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International Journal of Current Research
Vol. 9, Issue, 07, pp.54006-54011, July, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

POLYCYSTIC OVARY SYNDROME IN ADOLESCENCE: NEW THERAPEUTIC APPROACH WITH INOSITOL AND ALPHA-LIPOIC ACID

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ARTICLE INFO

Article History:
Received 03rd April, 2017
Received in revised form
17th May, 2017
Accepted 24th June, 2017
Published online 26th July, 2017

Key words:

Adolescents,
Polycystic Ovary Syndrome,
Inositol and Alpha-lipoic acid.

ABSTRACT

Objective: To evaluate the efficacy of a new therapeutic approach in adolescents with Polycystic Ovary Syndrome (PCOS), based on Alternative Insulin Sensitizers as Inositol and α-Lipoic Acid, natural antioxidant, at the dose, twice daily.
Design: Retrospective study.
Setting: University of L'Aquila, San Salvatore Hospital, Pediatric Department
Patients: 26 female adolescents (mean age 14.7 ± 1.9)
Intervention: Therapeutic approach with inositol and alpha-lipoic acid for 6 months
Main outcome measures: Anthropometric data were assessed both at baseline time (time 0) and after therapeutic intervention (time 1) together with oral glucose tolerance test, luteinizing hormone releasing hormone stimulation test and hormonal profile.
Results: After a six-months treatment, the patients showed a reduction in body weight and BMI(24.25 ± 5.21 vs 23.54 ± 4.97, p 0,01), significant improvement of Testosterone (0.60 ± 0.37 vs 0.45 ± 0.19, p 0,03), Triglycerides (75.07 ± 24.84 vs 64.61 ± 30.05, p 0,008) and serum basal luteinizing hormone (LH) concentration (5.24 ± 2.96 vs 4.34 ± 2.60), as well as augmented insulin sensitivity (HOMA-IR 2.41 ± 1.71 vs 1.67 ± 2.05, p 0,03).We also found a positive correlation between the decrease of LH levels and Testosterone levels, DHEAS, D4-Androstenedione and Total Cholesterol. Moreover all adolescents showed hirsutism and acne reduction and the menstrual cycle regularisation.
Conclusion: In adolescents with PCOS, treatment based on Alternative Insulin Sensitizers as Inositol and α-Lipoic Acid represents the most suitable choice both for clinical evidence of efficacy and for the absence of side effects.

Citation: Maria Laura Iezzi, Gaia Varriale, Nunzia Torge, Stefania Lasorella, Luca Zagaroli and Alberto Verrotti, 2017. "Polycystic ovary syndrome in adolescence: New therapeutic approach with inositol and alpha-lipoic acid", *International Journal of Current Research*, 9, (07), 54006-54011.

INTRODUCTION

Polycystic ovary syndrome (PCOS) represents a very complex and heterogeneous condition defined by specific clinical, biochemical and ultrasound criteria. The PCOS is the most common endocrine disorder among women of reproductive age, it is the most common androgen excess disorder accounting for 72-84% of adult hyperandrogenism (Azziz *et al*., 2004; Carmina *et al*., 2004; Huang *et al*., 2010). In adult women, PCOSclassic clinical presentation may include: menstrual irregularities, chronic anovulation associated with infertility, polycystic ovarian morphology, hirsutism and obesity with hyperinsulinemia and increased risk of type 2 diabetes (Stein and Leventhal, 1935). A uniform definition of PCOS does not exist, due to its wide and heterogeneous nature. It is clear to us, however, that the disorder is an endocrinopathy, and thus it should be considered as a syndrome, rather than as a disease (Carmina and Rogerio A. Lobo, 2013). Three international conferences provided the diagnostic criteria for the diagnosis of PCOS. First the National Institutes of Health (NIH) conference criteria (1990) included the presence of clinical and/or biochemical hyperandrogenism, chronic anovulation and exclusion of other causes of these symptoms (Zawadski and Dunaif, 1992). The Rotterdam consensus criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Work-shop Group) (2004) defined PCOS as an ovarian dysfunction syndrome along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology and no single diagnostic criterion was considered sufficient for clinical diagnosis, which required the presence of at last two of the three diagnostic criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). In 2006 the Androgen Excess-PCOS Society defined PCOS by the presence of clinical and/or

