

# Bye-bye Chiro-inositol – Myo-inositol: true progress in the treatment of polycystic ovary syndrome and ovulation induction

M. GALLETTA, S. GRASSO, A. VAIARELLI\*, SCOTT J. ROSEFF\*\*

Reproductive Medicine Unit, Hera Association, Catania (Italy)

\*Department of Obstetrics and Gynecology, Messina University (Italy)

\*\*Palm Beach Center for Reproductive Medicine, Wellington, FL (USA)

**Abstract.** – Polycystic ovary syndrome (PCOS) is a multifactorial syndrome affecting 10% of women in reproductive age. Insulin sensitizers are the best therapeutic option for PCOS patients; among which there is Inositol.

Inositol is a polyalcohol existing as nine different stereoisomers, two of which have been shown to be insulin mediators: myo-inositol (MI) and D-chiro-inositol (DCI).

So far only MI have been shown to be present in the follicular fluid and in a direct comparison between MI and DCI only MI was able to improve oocyte and embryo quality.

Therefore, could we say “bye-bye D-chiro-Inositol” in the practice of clinical gynecology and reproductive medicine?

*Key Words:*

Chiro-inositol, Myo-inositol, Polycystic ovary syndrome.

## Introduction

The history of inositol-based-treatment for Polycystic Ovary Syndrome (PCOS) has its roots in the studies performed by Larner et al<sup>1,2</sup> who aimed to unravel the causes of, and eventually find a possible treatment of, type 2 diabetes mellitus. Indeed, in 1993, Larner<sup>2</sup> showed that the administration of two inositol phosphoglycans containing myo-inositol (MI) or D-chiro-inositol (DCI) reduced hyperglycemia in a dose-dependent manner.

In 1999, Nestler et al<sup>3</sup> were the first to report the efficacy of D-chiro-inositol in the treatment of obese PCOS women. Data were astonishing: 50% of women ovulated after 4 weeks of treat-

ment, and the authors also reported an increase in insulin sensitivity along with a reduction of serum androgen levels. In 2002, additional data<sup>4</sup> were produced demonstrating the same effects in lean PCOS women.

Additional studies by Baillargeon et al<sup>5,6</sup> shed light on metformin's mechanism of action. They showed that metformin increased the insulin-stimulated release of DCI-phosphoglycans. Furthermore, they showed an altered DCI urinary clearance in PCOS women. Once more, these data suggested a direct correlation between the availability of inositol phosphoglycans and insulin resistance.

Unfortunately, a subsequent study Cheang et al<sup>7</sup> in 2008 ended prematurely due to the sudden unavailability of the study medication, which was provided by Insmed Pharmaceuticals (NJ, USA). In this study, the Authors were not able to reconfirm the data obtained in 1999, but they were able to find a direct correlation between insulin-stimulated release of DCI-containing phosphoglycans and insulin sensitivity. No data were reported about MI-containing phosphoglycans.

In the same year, a research group based at the AGUNCO Obstetrics and Gynecology Center in Rome (Italy)<sup>8</sup>, under the direction of Unfer, was inspired by the results obtained by Nestler in 1999. Unfer's group began to study the effects of MI in the treatment of PCOS patients. Their results showed that MI could be as effective as DCI in the treatment of PCOS metabolic imbalances and ovarian dysfunction. Their study was conducted over a period of 16 weeks, during which the treated group showed regular menstrual cycles. On the basis of these results, MI was proposed as a novel method for ovulation induction in PCOS patients, and they demonstrated a 40% pregnancy rate<sup>9</sup>.

