Abstract. – OBJECTIVE: Polycystic ovary syndrome (PCOS) is an endocrinological and metabolic disorder widely diffused and diagnosed in women of reproductive age. The pathology exhibits alteration of the reproductive functions, including conditions as hyperandrogenism, menstrual cycle irregularity, type 2 diabetes. These conditions are visible in the patients through phenotypical manifestations as hirsutism, acne, and obesity. Even if the syndrome is characterized by common features among both adult and adolescent women, the diagnostic criteria are different for the two age categories and to date still controversial. We investigated different treatments in PCOS adolescents with non-severe metabolic conditions, to evaluate which could be the appropriate therapeutic approach for these patients.

PATIENTS AND METHODS: We enrolled lean teenagers with PCOS, and we divided the patients in two age ranges: 13-16 years old and 17-19 years old. They were treated for 3 months either with oral contraceptive pills (OCP) drospirenone/ethinylestradiol (group A), myo-Inositol (myo-Ins) (group B), or OCP plus myo-Ins (group C). Data were analyzed with a descriptive statistics summarizing quantitative variables including median, 25th and 75th percentiles.

RESULTS: We pointed out that the group of 13-16 years old lean teenagers treated with myo-Ins exhibit a significant decrease of weight and body mass index (BMI), and an effective improvement the metabolic and hormonal parameters achieved with a non-pharmacological treatment. In the older teenagers aged 17-19 years, data highlights that myo-Ins treatment in combination with OCP prevents the increases of weight and BMI, improves the metabolic profile of the patients, and strongly ameliorates the hormonal parameters analyzed.

CONCLUSIONS: The results indicate a different scenario in the two age ranges considered and interestingly suggest an important role of myo-Ins in the PCOS context. A therapy based on this natural compound alone or in combination with OCP seems effective to improve both metabolic and hormonal parameters of PCOS adolescents and thus could represent a novel and valid option to consider for the treatment of this syndrome.

Key Words: Myo-Inositol, PCOS, Lean PCOS teenagers, α-lactalbumin.

Introduction

Polycystic ovary syndrome (PCOS) is nowadays considered the most common metabolic and endocrinological disorder in women of reproductive age1, with an estimated prevalence worldwide between 6 and 20%2. The pathology is characterized by hallmarks including biochemical or phenotypical hyperandrogenism, menstrual dysfunction (irregular bleeding) and polycystic-like ovarian morphology3. According to the Rotterdam criteria, the PCOS diagnosis is assigned when at least two out of three of these features are observed4. The causes of the syndrome are to date still unclear considering the complex pathophysiology, the multiple clinical aspects and the insufficient experimental data published.

Patients affected by PCOS exhibit altered neuroendocrine regulation of gonadal function.
Dysregulation of hypothalamic network is frequently associated with altered gonadotropin secretion, particularly the luteinizing hormone (LH) and the follicle-stimulating hormone (FSH)\(^5\). This condition of high LH production and increased LH/FSH ratio alters the folliculogenesis and the physiological steroidogenesis\(^6\). In the ovary, theca and granulosa cells respectively possess LH and FSH responding elements\(^6\). During the folliculogenesis, LH induces androstenedione production in the theca, while FSH promotes the conversion of androstenedione to estrone via aromatase activity in the granulosa cells\(^7\). In PCOS patients, high LH levels overstimulate theca cells inducing hyperplasia, and enhance the androgen production favoring hyperandrogenism occurrence\(^7\). Furthermore, the dysregulation of gonadotropin signaling can provoke follicle arrest at the preovulatory stage, leading to the characteristic polycystic appearance of the ovary\(^8\).

PCOS frequently occurs during adolescence. In this context, the diagnosis of the syndrome is different, considering the difficulty to adopt the same parameters as in adult patients\(^8\). Commonly, abnormal uterine bleeding pattern coupled with evidence of hyperandrogenism as high testosterone (T) levels or moderate-severe hirsutism are accepted as diagnostic criteria in adolescence\(^10\). Often in adolescence, the phenotypic expression of the pathology as hyperandrogenism is visible through esthetic effects, such as acne, hirsutism, acanthosis nigricans, and obesity. Being these effects highly noticeable, during the adolescence they can lead to burdensome complications in the psyche of these young girls\(^11\).