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biochemical hyperandrogenism and one additional criterion between chronic anovulation/ovarian dysfunction and/or polycystic ovaries documented by ultrasonography (Azziz *et al*., 2006). In 2009 these criteria were further consolidated by the Task Force statement (Azziz *et al*., 2009). PCOS is also associated with a number of metabolic disorders, such as insulin resistance and compensatory hyperinsulinemia, dyslipidemia and obesity; the high prevalence of insulin resistance and hyperisulinemia among adolescent with PCOS is well recognized (Witchel *et al*., 2015), both in lean or obese girls and exacerbate the hyperandrogenism and reproductive and metabolic manifestations of PCOS, as well as acutaneous nigricans, acutaneous manifestation of insulin resistance, (Hecht Baldauff and Arslanian, 2015). Insulin resistance, defined as decreased insulin-mediated glucose utilization, in both obese and non-obese women, is involved in the development of cardiometabolic disturbances such as dysglycaemia, hyperlipidemia, type 2 diabetes, hypertension and myocardial infarction (Reem *et al*., 2015). The cause of the insulin resistance is not yet clear, but a post-receptor defect that could affect glucose transport has been proposed (Baillargeon *et al*., 2006; Dunaif, 1997). Inositolphosphoglycans (IPGs) second messenger pathway is known to have a role in activating enzymes that control glucose metabolism. The insulin resistance may be induced by a defectin the inositol phosphoglycans (IPG) second messenger due to Inositol scarcicity in tissue or an altered metabolism of inositol or IPG mediators (Nordio and Proietti, 2012; Gooding *et al*., 2014; Genazzani *et al*., 2014).

These recent knowledges have opened a new horizon in the clinical management of PCOS. Inositol belongs to the vitamin B complex and it is epimerized in our body into nine stereoisomers, among them myo-inositol (MYO) and D-chiro-inositol (DCI). Both these stereoisomers have been used in the treatment of PCOS patients (Galazis *et al*., 2011; Papaleo *et al*., 2009). To date, studies and reviews clearly demonstrated that inositolo administration improves insulin resistance in PCOS patients, correcting also the hormonal profiles and ameliorating ovarian function both in spontaneous and in induced ovarian cycles, since it acts as a second messenger (Galazis *et al*., 2011; Morgante *et al*., 2011). Furthemore, recently, authors showed that the administration of inositol, combined with alpha lipoic acid (ALA), can be used as a dietary supplement in insulin-resistant patients in order to increase their insulin sensitiveness (Cianci *et al*., 2015). ALA is a potent natural antioxidant and an enzyme cofactor of the respiratory chain and its controlled release has been reported to improve the oxidative stress, implicated (Evans *et al*., 2003; Fenkci *et al*., 2003) in the molecular mechanisms of insulin resistance and to improve glucose control (Evans *et al*., 2002; Masharani *et al*., 2010). The original association of inositol and ALA represents one of the best association available showing an effective mechanism of action, leading to a reduction of the accompanying symptoms of the disease in these women (Cappelli *et al*., 2013). So far, all published data referred to adult population, therefore, the aim of our study was to evaluate the effects of myo-inositol and ALA combination in adolescent with PCOS disorders.

MATERIALS AND METHODS

Study population

We present a retrospective study, involving 26 female patients, visited in Pediatric Endocrinology and Adolescentology Clinic of L'Aquila. Thi girls referred to our service because of menstrual irregularities. The unique adopted criterion of inclusion was the diagnosis of PCOS according to Rotterdam's criteria. Patients who suffered of other associated endocrinological or chronic diseases were excluded from the study. The patients receveid oral administration with 1000 mg of inositol/die plus 400 mg of alpha-lipoic acid/twice die for six months period. Anthropometric data were assessed both at baseline time (T0) and after six months of therapeutic intervention (T1) together with oral glucose tolerance test (OGTT), luteinizing hormone releasing hormone stimulation test (LHRHT) and hormonal, lipemic and metabolic profile. Height was measured to the nearest 0,1 cm using a wall-mounted Harpenden stadiometer; body weight was measured to the nearest 0,1 kg and body mass index (BMI) was calculated as weight in Kg/(heigth in m)^2. Puberty stage was estimated with Tanner scale. The Ferriman-Gallway score was used for the evaluation of hirsutism. The possibility of adverse events was assessed every three months throughout clinical monitoring and laboratory tests. Written informed consent for data collection was obtained from all subjects and parents at the moment of recruitment in the study and before the first data collection. All procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation.

