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A retrospective study "myo-inositol is a cost-saving strategy for controlled ovarian stimulation in non-polycystic ovary syndrome art patients."

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Abstract

Background Fertility care represents a financial burden on patients and healthcare services alike and can represent a barrier to entry for many couples. Controlled ovarian stimulation (COH) is routinely used as part of in vitro fertilization and intracytoplasmic sperm injection (ICSI) procedures, as such the use of gonadotropins is a major contributing factor to the cost of the procedure. Recent studies have shown that myo-Inositol (myo-ins) may reduce the amount of gonadotrophins required in assisted reproductive technology (ART) procedures. This retrospective study measured the effect of myo-ins on the number of recombinant follicular stimulating hormone (rFSH) units used in IVF and ICSI and the relative cost to verify if this may be a cost saving strategy. We also investigated the oocyte and embryo quality, implantation rate, abortion rate, clinical pregnancy, and ovarian hyperstimulation syndrome.

Methods A total of 300 women undergoing either IVF or ICSI were distributed between two distinct and equal patient groups of 150 women. In control group (group A), folic acid (FA) alone was prescribed, meanwhile the treated group (group B) were prescribed FA, myo-Inositol (myo-ins) and alpha-lactalbumin (α-LA), both groups started this oral treatment in the middle of the luteal phase.

Results Myo-Ins supplementation in the treatment group significantly reduced the number of units of rFSH used in COH vs. the control group (2526 vs. 1647, $p < 0.05$); however, no changes were seen in other measured outcomes, likely due to the short treatment period.

Conclusions The use of myo-Ins presents a safe method for reducing the amount and subsequent costs of rFSH usage in ART protocols.

Trial registration The trial was retrospectively registered with the Institutional Review Board of ALMA RES IVF Center, trial number n°2/2024.

Keywords IVF, ICSI, myo-Inositol, OHSS, COH, PCOS, Pharmacoeconomics

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Background

The management of nutrition is vital for those women seeking pregnancy, and supplements containing substances such as myo-Inositol (myo-Ins), melatonin, vitamin D, and folic acid (FA) have become a routine part of fertility care and contribute towards positive outcomes of in-vitro fertilization (IVF) procedures [1–4]. The use of IVF has continued to increase in recent years due to a variety of factors such as couples electing for later pregnancies or rising rates of obesity and associated metabolic issues, which are harmful for fertility in both women and men [5, 6].

Myo-Ins is an insulin-sensitizing natural molecule that facilitates cellular glucose uptake, and as such it has found applications within nutraceuticals for the treatment of polycystic ovary syndrome (PCOS) and the prevention of gestational diabetes mellitus (GDM) [7, 8]. In addition to playing a key role in glucose metabolism, myo-Ins has crucial functions in the physiology of human reproduction [9, 10], with elevated myo-Ins levels in human follicular fluid correlating positively with satisfactory oocyte quality [11]. Myo-Ins acts as a second messenger of FSH, regulating FSH-mediated pathways that govern the proliferation and maturation of granulosa cells [12]. This consequently modulates the production of anti-müllerian hormone (AMH), which plays a fundamental role in determining the maturation and transport of the oocyte in the oviduct, and ensures good embryo quality [13]. Furthermore, myo-Ins demonstrates positive effects during in vitro maturation, fertilization, and early cleavages of human oocytes and embryos in assisted reproductive treatments (ART) [14].

The financial burden that ART puts on patients and healthcare systems is a factor that must be considered in fertility care, as high costs may prevent couples from attempting or repeating subsequent cycles, especially when success at the end of the treatment is not guaranteed [15]. In this regard, the Italian Health System partially covers the expenses for the treatments carried out in public centers in combination with a fixed-rate contribution from the patient, which varies by region [16]. Furthermore, the National Health System covers the costs of all gonadotropins used for controlled ovarian hyperstimulation (COH) within ART protocols, regardless of whether they are carried out in public or private clinics, which results in a large economic burden. As all ART protocols generally begin with an initial step of COH, cost reducing measures, without comprising patient care or ART outcomes are highly sought after [17].