Combined oral contraceptive pills (OCPs) are widely prescribed to treat PCOS manifestations. OCPs contain both an estrogen derivate and a progestogen, acting primarily through inhibition of the ovulation via negative feedback to the hypothalamus and thickening of the cervical mucus\(^12\). The contraceptive therapy is proven to restore the correct menstrual pattern, and to significantly reduce the hyperandrogenic manifestations in PCOS patients\(^13\). However, evidence collected by clinical experience demonstrates the existence of side effects for prolonged OCP treatments that may vary from the simple weight gain to alteration of the cardiometabolic parameters\(^14\). Given these findings, the treatment approach adopted is the prescription of OCPs with different anti androgenic potential\(^15\) or the evaluation of alternative treatments\(^16\).

Frequently, PCOS is associated with forms of insulin resistance (IR) and diabetes\(^17,18\), and the condition worsens in the overweight-obese PCOS women affected by a more severe dysmetabolism and insulin insensitivity\(^19\). OCPs are usually adopted as treatment for hirsutism and irregular menses but not for obesity, IR or type-2 diabetes mellitus\(^20\).

Therefore, besides OCPs, PCOS treatment requires the use of insulin sensitizers\(^21\) like myo-Inositol (myo-Ins)\(^22,23\). As PCOS is typically characterized by ovarian alteration of the inositol profile\(^24\), treatments based on inositol, in particular myo-Ins, have been widely investigated in this pathological context. Evidence highlights a pivotal role of inositols in the physiology of the reproductive system, in the improvement of the metabolic parameters and in promoting positive outcomes in assisted reproductive techniques\(^25-27\).

Myo-Ins, an important constituent of follicular microenvironment, seems effective in PCOS treatment, promoting oocyte development and maturation, and mediating FSH signaling\(^28\). Additionally, acting as second messenger of insulin myo-Ins improves hormonal and metabolic parameters in PCOS patients by reducing insulin plasma levels, homeostasis model assessment index (HOMA index), as well as LH, LH/FSH, T, and prolactin\(^29\).

Myo-Ins treatment ameliorates PCOS condition, particularly in the teenager patients\(^30\). The positive effects of its administration along with the absence of side effects\(^31\), led the way to a possible long-term use of this molecule alone or in association with OCPs\(^32,33\). In adolescents affected by PCOS, myo-Ins may represent a safe and effective therapy to counteract clinical manifestations, to restore the correct menstrual cycle, and to prevent further complications.

Giving the variable pathological scenario, a clinical approach commonly accepted is lacking to date. In this study we excluded overweight-obese teenagers to uniform the conditions and to better understand the treatment efficacy in non-severe metabolic conditions. We treated the adolescents with myo-Ins and OCPs in single administration and in combination to evaluate which could be the appropriate clinical approach for young women affected by PCOS. This study is an extension of a previous clinical study which demonstrates that the administration of myo-Ins represents an effective approach to prevent and ameliorate metabolic alterations in PCOS teenagers. When myo-Ins is combined with OCPs
an improved antiandrogenic effect is observed, along with an improvement of the metabolic profile and a rebalance of the weight gain induced by OCP treatment alone\cite{30}.

Therefore, the aim of this study is to investigate the effects of different therapies in lean PCOS teenagers and to evaluate if the administration of the OCPs can be avoided in case the prescription is not strictly required.

### Patients and Methods

One hundred eighteen adolescent girls aged 13-19 affected by PCOS were enrolled in the study. The diagnosis was assigned according to Adolescent Diagnostic Criteria\cite{10}.

Patients within two years of menarche, and those with Body Mass Index (BMI) >25 kg/m\(^2\) were excluded from the study.

Part of the participants were enrolled in Georgia at the Archil Khomasuridze Institute of Reproduction before 2016. The remainder of the participants was enrolled between May 2020 and March 2021 at Agunco Medical Center, Rome, Italy.