Laboratory measurements

The blood sampling, by venipuncture with aseptic technique was performed in fasted patients for at least eight hours. To investigate hormonal profile, was somministrated LHRH test, iniecting i.v. a bolus of 100 μgr/m^2 of Luteinin Hormone Releasing Factor, (Lutrelef®) to dose simultaneously LH e FSH hormones at time 0, 10', 20', 40' and 60' after the stimulus. For the determination of LH has been used the ARCHITECT LH® test, a two-step chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of human luteinizing hormone (LH) in human serum and plasma. The test is automatically calculated the hormone's concentrations (expressed in mIU/mL), measuring between 0,09 and 250 mIU/mL, based on inter-assay precision of a CV (coefficient of variation) of 22% (functional sensitivity). For the determination of FSH has been used the ARCHITECT FSH® test, a two-step chemiluminescent microparticle immunoassay (CMIA). The test is automatically calculated the FSH's concentrations (expressed in mIU/mL), measuring between 0,00 and 150 mIU/mL, based on inter-assay precision of a CV (coefficient of variation) of 10% (functional sensitivity). For the determination of DHEA-S has been used the ARCHITECT DHEA-S® test, a deleyed one-step chemiluminescent microparticle immunoassay (CMIA). The test is automatically calculated the hormone's concentrations (expressed in microg/dL), measuring between 3,0 and 1500 microg/dL, based on inter-assay precision of a CV (coefficient of variation) of 10% (functional sensitivity). For the determination of Testosteron has been used the ARCHITECT 2nd Generation Testosterone® test, a deleyed one-step chemiluminescent microparticle immunoassay (CMIA). The test is automatically calculated the testosterone's concentration (expressed in nmol/L), measuring between 0,03 and 35 nmol/L, based on inter-assay precision of a CV (coefficient of variation) of 10% (functional sensitivity).

For the determination of Estradiol has been used the ARCHITECT Estradiol® test, a deleyed one-step

chemiluminescent microparticle immunoassay (CMIA). The test is automatically calculated the hormone's concentrations (expressed in nmol/L), measuring between 0,00 and 70,0 nmol/L, based on inter-assay precision of a CV (coefficient of variation) of 20% (functional sensitivity). For the determination of DHEA-S has been used the ARCHITECT DHEA-S® test, a deleyed one-step chemiluminescent microparticle immunoassay (CMIA). The test is automatically calculated the hormone's concentrations (expressed in microg/dL), measuring between 3,0 and 1500 microg/dL, based on inter-assay precision of a CV (coefficient of variation) of 10% (functional sensitivity). The determination of Delta-4-androstenedione was done with IMMULITE 2000® test, a chemiluminescent microparticle immunoassay (CMIA). The test is automatically calculated the hormone's concentration (expressed in ng/mL), measuring between 0,3 and 10 ng/mL, based on inter-assay precision of a CV (coefficient of variation) of 10% (functional sensitivity). To investigate the metabolic profile, an OGTT (oral glucose tollerance test) was performed (1,75 g/kg, max 75g pro capite) and plasma glucose and insulin was obtained to calculate the glucose/insulin ratio (glucose/insulin < 6: insulin resistance). The insulin resistance was estimated using the homeostasis model assessment (HOMA-IR); values > 2,5 indicated insulin resistance. For the determination of triglycerides, total and HDL cholesterol has been used ARCHITECT c Systems and the AEROSET System®, while for the LDL cholesterol the test used was MULTIGENT Direct LDL Assay®; both techniques based on immunoassay.

Statistical Analysis

Anthropometric and laboratory parameters were reported as mean values +/- standard deviation (SD). After checking whether the variables were normally distributed, Student's *t* test for matched data test was used to determine statistical differences in continuous variables before and after the treatment. In the entire group of patients, linear associations between variables were described using Spearman correlation coefficients (Rho). All values of $p < 0.05$ were considered statistically significant.

Ethics

The study was approved by Clinical Research Ethics Committee of San Salvatore Hospital. All subjects were counseled before recruitment and completed written informed.