A recent meta-analysis of randomized controlled trials in PCOS and non–PCOS infertile patients undergoing ART [18] reported that the administration of myo-Ins, before starting COH, significantly lowers the units of rFSH required, reducing the length of COH and the risk of developing ovarian hyperstimulation syndrome (OHSS). Additionally, prior literature has highlighted that myo-Ins supplementation increases the number of viable oocytes, thus potentially increasing the clinical pregnancy rate [19]. With this in mind, we conducted a retrospective controlled study to evaluate the effect of myo-Ins supplementation on the amount of rFSH units required for the COH of patients undergoing ART, and whether this resulted in a significant cost-saving approach for the procedure. The majority of prior studies that have investigated the use of myo-Ins in ART were conducted in PCOS patients, with relatively few studies in non PCOS populations; therefore, to expand the potential use of myo-Ins into the greater population, we included only non-PCOS patients. The primary outcome and main objective of this study was therefore to measure the effect of myo-Ins on the number of rFSH units used and the relative cost, to evaluate whether myo-Ins may effectively represent a cost saving strategy for the Italian Health System. Furthermore, we also measured as secondary outcomes the oocyte and embryo quality, implantation rate, abortion rate (AR), clinical pregnancy, and OHSS.

Methods

Study design and participants

This was a retrospective study carried out at the Alma Res Fertility Center in Rome (Italy). The approval of study was recorded as n°2/2024 by the Institutional Review Board of ALMA RES IVF Center and conducted according to the ethical principles of the Declaration of Helsinki. Upon enrollment, all participants were required to sign an informed consent form.

Inclusion criteria for the study population were as follows: infertility of different etiology, age < 40 years, BMI in the range 18.5–24.9 kg/m^2, level of basal FSH below 15 mIU/ml on day 3. Patients not eligible for homologous ART treatment or who presented with at least one of the following characteristics were excluded from the study: presence of insulin resistance (IR) (Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) > 2.5, hyperglycemia, hyperprolactinemia, hypothyroidism or androgen excess, diagnosis of PCOS according to Rotterdam criteria [20]; ongoing treatment with hormones or drugs that can potentially influence ovulation.

The outcomes of the study were selected following the health economic analysis plan, which was designed to highlight the economic advantages for the National Health System when myo-Ins is administered before an ICSI procedures for PCOS patients. Also, we decided to measure the canonical ICSI outcome to describe possible differences between the study group and the control. The flowchart of the study is summarized in Fig. 1.

