
Age (years)[a]	31 ± 3	30 ± 4	.80
Primary infertility[b]	46 (92)	41 (78)	.09
Duration of infertility[a]	5 ± 1.69	5 ± 1.69	.65
Regular cycles[b]	12 (24)	17 (32.7)	.67
BMI (kg/m^2)[a]	26 ± 3.1	27 ± 4.2	.22

Data were presented as [a]mean ± SD; [b]n (%).

but comparing between the groups was no different. This could perhaps be explained by direct actions of inositol on the ovary with improvements in ovarian reserve markers although a recent meta-analysis does not confirm to improvements in ovarian reserve markers with inositol [23]. AMH is a surrogate marker for severity of PCOS, and higher levels of >7.0 ng/ml [24] being associated with adverse response to stimulation including poor response. This effect of myo-inositol may benefit PCOS women with higher levels of baseline AMH levels making decisions on gonadotropin doses for IVF cycles. Modifying the hormone levels with prior myo-inositol will improve outcomes. The changes in metabolic parameters including blood sugar (fasting and post-prandial), fasting insulin, HOMA-IR, lipids (total cholesterol, LDL, and HDL) between baseline and 3 months post medications were significant in both groups, but between groups was significant with Met as regards fasting insulin and HOMA-IR. Despite higher improvement in insulin and HOMA-IR levels, Met did not show lower OHSS risks than myo-inositol, indicating that mechanism more than insulin pathways is involved in OHSS.

The limitations of the study were that it recruited both obese and lean PCOS for insulin sensitizers, irrespective of the insulin resistance. Even though fasting insulin and HOMA-IR was checked in both groups, they are not an absolute indicator of insulin resistance. Further, fewer patients underwent a fresh transfer for reasons other than OHSS, limiting the pregnancy rate per fresh transfer. To provide results in favor of either insulin sensitizer using live birth rate as a primary outcome, we would involve recruiting a huge number (approximately 1800

Table 4. Baseline and post-treatment parameters.

Parameters	Myoinositol ($n = 50$)	Metformin ($n = 50$)	p Value
Regular cycles[b]			
Baseline	12 (24)	17 (32.7)	.67
3 months	40 (80)	24 (46.2)	<.001
p Value	<.001	.035	–
BMI (kg/m^2)[a]			
Baseline	26 ± 3.1	27 ± 4.2	.22
3 months	24 ± 3.5	24 ± 2.7	.52
p Value	<.001	.004	
Serum LH (mIU/ml)[c]			
Baseline	7.8 (8.0–20.0)	6.3 (2.6–18)	.11
3 months	6.7 (2–17)	5.5 (2–24)	.25
p Value	<.001	<.001	
Serum FSH (mIU/ml)[c]			
Baseline	5.7 (2.1–8.1)	7.1 (4.1–13.2)	<.001[d]
3 months	5.6 (1.5–8.8)	5.3 (2.9–8.8)	.65
p Value	.809	<.001	
LH/FSH ratio[c]			
Baseline	1.4 (0.06–4.9)	0.8 (0.2–3.0)	.001[d]
3 months	1.1 (0.4–4.5)	1.0 (0.3–4.6)	.22
p Value	.002	.131	
Serum SHBG (nmol/l)[a]			
Baseline	12 ± 3.3	12 ± 3.2	.86
3 months	32 ± 9.7	28 ± 8.5	.03
p Value	<.001	<.001	
Serum testosterone (ng/ml)[a]			
Baseline	0.50 ± 0.16	0.52 ± 0.16	.48
3 months	0.36 ± 0.10	0.37 ± 0.10	.75
p Value	<.001	.618	
Fasting blood glucose (mg/dl)[a]			
Baseline	91 ± 8.9	93 ± 11.6	.40
3 months	82 ± 7.0	83 ± 7.1	.54
p Value	<.001	<.001	
Postprandial blood glucose (mg/dl)[a]			
Baseline	116 ± 20.4	115 ± 30.4	.87
3 months	101 ± 13.4	107 ± 15.2	.04
p Value	<0.001	0.014	
Fasting insulin (mIU/ml)[b]			
Baseline	12.24 ± 4.56	11.03 ± 4.62	.12
3 months	8.02 ± 2.74	6.314 ± 2.31	.00
p Value	.001	.001	
HOMA-IR[c]			
Baseline	5.18 ± 2.41	4.56 ± 2.17	.12
3 months	2.97 ± 1.09	2.31 ± 6.99	<.001
p Value	.001	.001	
Total cholesterol (mg/dl)[a]			
Baseline	160 ± 25	167 ± 28	.22
3 months	134 ± 20	141 ± 21	.08
p Value	<.001	<.001	
LDL (mg/dl)[a]			
Baseline	97 ± 23	101 ± 19	.40
3 months	85 ± 12	85 ± 14	.93
p Value	<.001	<.001	
HDL (mg/dl)[a]			
Baseline	41 ± 6	41.8 ± 5.4	.90
3 months	48 ± 5	48 + 5.4	.62
p Value	<.001	<.001	
AMH (ng/ml)[a]			
Baseline	8.4 (4.5–21)	10.3 (4.6–23)	.001[d]
3 months	3.7 (1–18)	7.4 (3–44)	.00
p Value	<.001	<.001	
AFC[a]			
Baseline	23.1 ± 3.4	24.8 ± 4.1	.02[d]
3 months	22.1 ± 3.7	22.5 ± 4.0	.60
p Value	<.001	<.001	
Ovarian volume[a]			
Baseline	16.5 ± 3.0	15.8 ± 2.7	.22
3 months	12.5 ± 2.8	13.3 ± 2.8	.37
p Value	<.001	<.001	–
GI side effects (bloating sensation)[b]			
At 1 month	8 (16)	34 (65)	.00
At 3 months	4 (8)	36 (69)	.00
p Value	.206	.564	–