The participants and/or their mothers (guardians) signed and approved a written consent according to the declaration of Helsinki before participating to the trial and the Ethical Committee from Archil Khomasuridze Institute approved the study in Georgia while the Internal Review Board of Agunco approved the study in Italy. A healthy lifestyle was firstly recommended to all the patients as nonpharmacological approach, with reduced carbohydrate intake and gentle exercise.

Patients were stratified in two groups by age: first group 13-16 and second group 17-19. Then, they were randomly divided into three different treatment groups. Group A: 21 patients aged 13-16 and 19 patients aged 17-19 receiving monophasic low-dose combined OCP (drospirenone 3 mg/ethinylestradiol 0.03 mg, Bayer Health Care Pharmaceuticals), taken in the evening in a cyclic regimen (21 days) for 3 months; group B: 18 patients 13-16 and 20 patients 17-19 treated with myo-Ins (2 g myo-Ins, 50 mg α-lactalbumin, 200 mcg folic acid, Lo.Li. pharma s.r.l., Rome, Italy) twice a day for 3 months; group C: 19 patients 13-16 and 21 patients 17-19 treated with a combination of drospirenone/ethinylestradiol and myo-Ins in the same regimen for 3 months.

The analysis of the parameters was conducted at baseline and after 3 months of treatment.

### Statistical Analysis

Descriptive statistics summarizing quantitative variables including median, 25th and 75th percentiles. Kruskal-Wallis Test was performed to compare differences among the three groups, while Wilcoxon Two-Sample Test was used in order to evaluate differences between groups in pairs for the parameters evaluated in the study. Changes from baseline were analysed using the Wilcoxon signed rank sum test. Statistical analysis was implemented at two-sided with a 0.05 significance level, using SAS® version 9.4 (SAS Institute Inc. 100 SAS Campus Drive Cary, NC, USA) and StataTM version 8.2 (StataCorp LLC, College Station, TX, USA).

### Results

Patients were divided in two groups according to their age as: 13-16 and 17-19 years.

Patients’ characteristics at baseline exhibit no significant differences between the three treatment groups (Table I).

#### Adolescents 13-16 Years Old

The younger teenagers (13-16 years old) of the group A treated with OCP (drospirenone/ethinylestradiol) exhibited weight increase after treatment, with a median value of the variations of 1 kg. Myo-Ins administration significantly contrasted the weight gain in group B and C, compared to group A. The treatment with myo-Ins reduced the weight by respectively a median value of 1.25 kg in group B and of 1 kg in group C (Table II). The same trend was observed for BMI with a reduction detected in group B and group C respectively of a median value of 0.50 and 0.38 kg/m\(^2\) (Table II). The variations between groups B and C vs. group A were both significant, while no significant difference was observed between group B and C variations.

The LH/FSH reduction observed over the treatment period was significant in every treatment group, with a similar variation detected in group A and group C. The differences between the variation observed in group A and group C were not significant, while the variations between group A and group B and those between group B and group C were both significant.

The 13-16 years teenagers exhibited a significant reduction in T levels measured in each treatment adopted. The variations comparison between group A and group B was not significant.
while the variation observed in group C significantly affected the T reduction, compared to the variations measured in groups A and B. A similar trend was reported for free testosterone (free T), in which a significant reduction was observed in every treatment group considered. The combined treatment in group C induced no significant variation of free T with respect to the single treatment in group A and B. A significant variation was observed in the free androgen index (FAI) in group B and C, indicating that OCP is more effective to down-regulate the free androgens in the 13-16 years teenagers. The sex hormone binding protein (SHBG) expression resulted significantly increased in each treatment group considered. The comparison of the variations indicated that group C exhibited a greater increase of SHBG parameter over the treatment period.

Data are indicated as median value and in parenthesis the 25th and 75th percentiles. For each parameter, the significance of the differences between the treatment groups is expressed with the p-value. Body mass index (BMI), testosterone (T), free testosterone (free T), homeostasis model assessment index (HOMA index), oral contraceptive pills (OCP), myo-Inositol (myo-Ins).