RESULTS

The 26 female are in the age range 12-17 years (mean age 14.7 ± 1.9), having different grades of hirsutism, acne and obesity. The unique adopted criterion of inclusion was the diagnosis of PCOS according to Rotterdam's criteria. Baseline data of the patients are outlined in Table 1. Pre-treatment (T0) and post-treatment with inositol plus alpha-lipoic acid (T1) clinical and metabolic features are shown in Table 2. Student's *t* test for matched data evidences statistically significant reduction in

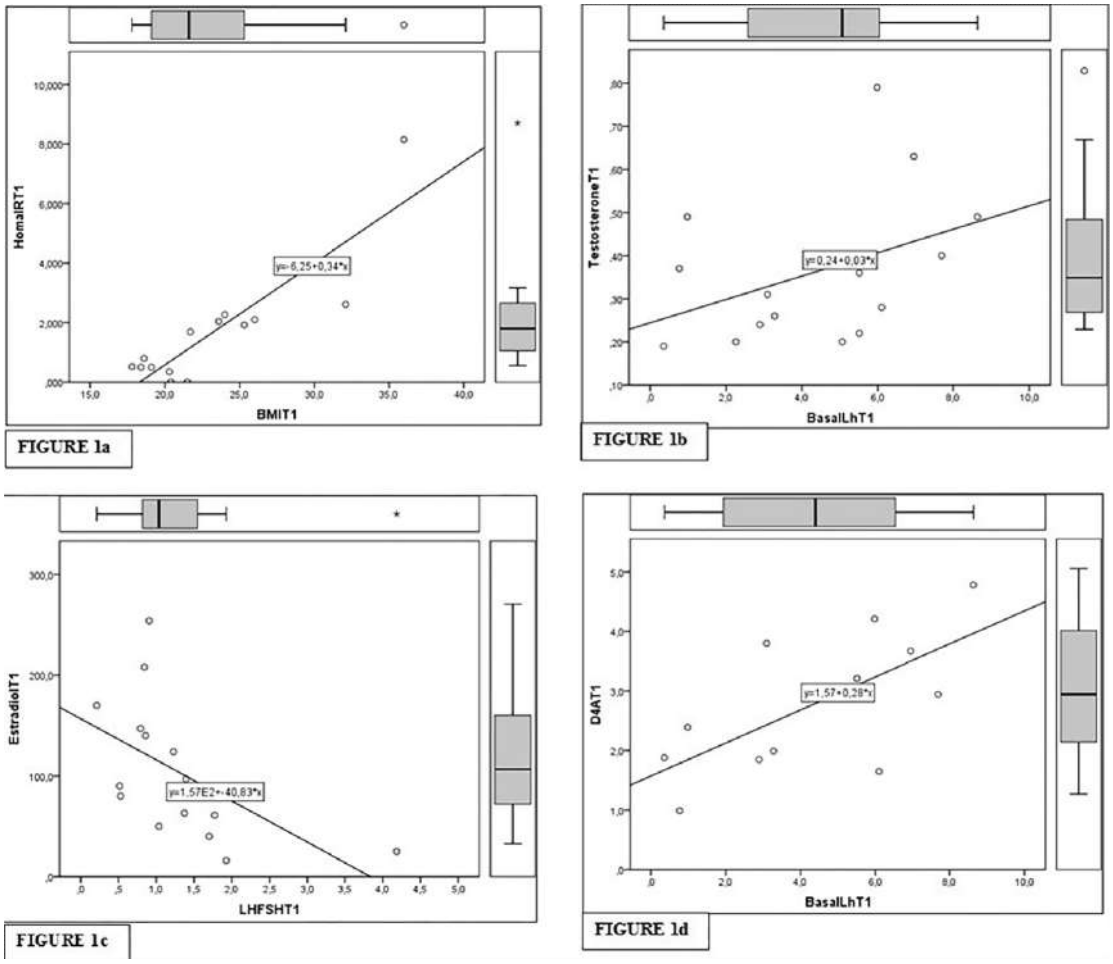

Figure 1. No-parametric correlation of Spearman after 6 months of treatment with inositol and α-lipoic acid between: 1a: BMI and HOMA-IR (Rho: 0,753; p: 0,002), 1b: basal LH and testosterone (Rho: 0,500; p: 0,05), 1c: LH/FSH ratio and estradiol (Rho: - 0,69; p: 0,004, 1d: basal LH and Delta-4-androstenedione (Rho: 0,573; p: 0,05)