In order to fully elucidate all of the possible beneficial effects that PCOS patients could receive from a MI-based treatment, the AGUNCO group performed additional studies in which investigators<sup>10,11</sup> were able to show that MI treatment lowered insulin and androgen levels, increased insulin sensitivity, and was effective in treating hirsutism. Zacche et al<sup>12</sup>, Costantino et al<sup>13</sup> were also able to demonstrate an improvement of acne and a normalization of hypertension and dyslipidemia in MI-treated women. In addition to these results, a breakthrough article was published in collaboration with the San Raffaele Institute in Milan (Italy)<sup>14</sup> in which it was shown that MI supplementation improved oocyte quality of PCOS women undergoing in vitro fertilization and embryo transfer (IVF-ET). Noteworthy, in this study, it was shown a reduced total dosage of international units (IU) of recombinant FSH (rFSH) administered, as well as the number of cancelled IVF cycles. Follow-up studies<sup>15</sup> confirmed these findings by demonstrating that the combined administration of MI plus melatonin improved oocyte and embryo quality.

Currently, several other aspects of MI-based treatment are being investigated: in particular, a direct comparison between MI and DCI has been performed in order to elucidate their effects on oocyte quality. In one study, Unfer and colleagues found that only MI, rather than DCI, was able to improve oocyte and embryo quality and, in line with previous data, just the MI group benefited from ovarian stimulation with less IU of rFSH.

Data from other groups showed that DCI is synthesized by an epimerase that converts MI into DCI, with each tissue having its own particular conversion rate, likely due to the specific needs for the two different molecules<sup>2,16</sup>. In particular, it was shown that the DCI to MI ratio was itself insulin dependent. In fact, in subjects suffering from type 2 diabetes, the DCI/MI ratio was reduced<sup>16-19</sup>, and less DCI was synthesized due to a reduction in epimerase activity<sup>16-19</sup>. All of these studies were performed on insulin sensitive tissues such as muscle and liver. However, unlike tissues such as muscle and liver, ovaries do not become insulin resistant<sup>20-22</sup>. Based on these data, Unfer et al developed a theory that identified a “DCI paradox”<sup>23</sup>. They suggested that ovaries in PCOS patients likely present an enhanced MI to DCI epimerization that leads to a MI tissue depletion that could eventually be responsible for the poor oocyte quality characteristic of these patients<sup>24</sup>.

Based on all of these observations, and if the “DCI paradox” is confirmed, could we say “bye-bye D-chiro-Inositol” in the practice of clinical gynecology and reproductive medicine?

## References

- 1) BROMBERG WJ, EDLICH RF. Joseph Lerner's personal odyssey: search for the cause and cure of non-insulin-dependent diabetes mellitus. *J Emerg Med* 1994; 12: 681-684.
- 2) LARNER J. D-chiro-inositol—its functional role in insulin action and its deficit in insulin resistance. *Int J Exp Diabetes Res* 2002; 3: 47-60.
- 3) NESTLER JE, JAKUBOWICZ DJ, REAMER P, GUNN RD, ALLAN G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. *N Engl J Med* 1999; 340: 1314-1320.
- 4) IUORNO MJ, JAKUBOWICZ DJ, BAILLARGEON JP, DILLON P, GUNN RD, ALLAN G, NESTLER JE. Effects of d-chiro-inositol in lean women with the polycystic ovary syndrome. *Endocr Pract* 2002; 8: 417-423.
- 5) BAILLARGEON JP, IUORNO MJ, JAKUBOWICZ DJ, APRIDONIDZE T, HE N, NESTLER JE. Metformin therapy increases insulin-stimulated release of D-chiro-inositol-containing inositolphosphoglycan mediator in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2004; 89: 242-249.
- 6) BAILLARGEON JP, DIAMANTI-KANDARAKIS E, OSTLUND RE, JR., APRIDONIDZE T, IUORNO MJ, NESTLER JE. Altered D-chiro-inositol urinary clearance in women with polycystic ovary syndrome. *Diabetes Care* 2006; 29: 300-305.
- 7) CHEANG KI, BAILLARGEON JP, ESSAH PA, OSTLUND RE, JR., APRIDONIDZE T, ISLAM L, NESTLER JE. Insulin-stimulated release of D-chiro-inositol-containing inositolphosphoglycan mediator correlates with insulin sensitivity in women with polycystic ovary syndrome. *Metabolism* 2008; 57: 1390-1397.
- 8) GERLI S, PAPALEO E, FERRARI A, DI RENZO GC. Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. *Eur Rev Med Pharmacol Sci* 2007; 11: 347-354.
- 9) PAPALEO E, UNFER V, BAILLARGEON JP, DE SANTIS L, FUSI F, BRIGANTE C, MARELLI G, CINO I, REDAELLI A, FERRARI A. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. *Gynecol Endocrinol* 2007; 23: 700-703.
- 10) GENAZZANI AD, LANZONI C, RICCHIERI F, JASONNI VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. *Gynecol Endocrinol* 2008; 24: 139-144.
- 11) MINOZZI M, D'ANDREA G, UNFER V. Treatment of hirsutism with myo-inositol: a prospective clinical study. *Reprod Biomed Online* 2008; 17: 579-582.