Data were presented as [a]mean ± SD; [b]n (%); [c]median (min–max); [d]Values between both the groups was significantly higher in group 1, was just a chance finding and the outcome was adjusted accordingly.

Table 2. Primary outcome.

Parameters	Myoinositol	Metformin	Difference 95% CI (*p* value)
Intention to treat	(*n* = 50)	(*n* = 52)	13.1 (−1.1, 27.3) .07
n	50	52	17.1 (1.1, 33.0)[a] .13
OHSS present[a] (mild)	5 (10.0)	12 (23.1)	
Per protocol	(*n* = 50)	(*n* = 52)	10.0 (−3.9, 23.8) .16
n	50	50	13.1 (−2.5, 28.7)[a] .10
OHSS present[a] (mild)	5 (10.0)	10 (20.0)	
OHSS/IVF cycles[a]	(*n* = 37)	(*n* = 44)	9.0 (−7.5, 22.5) .29
	5 (13.5)	10 (22.5)	
Clinical pregnancy rate[b]	18 (36.0) (*n* = 50)	9 (18.0) (*n* = 50)	18.0 (0.9, 35.0) .04
Spontaneous pregnancy rate[b]	13 (26.0) (*n* = 50)	6 (12.0) (*n* = 50)	14.0 (−1.1, 29.1) .07
IVF pregnancy rate[b]	5 (10.0) (*n* = 50)	3 (6.1) (*n* = 50)	3.9 (−6.8, 14.6) .71
IVF pregnancy rate/number of IVF cycles[b]	5 (13.5) (*n* = 37)	3 (6.4) (*n* = 44)	−6.7 (−20.0, 6.6) .31
Cumulative pregnancy rate (including FET)[b]	16 (43.2) (*n* = 37)	10 (22.7) (*n* = 44)	20.5 (0.11, 39.1) .05

Data represented as *n* (%), [a]adjusted for baseline LH/FSH ratio and AMH, [b]*n* (%).

Table 3. Secondary outcome.

Parameters	Myoinositol (*n* = 37)	Metformin (*n* = 44)	*p* Value
Total dose of FSH[a] (IU)	2200 (1233–4596)	2420 (1121–4230)	.09
Total days of stimulation[a]	11 (9–15)	12 (8–18)	.14
Follicles[a]	16 (3–25)	15 (2–20)	.09
ET on day of trigger[a]	8 (6.5–9.5)	7.5 (6–9)	.09
E_2 (pg/ml)[a]	4163 (557–13,003)	4229 (217–13,493)	.84
P_4 (ng/ml)[a]	1.2 (0.16–4.9)	1.3 (0.07–4.8)	.50
Number of oocytes retrieved[a]	14 (0–18) (*n* = 37)	12 (0–16) (*n* = 44)	.09
Number of metaphase II oocyte	8 (0–15) (*n* = 37)	5 (0–13) (*n* = 44)	.27
Number of Grade 1 oocyte[a]	8 (0–15) (*n* = 37)	6.5 (0–11) (*n* = 44)	.20
Fertilization rate[a]	71 (40–100) (*n* = 37)	47 (0–87) (*n* = 44)	<.001
Number of embryos[a]	6 (0–18) (*n* = 37)	4 (0–9) (*n* = 44)	<.001
Cleavage rate[b]	96.0 ± 10.0 (*n* = 37)	85.5 ± 16.9 (*n* = 44)	.008
Number of grade 1 embryos[a]	3 (0–15) (*n* = 37)	2 (0–18) (*n* = 44)	.04
Number of embryos frozen[a]	3.14 (0–15) (*n* = 37)	1.79 (0–8) (*n* = 44)	.39
Implantation rate[a]	12 (0–100) (*n* = 27)	6.52 (0–50) (*n* = 23)	.53

Data represented as [a]median (min–max); [b]mean ± SD.

subjects). Such a large sample size for this study would be feasible only from a multi-centric trial and would require long duration.