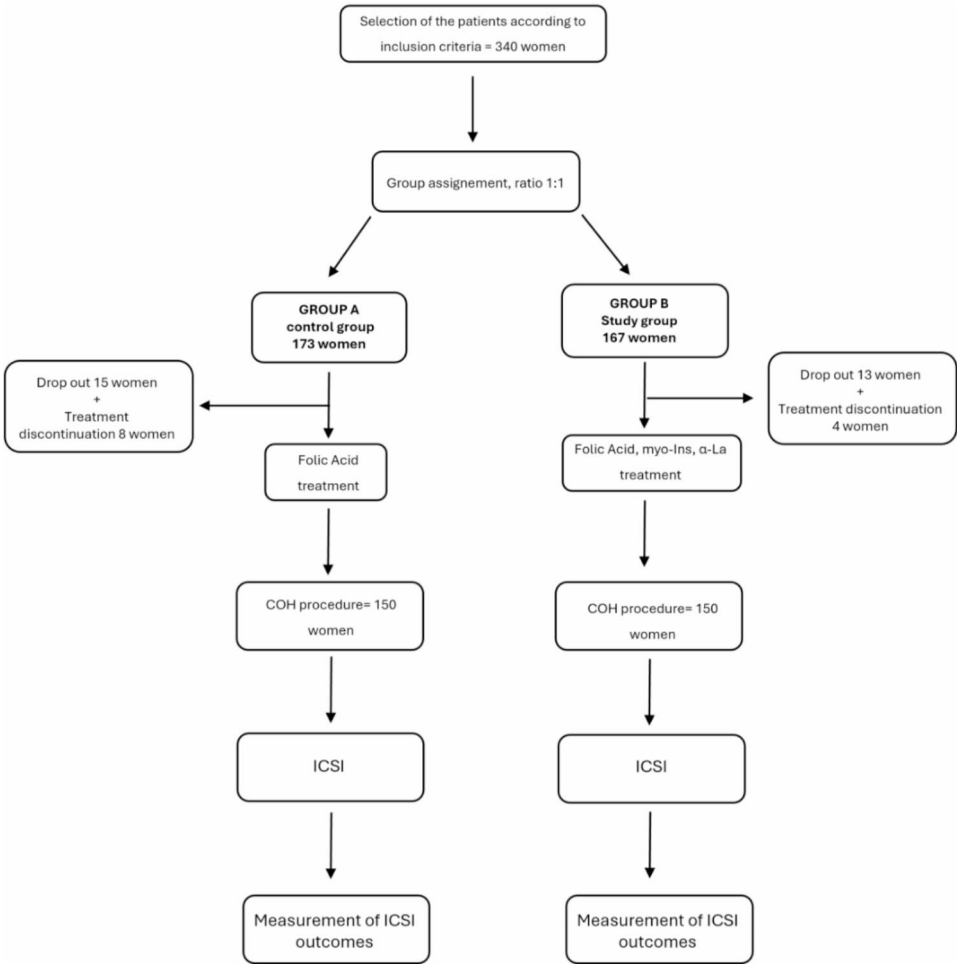

Fig. 1 Flowchart of the study. Summary of the design and main steps followed in the study. Myo-Ins: myo-Inositol, α-La: α-Lactalbumin, COH: controlled ovarian hyperstimulation

Methods and treatments

The present study was structured according to an economic analysis plan which provided the comparison of two different study groups who followed two different dietary supplementations for 4 weeks before COH. The study aimed to identify significant differences in the cost of the procedures when performed in group A or in group B.

The study population was composed of 340 infertile women aged below 40 years attending the ART program at Alma Res Fertility Center were evaluated for inclusion in the present study over a 24-month period (November 2021-November 2023), and equally assigned between two homogeneous groups: control group (group A) and treated group (group B). 15 patients in group A and 13 in group B dropped out before COH. In Group A, treatment was terminated in 8 patients, 2 of them because of excessive response to stimulation (estradiol > 4500 pg/ml) and 6 because of poor response to stimulation. In addition, 4 patients in Group B were poor responders and treatment was terminated. Follicular aspiration according to the study setting was performed in 150 patients in group A and in 150 in group B and a total of 300 (150 per group) were considered in the statistical analysis. All participants underwent pituitary desensitization by subcutaneous (s.c.) administration of a GnRH agonist (Fertipeptil®, Ferring Pharmaceuticals, long protocol – 0.1 mg daily, starting from the middle luteal phase). Women in group A (control group) were assigned to receive 400 μg of folic Acid (FA) daily for 4 weeks, starting from the middle luteal phase and during COH until 14 days after fresh embryo transfer. Women in group B (treated group) were assigned to receive myo-Ins (2.0 g), α-lactalbumin (50 mg) and FA (200 μg) two times a day for 4 weeks from the middle luteal phase and during COH until 14 days after embryo transfer. In the case of pregnancy, the treatment in both groups was extended until week 12 of gestation. The treatments were properly chosen to better describe the advantages of myo-Ins use in COH procedures.

Basal FSH, estradiol (E2), progesterone (P4) and Anti-mullerian hormone (AMH) were measured at day 2–5 of the menstrual cycle by commercial ELISA® or Elecsys Cobas® assay kits. Recombinant FSH (rFSH; Gonal F®, Merck) and recombinant hCG (rhCG; Ovitrelle®, Merck) were used for COH, with starting doses of rFSH between 100 and 300 IU as determined by Body Mass Index (BMI) and the AMH level measured in the previous cycle to optimize gonadotropin dosage. Particularly, the adjustment of rFSH doses to be used for the stimulation, was carried out for each patient according to a nomogram using patient characteristics, specifically BMI, age, and AMH, that allowed for selection of the appropriate starting dose of exogenous gonadotrophin to be used in IVF cycles. Our system was developed from the nomogram of La Marca et al. in 2012 [21], by modifying the column of the basal FSH assay with the BMI.