- 12) ZACCHE MM, CAPUTO L, FILIPPIS S, ZACCHE G, DINDELLI M, FERRARI A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. *Gynecol Endocrinol* 2009; 25: 508-513.
- 13) COSTANTINO D, MINOZZI G, MINOZZI E, GUARALDI C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. *Eur Rev Med Pharmacol Sci* 2009; 13: 105-110.
- 14) PAPALEO E, UNFER V, BAILLARGEON JP, FUSI F, OCCHI F, DE SANTIS L. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. *Fertil Steril* 2009; 91: 1750-1754.
- 15) RIZZO P, RAFFONE E, BENEDETTO V. Effect of the treatment with myo-inositol plus folic acid plus melatonin in comparison with a treatment with myo-inositol plus folic acid on oocyte quality and pregnancy outcome in IVF cycles. A prospective, clinical trial. *Eur Rev Med Pharmacol Sci* 2010; 14: 555-561.
- 16) SUN TH, HEIMARK DB, NGUYEN T, NADLER JL, LARNER J. Both myo-inositol to chiro-inositol epimerase activities and chiro-inositol to myo-inositol ratios are decreased in tissues of GK type 2 diabetic rats compared to Wistar controls. *Biochem Biophys Res Commun* 2002; 293: 1092-1098.
- 17) LARNER J, CRAIG JW. Urinary myo-inositol-to-chiro-inositol ratios and insulin resistance. *Diabetes Care* 1996; 19: 76-78.
- 18) KENNINGTON AS, HILL CR, CRAIG J, BOGARDUS C, RAZ I, ORTMEYER HK, HANSEN BC, ROMERO G, LARNER J. Low urinary chiro-inositol excretion in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1990; 323: 373-378.
- 19) ASPLIN I, GALASKO G, LARNER J. chiro-inositol deficiency and insulin resistance: a comparison of the chiro-inositol- and the myo-inositol-containing insulin mediators isolated from urine, hemodialysate, and muscle of control and type II diabetic subjects. *Proc Natl Acad Sci U S A* 1993; 90: 5924-5928.
- 20) HARWOOD K, VUGUIN P, DIMARTINO-NARDI J. Current approaches to the diagnosis and treatment of polycystic ovarian syndrome in youth. *Horm Res* 2007; 68: 209-217.
- 21) MATALLOTAKIS I, KOURTIS A, KOUKOURA O, PANIDIS D. Polycystic ovary syndrome: etiology and pathogenesis. *Arch Gynecol Obstet* 2006; 274: 187-197.
- 22) RICE S, CHRISTOFORIDIS N, GADD C, NIKOLAOU D, SEYANI L, DONALDSON A, MARGARA R, HARDY K, FRANKS S. Impaired insulin-dependent glucose metabolism in granulosa-lutein cells from anovulatory women with polycystic ovaries. *Hum Reprod* 2005; 20: 373-381.
- 23) CARLOMAGNO G, UNFER V, ROSEFF S. The D-chiro-inositol paradox in the ovary. *Fertil Steril* 2011; 95: 2515-2516.
- 24) CHATTOPADHAYAY R, GANESH A, SAMANTA J, JANA SK, CHAKRAVARTY BN, CHAUDHURY K. Effect of follicular fluid oxidative stress on meiotic spindle formation in infertile women with polycystic ovarian syndrome. *Gynecol Obstet Invest* 2010; 69: 197-202.