Conclusion

Myo-inositol is equally beneficial as Met in reducing the risk of OHSS in women with PCOS undergoing antagonist cycles when given for 3 months prior to IVF cycles. With lesser gastro-intestinal side effects Myo-inositol may prove useful with better patient compliance when given for long term.

Author contributions

M.N. and K.R. conceived and designed the study. K.R. drafted the manuscript. M.N. and R.M. revised it critically and approved the final version of publication. M.K. helped with statistical analysis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

No external funding was either sought or obtained for this study.

References

[1] Joshi B, Mukherjee S, Patil A, et al. A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. Indian J Endocrinol Metab. 2014;18(3):317–324.

[2] Angik R. A comparative study of metabolic and hormonal effects of myoinositol VS metformin in women with polycystic ovary syndrome: a randomised controlled trial. Int J Reprod Contracept Obstet Gynecol. 2015;4:1.

[3] 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. 2004;19(1):41–47.

[4] Kahsar-Miller MD, Nixon C, Boots LR, et al. Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS. Fertil Steril. 2001;75(1):53–58.

[5] Geller DH, Pacaud D, Gordon CM, et al. State of the art review: emerging therapies: the use of insulin sensitizers in the treatment of adolescents with polycystic ovary syndrome (PCOS). Int J Pediatr Endocrinol. 2011;2011(1):9.

[6] Tang T, Glanville J, Orsi N, et al. The use of metformin for women with PCOS undergoing IVF treatment. Hum Reprod. 2006;21(6):1416–1425.

[7] Tso LO, Costello MF, Albuquerque LET, et al. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014;(11):CD006105. PMID 19370625

[8] Papaleo E, Unfer V, Baillargeon JP, et al. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Fertil Steril. 2009;91(5):1750–1754.

[9] Mendoza N, Diaz-Ropero MP, Aragon M, et al. 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. Gynecol Endocrinol. 2019;35(8):695–700.

[10] Lesoine B, Regidor PA. Prospective randomized study on the influence of myoinositol in PCOS women undergoing IVF in the improvement of oocyte quality, fertilization rate, and embryo quality. Int J Endocrinol. 2016;2016:4378507–4378505.
[11] Piomboni P, Focarelli R, Capaldo A, et al. Protein modification as oxidative stress marker in follicular fluid from women with polycystic ovary syndrome: the effect of inositol and metformin. J Assist Reprod Genet. 2014;31(10):1269–1276.
[12] Showell MG, Mackenzie-Proctor R, Jordan V, et al. Inositol for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018;12(12):CD012378.
[13] Medicine AS, In R, Alpha Scientists In Reproductive Medicine. The Alpha consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting. Reprod Biomed Online. 2012;25(2):146–167.
[14] The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Hum Reprod. 2011;26(6):1270–1283.
[15] Ovarian Hyperstimulation Syndrome, Management (Green-top Guideline No. 5) [Internet]. Royal College of obstetricians & gynaecologists.
[16] Smith V, Osianlis T, Vollenhoven B. Prevention of ovarian hyperstimulation syndrome: a review. Obstet Gynecol Int. 2020;2015:12–11.
[17] Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2017;1:CD012103–20.
[18] Diamanti-Kandarakis E, Christakou CD, Kandaraki E, et al. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol. 2010;162(2):193–212.
[19] Doldi N, Persico P, Sebastiano FD, et al. Gonadotropin-releasing hormone antagonist and metformin for treatment of polycystic ovary syndrome patients undergoing in vitro fertilization–embryo transfer. Gynecol Endocrinol. 2006;22(5):235–238.
[20] Jacob SL, Field HP, Calder N, et al. Anti-Müllerian hormone reflects the severity of polycystic ovary syndrome. Clin Endocrinol. 2017; 86(3):395–400.
[21] Morley LC, Tang T, Yasmin E, et al. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2017;11:CD003053.
[22] Lashen H. Role of metformin in the management of polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2010;1(3):117–128.
[23] Bhide P, Pundir J, Gudi A, et al. The effect of myo-inositol/di-chiro-inositol on markers of ovarian reserve in women with PCOS undergoing IVF/ICSI: a systematic review and Meta-analysis. Acta Obstet Gynecol Scand. 2019;98(10):1235–1244.
[24] Homburg R, Crawford G. The role of AMH in anovulation associated with PCOS: a hypothesis. Hum Reprod. 2014;29(6):1117–1121.