In all patients, blood estradiol level was lower than 50 pg/ml before ovarian stimulation. Follicle maturation was monitored daily, starting from the 5th day of stimulation by combined ultrasonography (US) and plasma E2 and P4 measurements. Ovulation was triggered with recombinant hCG (250 µg s.c.; Ovitrelle®, Merk) when plasma E2 was between 900 and 4500 pg/ml, and at least two follicles reached a mean diameter of 20 mm (two perpendicular measurements). Treatment was terminated and the patient removed from the study in the event of poor ovarian response, defined by < 3 growing follicles observed on the 9th day, or due to ovarian hyperstimulation identified by E2 levels > 4500 pg/ml. Oocyte retrieval was performed under transvaginal US guidance 36 h after hCG administration (considering the day of follicular aspiration to be day 0 of IVF program). To monitor the oocyte status, pronuclei and embryo development were monitored after 18 and 44 h respectively, following insemination. The insemination method was performed either by standard IVF (30%) or intra cytoplasmic sperm injection (ICSI, 70%) depending on the clinical need, being ICSI preferentially selected in the case of male factor, or when the number of oocytes retrieved was ≤ 3. The embryos obtained were sorted on day 3 into three categories, depending on their morphologic appearance. Grade A had > 6 equal and regular blastomeres without the presence of cytoplasm fragments; Grade B had < 6–8 unequal blastomeres with or without cytoplasmic fragments; Grade C were fragmented (> 50%) embryos. Fresh embryos were transferred approximately 72 h after insemination. Blastocysts were cultured and transferred at day five after classification in Class A-B-C depending on the morphological characteristic of the blastomeres. In detail, if the number of good quality embryos was < 3, the transfer was made on day 3; however, when the number of good quality embryos was ≥ 3, the embryos were transferred on day 5 to prolong the cultures. A double transfer was performed or patients ≥ 35 years old, who had records of failed previous attempts, and had moderate to low embryo quality, while in the case of high embryo quality, a single transfer was preferred. For younger patients (< 35 years), with no history of failed previous attempts, and moderate to good embryo quality, a single transfer was performed, while a double transfer was preferred in case of low-quality embryos.

All transfers were performed using the COOK catheter (Cook Sydney IVF Embryo Transfer Catheter®) under US control. All pregnancies were confirmed by rising levels of serum hCG and by the presence of the gestational sac during US examination, 4 weeks after the transfer. Both groups received the same luteal phase support, consisting of vaginal progesterone (Progeffik® 200 mg, one suppository from the day of the follicular aspiration). In the case of pregnancy, progesterone administration was extended until week 12 of gestation [4]. The cost of 1 Unit of rFSH (0.51 €) was calculated according to Italian Agency of Medicines [22].

Statistical analysis

Descriptive statistics summarizing quantitative variables included mean, standard deviation, standard error, median, 25th and 75th percentiles. T-Student test for two independent samples was used to compare quantitative variables between the group A and B. Comparisons in pairs of qualitative variables were performed using the Chi-Square Test or the Fisher's Exact Test.

Two-sided statistical analyses were performed using SAS (version 9.4), setting significance level below $p = 0.05$.

Results

According to the objectives of the present study we planned the following experimental setting to gather the information needed for the investigation.

In the first step of the study, precisely during the enrollment period we collected the baseline values of each patient regarding the anamnesis characteristics (Table 1) and additional information about infertility factors and number of previous ART treatments (Table 2).

In the second step we collected blood samples from each patient to assess the values of the hormonal parameters (Table 3).

During the COH we measured the amounts of rFSH doses used for each procedure in both study and control groups. Following COH we also measured the ICSI outcomes as summarized in Tables 4 and 5.

The two groups exhibit similar basal hormonal characteristics and number of previous treatments with none of the parameters having statistical differences.