Table 1. Baseline features in study population

Variables	Mean ± S.D. (n = 17)
Age at test (year)	14.7 ± 1.9
Weight (Kg)	65.51 ± 20.45
Height (cm)	160 ± 0.6
BMI (kg/m^2)	24.25 ± 5.21
Pubertal stage	P5B5

Table 2. Longitudinal analysis of anthropometric and biochemical data in patients

Parameters	T0	T1
Bmi	24.25 ± 5.21	23.54 ± 4.97*
Estradiol (e2)	40.8 ± 24.97	104.33 ± 68.95**
Basal fsh	4.21 ± 1.73	3.86 ± 1.68
Peak fsh	7.66 ± 2.89	9.12 ± 4.67
Basal lh	5.24 ± 2.96	4.34 ± 2.60*
Peak lh	29.25 ± 16.32	55.33 ± 78.25
Lh/fsh	1.22 ± 0.6	1.28 ± 0.94
Testosterone	0.62 ± 0.34	0.37 ± 0.18*
Dheas	238.85 ± 122.13	208.14 ± 136.30*
Delta 4-androstenedione	2.65 ± 1.70	3.19 ± 1.22
Cholesterol	157.15 ± 22.35	152.46 ± 20.80
Triglycerides	75.07 ± 24.84	64.61 ± 30.05*
Basal glycaemia	74.46 ± 10.50	72.93 ± 8.0
Peak glycaemia	136 ± 27.01	125.8 ± 20.52
Basal insulin	15.6 ± 10.85	12.2 ± 15.33*
Peak insulin	140.26 ± 47.79	118.74 ± 71.67
Homa-ir	3.09 ± 0.79	2.0 ± 0.83*

Legend: * p < 0,05 vs. T0; ** p < 0,01 vs. T0.

relation to patient's BMI (24.25 ± 5.21 vs 23.54 ± 4.97, p 0,01), triglycerides (75.07 ± 24.84 vs 64.61 ± 30.05, p 0,008), basal insulin 15.6 ± 10.85 vs 12.2 ± 15.33 p 0,017) with consequent improvement of the value of HOMA-IR (2.41 ± 1.71 vs 1.67 ± 2.05, p 0,03) the peak of insulin after OGTT was reduced too, but not statistically significant. In the same patients, there was a statistically significant reduction of basal LH (5.24 ± 2.96 vs 4.34 ± 2.60), testosterone (0.60 ± 0.37 vs 0.45 ± 0.19, p 0,03), DHEAS (238.85 ± 122.1 vs 208.14 ± 136.30) and improvement of estradiol (41.46 ± 25.3 vs 77.67 ± 74.5, p 0,040). Finally, no-parametric correlations of Spearman revealed statistically significant correlation between BMI and HOMA-IR at T1 (Rho 0.753, p 0.002), between basal LH and testosterone (Rho 0.500, p 0.05) and between basal LH and Delta-4-androstenedione (Rho: 0,573; p: 0,05) at T1 and a negative correlation between estradiol and LH/FSH post treatment (Rho -0.69, p 0.004) (Figure 1). None of the patients showed adverse events nor symptoms referable to the treatment.