Table I. Baseline values in the treatment groups.

<table>
<thead>
<tr>
<th>Baseline group 1: adolescents 13-16 years old</th>
<th>OCP (group A)</th>
<th>myo-Ins (group B)</th>
<th>OCP + myo-Ins (group C)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>53 (52-56)</td>
<td>55.5 (51.3-59.8)</td>
<td>56 (54.5-58)</td>
<td>0.222</td>
</tr>
<tr>
<td>BMI</td>
<td>19.6 (19.2-20.8)</td>
<td>21.63 (20.4-22.6)</td>
<td>21.9 (21.23.7)</td>
<td>0.328</td>
</tr>
<tr>
<td>T</td>
<td>0.6 (0.5-0.7)</td>
<td>0.8 (0.7-0.9)</td>
<td>0.8 (0.7-0.9)</td>
<td>0.365</td>
</tr>
<tr>
<td>Free T</td>
<td>3.7 (3.5-3.9)</td>
<td>3.8 (3.2-3.8)</td>
<td>2.9 (2.6-3)</td>
<td>0.949</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.5 (1.4-1.5)</td>
<td>1.3 (1.2-1.3)</td>
<td>1.8 (1.7-1.8)</td>
<td>0.365</td>
</tr>
</tbody>
</table>

Data referred to the variation over the treatment period calculated with Wilcoxon Two-Sample Test. *p < 0.05, **p < 0.01, ***p < 0.001 – Significant variations with respect to the baseline. *Significant variation (p < 0.05) group A vs. group B, †Significant variation (p < 0.05) group A vs. group C, §Significant variation (p < 0.05) group B vs. group C.

Table II. Parameters analyzed in the treatment groups of teenagers aged 13-16 years.

<table>
<thead>
<tr>
<th>Group 1: adolescents 13-16 years old</th>
<th>OCP (group A)</th>
<th>myo-Ins (group B)</th>
<th>OCP + myo-Ins (group C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>1.00***</td>
<td>-1.25***</td>
<td>-1.00**†</td>
</tr>
<tr>
<td>BMI</td>
<td>0.37***</td>
<td>-0.50***</td>
<td>-0.38***†</td>
</tr>
<tr>
<td>FSH</td>
<td>0.70***</td>
<td>-0.25*</td>
<td>0.10***§</td>
</tr>
<tr>
<td>LH</td>
<td>-2.60***</td>
<td>-2.00***</td>
<td>-3.40***§</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>-0.82***</td>
<td>-0.42***</td>
<td>-0.81***§</td>
</tr>
<tr>
<td>T</td>
<td>-0.20***</td>
<td>-0.10**</td>
<td>-0.40***§</td>
</tr>
<tr>
<td>FAI</td>
<td>-3.50***</td>
<td>-0.15**</td>
<td>-2.20***</td>
</tr>
<tr>
<td>Free T</td>
<td>-1.60***</td>
<td>-1.30***</td>
<td>-1.10***</td>
</tr>
<tr>
<td>SHBG</td>
<td>10.40***</td>
<td>5.25***</td>
<td>21.30***§</td>
</tr>
<tr>
<td>IRI</td>
<td>0.10</td>
<td>-2.25***</td>
<td>-2.00***</td>
</tr>
<tr>
<td>glyc</td>
<td>-0.20***</td>
<td>-0.35***</td>
<td>-0.20*</td>
</tr>
<tr>
<td>HOMA</td>
<td>-0.04</td>
<td>-0.54***</td>
<td>-0.45***§</td>
</tr>
</tbody>
</table>
The metabolic pattern was measured through immunoreactive insulin (IRI), glycemia (glyc) and HOMA index. In the 13-16 years teenagers IRI was significantly decreased in group B and group C, but no significant variations were detected in group A. The myo-Ins administration in group B reduced IRI more than the other treatments. In a similar trend, myo-Ins significantly decreased glyc in group B more than the other treatments, with a reduction value of 0.35. No significant differences in the variations were observed in group B and group C. Instead, the HOMA index variation was slightly increased in group A but not significantly, with a median value of 0.06. In group B and C, the HOMA index was significantly reduced with a median value of respectively 0.64 in group B and 0.45 in group C.