The number of units of rFSH used was the only parameter resulting statistically different between the two groups, with a mean value of 1647 (SD = 756) IU of rFSH

Table 1 Characteristics of patients at baseline. Mean values are reported, with standard deviation in brackets; statistical significance for $p < 0.05$; ns = not significant

Entry	Group A *n* = 150	Group B *n* = 150	*p*-value
Age (years)	35.69 (2.9)	35.16 (3.75)	ns
BMI (kg/m^2)	21.95 (2.17)	21.86 (2.77)	ns
Cycle length (days)	28.2 (2.17)	28.2 (2.6)	ns
Duration of infertility (years)	3.6 (2.1)	3.7 (1.8)	ns
Previous ART treatment	1.1 (0.7)	1.2 (0.8)	ns

Table 2 Infertility factors and number of previous ART treatments. Mean percentage values are reported, with standard deviation in brackets; statistical significance for $p < 0.05$; ns = not significant

Entry	Group A *n* = 150	Group B *n* = 150	*p*-value
Primary infertility % (n)	84 (126)	86 (129)	ns
Tubal factor / combined/endometriosis%(n)	42 (63)	40.4 (61)	ns
Male factor/combined %(n)	34 (51)	31.6 (47)	ns
Idiopathic/ Unexplained infertility %(n)	24 (36)	28 (42)	ns
N° 0 previous ART treatment (%)	40 (27)	38 (25)	ns
N° =>1 previous ART treatment (%)	110 (73)	112 (75)	ns

Table 3 Hormonal parameters at baseline and COH mean values are reported, with standard deviation in brackets; statistical significance for $p < 0.05$; ns = not significant

Entry	Group A *n* = 150	Group B *n* = 150	*p*-value
AMH (ng/ml)	2.77 (2.6)	2.54 (1.86)	ns
Basal FSH (mIU/ml)	6.96 (4)	7.8 (2.4)	ns
Basal Estradiol (pg/ml)	38.85 (6.4)	40.51 (13.39)	ns
Estradiol at hCG (pg/ml)	2015 (865)	1967 (677)	ns
Progesterone at hCG (ng/ml)	0.77 (0.29)	0.82 (0.3)	ns
Endometrium at hCG (mm)	11.48 (1.18)	11.40 (1.4)	ns

Table 4 COH parameters and ART outcomes. Mean values are reported, with standard deviation in brackets; statistical significance for $p < 0.05$; ns = not significant

Entry	Group A *n* = 150	Group B *n* = 150	*p*-value
Gonadotropins (IU)	2526 (974.4)	1647 (756)	< 0.05
Oocytes retrieved (COCs)	5.9 (2.1)	5.48 (2.21)	ns
Metaphase II oocytes	4.81 (1.38)	4.48 (1.87)	ns
2PN oocytes fertilized	3.85 (1.1)	3.59 (1.5)	ns
Top quality embryos/blastocysts transferred	1.52 (0.54)	1.47 (0.53)	ns

Table 5 Characteristics of patients mean values are reported, with standard deviation in parentheses; statistical significance for $p < 0.05$

Entry	Group A *n* = 150	Group B *n* = 150	*p*-value
Positive hCG n (%)	39 (26)	44 (29)	ns
Implantation rate n/n (%)	45/234 (19.2)	49/222 (22)	ns
Abortion rate n (%)	7(18.8)	6 (13.6)	ns
Ongoing pregnancy/Started patient (%)	32/150 (21)	38/150 (25)	ns
Twin pregnancy n (%)	6 (16)	5 (15.6)	ns

in the group of patients treated with myo-Ins versus 2526 (SD = 974) IU of rFSH in the control group.

In both a private and public structures where IVF is conducted, the primary contributor for similar procedures is the cost of the hormonal protocol used for the ovarian stimulation. In this regard the present study setting aimed to compare the difference in terms of costs between the two different protocols followed by the study group and the control group before COH. The cost of each COH protocol conducted before ICSI procedure was calculated being according to AIFA (ITALIAN AGENCY OF MEDICINES) where the specified cost of