DISCUSSION AND CONCLUSION

The etiology of PCOS is complex and not well understood; primary intrinsic ovarian pathology in combination with hypothalamic-pituitary-ovarian axis abnormalities may lead to increased ovarian androgen secretion, although various etiological factors are suspected to be involved. In the past decade, increasing compelling evidence has been accumulated supporting the central role of insulin resistance. Decrease in insulin sensitivity with a compensatory increase in insulin secretion and hyperinsulinemia may also play a role as it can lead to direct stimulation of ovarian synthesis of androgen by ovarian theca cells and inhibits hepatic production of sex hormone binding globulin (SHBG), and therefore, to an increased bioavailability of free testosterone level (Bizzarri and Carlomagno, 2014). This hyperandrogenism exacerbes the reproductive and metabolic manifestations of PCOS in adolescents however at the present time, none of the current definitions of PCOS include obesity, insulin resistance, or hyperinsulinemia as a diagnostic criterion (Witchel *et al*., 2015). Many studies demonstrated a beneficial effect of use of metformin on the metabolic and reproductive disturbances in this condition both in women and in adolescence (Bizzarri *et al*., 2014; Nestler *et al*., 2000). Though these treatments improve the ovarian function and reduce the hyperandrogenic condition improving menstrual cyclicality, they can induce various side effects such as gastrointestinal, reducing patients' compliance. Now there are some data that the use of alternative oral insulin-sensitizing compounds MYO have been widely used as treatment. Recent studies and reviews clearly demonstrated that MYO administration improves insulin resistance in adult PCOS patients, correcting also the hormonal profiles and ameliorating ovarian function both in spontaneous as well as in induced ovarian cycles (Galazis *et al*., 2011; Papaleo *et al*., 2009; Morgante *et al*., 2011; Genazzani *et al*., 2012). Today the association with alpha lipoic acid (ALA) is used in insulin-resistant patients in order to strengthen the mechanism of action with improvement of implicated oxidative stress (Cianci *et al*., 2015; Evans *et al*., 2003; Fenkci *et al*., 2003; Evans *et al*., 2002; Masharani *et al*., 2010). Because all of these observations were performed in adult PCOS patients, in the present study, we showed that a combined MI and ALA therapy was able to restore hormonal and metabolic parameters in PCOS young adolescents earlier having to intervene with other therapies.

We evaluated the efficacy of 6 months with MYO and ALA combination in young adolescent women with PCOS, without prescribing changes in lifestyle. During the treatment interval no dietary restriction was adopted, but all patients reported at last a minimal loss of weight that resulted in a significant reduction of BMI (24.25 ± 5.21 vs 23.54 ± 4.97, p 0,01). Furthermore, our results have demonstrated a significant improvement of metabolic parameters such us triglycerides (75.07 ± 24.84 vs 64.61 ± 30.05, p 0,008) and basal insulin (15.6 ± 10.85 vs 12.2 ± 15.33 p 0,017) with significant reduction of insulin resistance: HOMA-IR (2.41 ± 1.71 vs 1.67 ± 2.05, p 0,03) after therapy. According to date relating to adult populations from others authors, our results underscore the role of inositol as a modulator of the metabolic pathway mediated by insulin, suggesting an improvement of the intracellular activity of IPG mediators, and finally a better insulin sensitivity (Nordio and Proietti, 2012; Genazzani *et al*., 2014; Genazzani *et al*., 2012; Kamenov *et al*., 2015). Moreover, others studies, conducted in all cases of adult women, have shown as alpha lipoic acid administration, correcting oxidative stress, could have a beneficial effect on triglycerides and other lipid values (Cianci *et al*., 2015; Masharani *et al*., 2010). In the same patients, there was a statistically significant decrease of basal LH (5.24 ± 2.96 vs 4.34 ± 2.60, p 0,043), and increase of estradiol (41.46 ± 25.3 vs 77.67 ± 74.5, p 0,040) sign of improvement of ovarian function and oocyte quality; furthermore, there waslowering of testosterone (0.60 ± 0.37 vs 0.45 ± 0.19, p 0,03) and DHEAS (238.85 ± 122.13 vs 208.14 ± 136.30), showing a reduction of hyperandrogenism, similarly to others previous reports (Cianci *et al*., 2015; Masharani *et al*., 2010). Finally, no-parametric correlations of Spearman revealed statistically significant positive correlation between BMI and HOMA-IR (Rho 0.773, p 0.00), between basal LH and testosterone (Rho 0,679, p 0,005) and between basal LH and Delta-4-androstenedione (Rho: 0,573; p: 0,05) and a negative correlation between estradiol and LH/FSH post

treatment (Rho -0.688, p 0.003), proving that the improvement of hyperandrogenism is directly correlated to that of ovarian function. Results have shown that the treatments normalize the metabolic parameters with improvement of insulin sensitivity and hormonal profile in these young girls. In conclusion, we suggest that a combined therapy of MI plus ALA may be the first line approach treatment in PCOS during the adolescence, so as to avoid serious side effects of traditional therapies and to reduce the risk of developing a metabolic disease.

Acknowledgements:

(none)

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