Adolescents 17-19 Years Old

In the older teenagers (17-19 years) the analysis of the weight and BMI parameters exhibited an analogue trend as observed in the younger patients (13-16 years). In detail, group B and group C reported a significant reduction of body weight and BMI. No significant difference was observed comparing the variations in group B and in group C. On the other hand, in group A was observed a significant increase of body weight with a median value of 1 kg, and a significant BMI variation with a median value of 0.35 (Table III). The difference in the variations observed after treatment in group B and C was not significant.

### Table III. Parameters analyzed in the treatment groups of teenagers aged 17-19 years.

<table>
<thead>
<tr>
<th>Group 2: adolescents 17-19 years old</th>
<th>OCP (group A)</th>
<th>myo-Ins (group B)</th>
<th>OCP + myo-Ins (group C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight 1.00***</td>
<td>-1.25***</td>
<td>-1.00*†</td>
<td></td>
</tr>
<tr>
<td>BMI 0.35***</td>
<td>-0.51***</td>
<td>-0.37†</td>
<td></td>
</tr>
<tr>
<td>FSH 0.50***</td>
<td>-0.15†</td>
<td>0.3†</td>
<td></td>
</tr>
<tr>
<td>LH -2.50***</td>
<td>-2.25***</td>
<td>-3.00***</td>
<td></td>
</tr>
<tr>
<td>LH/FSH -0.79***</td>
<td>-0.49†</td>
<td>-0.78***</td>
<td></td>
</tr>
<tr>
<td>T -0.20***</td>
<td>-0.10*</td>
<td>-0.50***</td>
<td></td>
</tr>
<tr>
<td>FAI -3.40***</td>
<td>-1.40***</td>
<td>-4.60***</td>
<td></td>
</tr>
<tr>
<td>Free T -1.60***</td>
<td>-0.80***</td>
<td>-1.40***</td>
<td></td>
</tr>
<tr>
<td>SHBG 9.90***</td>
<td>6.25†</td>
<td>15.40***</td>
<td></td>
</tr>
<tr>
<td>IRI 0.60</td>
<td>-2.85***</td>
<td>-2.00***</td>
<td></td>
</tr>
<tr>
<td>glyc -0.10***</td>
<td>-0.30***</td>
<td>-0.20**</td>
<td></td>
</tr>
<tr>
<td>HOMA 0.06</td>
<td>-0.64***</td>
<td>-0.45**</td>
<td></td>
</tr>
</tbody>
</table>

Data referred to the variation over the treatment period calculated with Wilcoxon Two-Sample Test. *p < 0.05, **p < 0.01, ***p < 0.001-Significant variations with respect to the baseline. †Significant variation (p < 0.05) group A vs. group B, §Significant variation (p < 0.05) group A vs group C. †Significant variation (p < 0.05) group B vs. group C.
Discussion

PCOS is a prevalent endocrinopathy in females with a strong impact that worsens the patients’ quality of life. PCOS occurrence is due to multifactorial causes, including genetic, epigenetic, endocrine, and environmental factors, and brings to a series of pathophysiological implications. The etiology of PCOS is frequently associated with a neuroendocrine imbalance affecting ovarian physiology. Patients often present hyperandrogenism associated with aberrant oocyte maturation, and premature arrest of activated primary follicles. Phenotypically this impaired reproductive network is associated to hallmarks, including irregular menses, hirsutism, chronic anovulation, and infertility.

Even if common features exist between adolescents and adult women with PCOS, differences in the diagnosis, treatments and etiopathogenesis suggest discriminating the clinical approach to adopt in the two different classes. PCOS diagnosis in adolescents is more challenging than in adults, considering that conditions as hyperandrogenism and oligo-anovulation are frequent in the puberty period and generally come to a resolution without intervention. Young women usually exhibit a physiologically unbalanced hormonal panel, which characterizes the reproductive maturation and needs time to normalize. For this reason, a standard definition of PCOS in teenagers is still controversial.