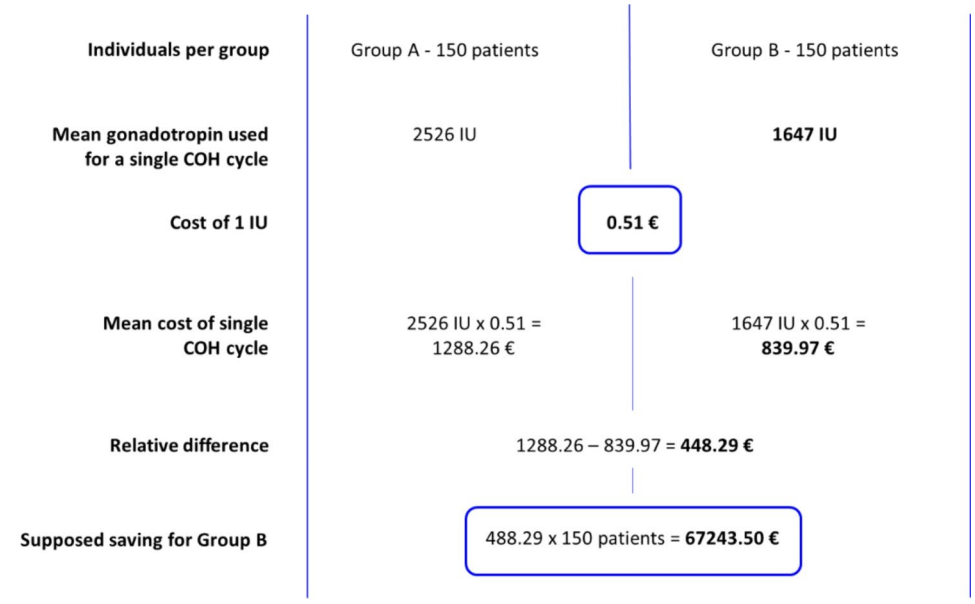

Fig. 2 Summary of cost saving in COH cycles. Schematic representation of the cost saving calculated between the study and the control group. Given a fixed price for a single unit of gonadotropin charged to the Italian Health System, by multiplying this cost for the mean values of the gonadotropin used in each group we observe a relative difference representing a cost saving when myo-Ins is used before COH procedure

1IU of rFSH is 0.51 € [22]. To calculate the cost saving between the two groups, the price of one COH cycle in both groups was multiplied by the number of completed cycles as follows:

Group A: Mean COST of one control COH cycle: $2526 \times 0.51 = 1288.26$ €.

Group B: Mean COST of one myo-Ins COH cycle: $1647 \times 0.51 = 839.97$ €.

In the light of this evidence the relative different cost between COH cycles is derived from: 1288.26–839.97 = 448.29, as summarized in Fig. 2. Consequently, an overall supposed savings for the Italian Public Health System accounts for 67243.50 € in myo-Ins treated group.

Discussion

The objective of the present study was to evaluate whether the use of myo-Ins may represent a cost-saving strategy for the National Health System. For this purpose, we compared the advantage of myo-Ins supplementation on COH conducted with gonadotropins vs. standard protocols of COH performed without myo-Ins administration. In summary this study demonstrated that the myo-Ins group needed a significantly reduced number of gonadotropin units for COH procedures with respect to control. Furthermore, by reducing the amount of COH required for a successful ART cycle myo-Ins supplementation represents an effective cost-saving strategy for the state, who covers the expenses for the gonadotropins. The results of this investigation confirm the findings reported in previous studies [23, 24], where is specifically demonstrated that the treatment with myo-Ins allows a significant reduction of the amount of rFSH units necessary for ovarian stimulation protocols in non-PCOS patients undergoing ART procedures, with respect to standard COH with gonadotropins. This evidence applies COH is used in ART cycles to yield a group of mature oocytes to be inseminated either by classic IVF or by ICSI [25]. Depending on the situation, the transfer of the best fresh embryo(s) may be carried out immediately after COH. Alternatively, to minimize risks related to embryo transfer after COH, or in case of surplus of high-quality embryos, cryopreservation remains a viable option for future embryo transfer if needed [26]. More recently the "freeze all" approach has been proposed and well utilized both for the prevention of alterations to the physiological endometrial maturation process commonly linked to the COH [27, 28], or to allow genetic testing for preimplantation evaluation of blastocysts [29].

Previous studies have demonstrated the effectiveness of myo-Ins in improving COH outcomes. The meta-analysis by Zheng et al., including a total of 935 women supplemented with myo-Ins prior to ICSI or IVF, concluded that the use of myo-Ins significantly improved the clinical pregnancy rate ($p = 0.03$), with a significantly reduced abortion rate ($p = 0.0006$) and a significant increase in the number of grade I embryos ($p = 0.02$) [19]. Interestingly, within the trials of the meta-analysis, significantly less rFSH was required ($p = 0.004$). This reduction of gonadotropin use is likely to reduce the probability of hyperstimulation. This is confirmed in the present study where we observed that myo-Ins supplementation prevents the risk of OHSS and increases the response rate

to gonadotropins. Indeed, two cases of OHSS risk and six cases of poor response were observed in the control group, whereas none and four, respectively, among patients treated with myo-Ins.

In-silico analyses recently highlighted that the use of myo-Ins reduces the use of rFSH units, and subsequently the cost of the treatments for women with PCOS seeking pregnancy [30]. This model used published data from three separate studies to evaluate the probability of progression through each step of the IVF procedure [2, 18, 24]. The results demonstrate a higher percentage of simulated pregnancies progressed to the next step (transition probabilities) of ART when rFSH was associated with myo-Ins treatment. This was most noticeable in: the number of oocytes after pick-up, fertilization after IVF, embryo transfer after both IVF and ICSI fertilization. These increased transition probabilities reduce the likelihood of a patient having to undergo subsequent cycles of IVF, which means saving the costs associated with this cycle. In total the average cost per pregnancy decreased from €14,148 in the rFSH group to €13,001 in the group of rFSH + myo-Ins. This data indicates that myo-Ins use allows a significant economic saving when projected over the numerous patients who resort to IVF with or without ICSI every year and highlights how myo-Ins may represent a cost-effective strategy in ART protocols.

Numerous studies demonstrated a fundamental role of myo-Ins in restoring altered ovarian physiology, especially in women with PCOS who exhibit anovulation and fertility issues [31]. Women with PCOS often suffer from altered glucose metabolism, which leads to increased glucose levels for a prolonged period, inducing an increased systemic insulin release [32]. When the tissues are subjected to high insulin levels, they lose their sensitivity to insulin signal so that a higher amount of insulin is needed to internalize the glucose, causing a phenomenon defined as insulin resistance (IR). As ovarian tissue does not become insulin resistant [33], systemic IR causes overstimulation of the insulin-dependent conversion of myo-Ins to D-chiro-inositol (D-chiro-Ins), leading to altered ratios between the two isomers in the ovaries [34]. In this context, several studies demonstrated that inositol supplementation is useful for reestablishing the correct ratio myo-Ins/D-chiro-Ins, thus restoring the ovarian response to gonadotropins and a physiological menstrual cycle [35].

The activity of myo-Ins is not limited to PCOS, as it is a vital molecule for human reproduction. Acting as a second messenger of FSH in the granulosa cells, it is an important regulator of follicular microenvironment and aids the selection of the dominant follicle during the oogenesis process favoring oocyte development [36]. Consequently, myo-Ins reduces the number of degenerated oocytes, ameliorates embryo quality, and improves fertilization and pregnancy rates also in non-PCOS populations [24, 37]. In the light of this evidence, we decided to evaluate the IVF outcomes described above in the two groups of women as secondary objective of the present study. The results retrieved from our investigation indicate that these metrics did not significantly improve in the current study. Possibly, this can be attributed to the duration of the treatment period with myo-Ins, 4 weeks, which is considerably less than the 2–4 months periods reported in prior work where an improvement of IVF outcomes is observed [23, 24].