The first-line treatment in adolescents with PCOS are OCPs, proven to reduce androgen excess, acne, and hirsutism. The treatment with OCPs increases the levels of SHBG after 3 months and reduces hirsutism after 6 months. Furthermore, OCPs may be prescribed to manage menstrual irregularity in lean PCOS girls not presenting metabolic comorbidities.

In an important percentage of cases, PCOS patients develop forms of IR associated with endocrine disorders and dysmetabolism of glucose. Interestingly, these patients are characterized by an increased incidence of diabetes, especially type 2, as described by several population and case-control studies. Evidence demonstrates that women in reproductive age, affected by metabolic abnormalities, often present myo-Ins depletion in the ovary district, leading to the idea that PCOS women may benefit from myo-Ins. Indeed, myo-Ins administration to PCOS women reduces hyperandrogenism and improves altered metabolic profile. The efficacy of therapy based on insulin sensitizer as myo-Ins has been evaluated through investigation of single treatment with myo-Ins compared with a combined administration of myo-Ins plus OCPs. A clinical study performed with drospirenone/ethinylestradiol OCP and myo-Ins on PCOS adolescents revealed that myo-Ins counteracts the weight gain induced by the OCP and prevent the BMI increase. Furthermore, it improves the insulinemic condition and the glucose metabolism of the patients, also ameliorating their hormonal profile. The administration of myo-Ins together with OCP reduces the LH secretion and downregulates the androgens production, as for the free T.

In similar condition, in the present study we treated lean PCOS teenagers to compare the efficacy of myo-Ins and oral contraceptives. The results of our study provide two different scenarios associated with the age ranges considered. In the younger teenagers (13-16 years) the treatment with myo-Ins results as effective as OCPs in the treatment of the PCOS manifestations. Interestingly drospirenone/ethinylestradiol induce a weight gain and a BMI increase, but this trend is clearly reversed in presence of myo-Ins. The groups treated with myo-Ins exhibit a significant decrease in body weight and BMI, highlighting its positive activity in counteracting one of the most visible OCPs side effect.

We observed a significant reduction in T and in free T levels in every treatment group with no significant difference between OCP and myo-Ins treatment. The only difference between the treatments regarding the androgen profile is observed in FAI, showing a significant variation in group B and C, indicating that OCP modulates this parameter more efficiently in the teenager aged 13-16. Regarding the hormonal profile, we also observed a significant increase of SHBG expression in the different groups, suggesting that both myo-Ins and OCP are able to influence the hormonal parameters evaluated. We did not observe any significant difference between the two treatments, and no significant improvement was observed with the combined administration of myo-Ins and OCP.

The metabolic pattern evaluated in the paper indicates that myo-Ins treatment in teenagers 13-16 years significantly decreases IRI and glyce more efficiently than the other treatments. An analogues effect is observed for the HOMA index significantly reduced in presence of myo-Ins and slightly increased with the OCP treatment.
The results collected confirm the positive role of myo-Ins administration in the improvement of metabolic PCOS parameters\(^7\).

Taken together these data introduce a potential novel approach based on myo-Ins in the treatment of lean PCOS younger teenagers. We highlighted for the 13-16 years group of patients, a positive effect of myo-Ins in ameliorating the metabolic condition and in counteracting weight and BMI increase induced by OCP treatment. Considering the comparable improvement achieved by the two treatments and the known side effects for prolonged OCPs administration\(^8\), myo-Ins treatment would be a more suitable choice for younger patients (13-16 years old target). Myo-Ins may represent a potential starting treatment for teenagers with PCOS, bypassing invasive pharmacological therapy, until the hormonal fluctuations become stable, and the clinical picture becomes more defined as described in the Rotterdam criteria. A softer approach with a natural molecule leads the possibility to postpone the OCPs therapy, improving in a similar rate the PCOS outcomes.

In the group of lean teenagers aged 17-19, the PCOS context changes as the OCP treatments are mainly prescribed for contraceptive purpose. For this age range, we observed several improvements in patients treated with the association of myo-Ins and OCP that guarantees an effective PCOS therapy and reduces the side effects of the pharmaceutical. The variations observed over the treatment period demonstrate that OCP treatment likely increase the body weight and consequently the BMI while myo-Ins administration significantly reduces these parameters. A stronger decrease in weight and BMI is observed when myo-Ins is combined with OCP, suggesting that the association enhances the effect of the single treatments.

Additionally, in the 17-19 years old teenagers, the association of myo-Ins and OCP induces a significant decrease in the LH/FSH ratio. The therapy also leads to a significant reduction in T and FAI over the treatment period, with a stronger rate compared to single treatments. Furthermore, free T levels significantly decreased with OCP plus myo-Ins treatment and the variation observed is comparable to that obtained with the administration of OCP alone. The modulation of the androgens in the older group of teenagers enrolled (17-19 years) suggests that the combination of myo-Ins and OCP may enhance the improvement of the parameters with respect to single treatments.

A synergistic effect of the administration of OCP and myo-Ins is highlighted also for SHBG, with a reduction significantly higher compared to the variations detected with single treatments. The modulation of the metabolic parameters observed for myo-Ins in the 13-16 years old group is detectable also in the 17-19 years patients. Thus, IRI, glyc and HOMA index are significantly reduced following myo-Ins treatment, either alone or in combination with OCP.

These data support the concept that a co-treatment with myo-Ins and OCP ameliorates the condition of lean adolescent PCOS in the 17-19 years group. The improvement in the hormonal parameters ensured by OCP seems enhanced in presence of myo-Ins. Likewise, myo-Ins associated with OCP counteracts the weight gain trend induced by OCP and improves the metabolic pattern in the older group. In the age range 17-19 years, when the OCP prescription is high both for PCOS treatment and for contraceptive purpose, the association of OCP with myo-Ins should be recommended as it improves the outcomes and the patient’s quality of life. Therefore, data indicate that myo-Ins allows an improvement in metabolic profile of PCOS patients that is not achievable with the only OCP treatment. Indeed, the reduction in weight and BMI observed seems reasonably associated with the improvement in metabolic parameters following myo-Ins treatment, either alone or with OCP.

Further investigations will be necessary to confirm the data gathered in the present study. Given the limited treatment period examined, the continuation of this trend during a prolonged therapy should be confirmed. Also, considering the absence of side effects documented during myo-Ins treatment, such molecule may represent both a safe alternative to OCPs or a co-treatment.

**Conclusions**

PCOS teenagers are patients with a complex hormonal and metabolic physiology. Myo-Ins treatment, instead of the prescription of OCP, should be evaluated to treat PCOS in younger adolescents (13-16 years). This approach guarantees improvements in weight and BMI parameters, ensures an effective improvement of the metabolic parameters, and could avoid or postpone pharmacological therapy during the adolescence of young women. In this way, prolonged treatments with myo-Ins could be prescribed, as they
come without the side effects of the OCPs, during the period in which the clinical pictures of the patients move toward more defined conditions. Myo-ins may represent a safe and functional therapy to treat the younger PCOS teenagers with a non-pharmacological approach.

The older teenagers (17-19 years) are mostly treated with OCPs, given the increasing demand of those pills both for anti-conceptional purpose and to counteract PCOS symptoms. In this context, the administration of myo-Ins combined with OCP counteracts the weight gain and the BMI increase caused by the pharmaceutical, guaranteeing a better improvement in the altered parameters than the OCP alone treatment.

In PCOS adolescent scenario, myo-Ins supplementation is a valid option for the treatment of the pathology, given its effective impact on PCOS parameters and on adolescents' quality of life.

Conflict of Interest
Michele Russo and Vittorio Unfer are employees at Lo.Li. Pharma s.r.l. (Rome, Italy). Vittorio Unfer is the inventor of the Italian patent No. 10201700010446 for the association of inositols and α-lactalbumin. All other authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service or company.

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Data Availability Statement
The datasets generated during and/or analyzed during the current study are not stored in a public repository but are available from the corresponding author on reasonable request.

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