In the present study most of the measured parameters did not show significant differences between the control and the treated group. In fact, the only significant difference between the two groups was the number of gonadotropins required for a single COH cycle: 2526 (sd 974.4 UI) in the control group vs. 1647 (sd 756 UI) in the treated group. This difference identifies a significant reduction of the rFSH doses required for COH when myo-Ins is supplemented to the patients. Calculations based on the data released by the Italian Agency of Medicines demonstrate that such difference observed with myo-Ins use results at least in overall 448.29€ saving per single COH cycle. The projection of the money saved for a single COH on the number of 150 participants in each group, becomes a total of 67243.50 € of cost-saving for the study group. This result may represent a notable saving strategy when extrapolated over the entire population of women undergoing COH cycles each year. In this regard is certainly important to highlight that the latest statement released from the Italian Ministry of Health indicates that the records of ART cycles performed in Italy in a year was 108,067 in 2021 [38]. This means that the projection of saving 448.29€ for each COH procedures becomes 48445355.43€ for all the ART procedures performed in a year in Italy and the trend of the procedures performed is still increasing. This therefore begs the question as to whether myo-Ins should be recommended as per standard practice of COH, also considering that it is a safe natural molecule with therapeutic effect both in PCOS and non-PCOS patients and it guarantees a cost saving strategy for the Italian Health System. In this regard, the reduction or better the minimization of rFSH doses is of primary importance to achieve the best outcomes without excessive economic burden [39, 40].

Some limitations to this study must be considered. Firstly, the number of patients included represents a small fraction of the overall Italian population seeking pregnancy through ART. To fully evaluate the cost-saving potential of myo-Ins implementation in IVF protocols (with or without ICSI), studies with larger population are required. Furthermore, this study considers only the Italian perspective, where the government acts as the single purchaser for gonadotropins; therefore, these results

should be transferred with caution to other states that have different health systems. Of note, we considered that non-PCOS patients exhibit a physiological activity of the reproductive apparatus less deregulated than in PCOS patients, so that they do not necessitate of a long period of myo-Ins supplementation levels. We supplemented the patients for 4 weeks in order to optimize the response to rFSH during COH procedure. Hence, we cannot exclude that longer treatment periods also in non-PCOS may significantly improve additional ART outcomes.

Conclusions

The present study compares two COH approaches (stimulation with rFSH versus stimulation with rFSH associated to myo-Ins supplementation), demonstrating the benefits associated with myo-Ins administration during ART procedures in terms of cost-effectiveness, in addition to reducing the risk of OHSS. The use of myo-Ins allows the reduction of the required amount of rFSH and consequently the overall cost for single embryos produced and transferred immediately after COH or following cryopreservation. According to the evidence on the benefits of associating myo-Ins treatment to rFSH stimulation for women with PCOS, this work demonstrates that COH with rFSH and myo-Ins should be considered a dominant strategy also for non-PCOS patients that undergo ART. This translates to a potential significant reduced financial impact on the Italian health system.

Abbreviations

α-LA	α-lactalbumin
AMH	Anti-Müllerian hormone
AR	Abortion rate
ART	Assisted reproductive technologies
BMI	Body Mass Index
COH	Controlled ovarian stimulation
E2	Estradiol
FA	Folic acid
FSH	Follicle-stimulating hormone
GDM	Gestational Diabetes Miletus
HOMA-IR	Homeostatic Model Assessment of insulin resistance
ICSI	Intracytoplasmic sperm injection
IR	Insulin resistance
IVF	In-vitro fertilization
Myo-ins	myo-Inositol
OHSS	Ovarian hyperstimulation syndrome
P4	Progesterone
PCOS	Polycystic ovary syndrome
rFSH	Recombinant follicle-stimulating hormone
s.c	Subcutaneous
US	Ultrasound

Author contributions

C.A gathered and analyzed data utilized in this study. C.A, M.R, S.H.M, and V.U conceptualized the study. C.A, M.R, S.H.M were major contributors to writing the manuscript. C.A, M.R, S.H.M, M.S.B.E, G.B, and V.U read, edited, and approved the final manuscript.

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Data availability

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

Declarations

Ethical approval and consent to participate

Ethical approval was granted from the Alma Res Fertility Center in Rome (Italy). The approval of study was recorded as n°2/2024 by the Institutional Review Board of ALMA RES IVF Center and conducted according to the ethical principles of the Declaration of Helsinki. Written consent was obtained from all participants.

Competing interests

M.R, S.H.M, and V.U are employees of Lo.Li. pharma s.r.l. All other authors report no conflict of interest.

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