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LETTER TO THE EDITOR

"Empiric" inositol supplementation in normal-weight non insulin resistant women with polycystic ovarian disease: from the absence of benefit to the potential adverse effects

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Dear Editor,

We read with great interest the manuscript titled "Evaluation of ovarian function and metabolic factors in women affected by polycystic ovary syndrome after treatment with D-Chiro-Inositol" by Laganà et al. [1] recently published in your prestigious Journal.

The authors conducted an interesting prospective cohort study evaluating the effects of D-chiro inositol (DCI) supplementation in non-overweight women affected by polycystic ovarian syndrome (PCOS).

Authors demonstrated that normal weight PCOS (BMI < 25) benefited from a 6 months dietary DCI supplementation with 1 gram daily. They observed menstrual cycle regularization and restoration of ovulation in 62.5 % of cases (30 of 48 patients) most likely due to significant improvements in the metabolic (evaluated by glucose profile and serum glucose to insulin ratio) and hormonal profile (evaluated by LH to FSH ratio and androgen levels) [1].

In our opinion, the manuscript by Laganà et al. is both interesting and innovative as only one other study investigating hormonal and metabolic changes following inositol supplementation in lean women with PCOS phenotype is reported in the literature [2].

Iuorno et al. [2] following 600 mg daily DCI supplementation for a period of 6–8 weeks described metabolic and hormonal improvements strictly comparable with the ones reported by Laganà. Interestingly, both study noted the rate of ovulation restoration after DCI supplementation. Intriguingly, despite both studies being conducted on a very small number of patients (48 women by Laganà et al. and 20 by Iuorno et al.), the rate of ovulation restoration was very similar, at around 60 %. Unfortunately, even if Laganà et al. achieved statistical significance evaluating the endpoint ovulation restoration, Iuorno et al. did not. Certainly our speculation does not take into account the statistical result, probably strongly influenced by methodology and sample size (study protocol by Laganà did not include a control group while Iuorno et al. performed a case–control study on 20 patients) but rather focuses on the possible mechanisms involved and on the different effects that DCI supplementation may have on non-overweight PCOS patients as opposed to the well documented improvements in ovulation restoration in obese PCOS women [3, 4].

Despite further studies with larger sample size are required to confirm evidences of DCI supplementation in lean PCOS patients, we aim to stress the importance this data, which may indirectly explain the differences in the pathophysiological mechanisms (respect to the obese women) responsible for chronic anovulation and open the door for future improvements in terms of treatment.

The most accredited theory for anovulation in PCOS women was insulin-resistance directly related with obesity

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which is responsible for worsening the insulin-resistance profile (cause–effect–cause) [5]. This assumption however, remains to be confirmed.

Emerging evidences regarding lean PCOS phenotype have discovered that anovulation may occur in the absence of insulin-resistance suggesting the presence of a subgroup of non-insulin resistant lean PCOS subtype" [5, 6].

Regarding the last subgroup of PCOS patients, emerging evidences seem to confirm the theory of a genetic predisposition to hyper-androgenemia since the "starting point" is the hyper responsiveness of theca cells to LH and insulin at physiological concentrations while in obese PCOS high levels of insulin are necessary (due to insulin resistance) to increase androgen production by theca cells [6].

So here we discover the "Achilles heel" of the DCI effects on lean PCOS women. Nearly half of the cases of lean PCOS women unresponsive to DCI supplementation may belong to the cohort of "genetic" non-insulin resistant PCOS women.

Accordingly, we are strongly suggesting that PCOS lean anovulatory patients be screened for insulin resistance. This practice, while routinely performed in obese women is frequently disregarded in lean patients.

Considering the impact that DCI therapy may have on the quality of oocytes when administered in lean PCOS without insulin resistance, neglecting the screening may be considered malpractice.

It is universally accepted that increased insulin resistance typically correlates with poor oocyte quality even after assisted reproduction techniques [7, 8].

One of the chief mechanisms responsible for poor oocyte quality in PCOS with increased insulin resistance is an increased intra-follicular oxidative status [7, 9].

Recently, Authors demonstrated that both folliculogenesis and ovulation physiologically occur in a context of "adequate" oxidative stress (balance between pro-oxidative and anti-oxidative states) [10, 11]. Intuitively all the conditions responsible for an increased intra-follicular oxidative status such as PCOS with insulin-resistance, endometriosis, dietary abnormalities and deficits in anti-oxidative agent and radical scavengers [12–15] are associated with poor oocytes quality similarly to the cases which, on the contrary, have a low intra-follicular oxidative status as recently demonstrated in patients assuming low dose aspirin during ovarian stimulation [16].

Surprisingly, in addition to the improvements on insulin and glycemic profile, DCI supplementation restores the physiological oxidative balance through the reduction of ROS levels in particular in follicular fluid [17, 18].

If on one hand the antioxidant property of DCI synergizes with the effects of an improved insulin profile in obese insulin-resistant PCOS, in lean PCOS typically not affected by increased oxidative status, the reduction of oxidative stress may alter the equilibrium in the follicular fluid and have the opposite effect, worsening the quality of oocyte and/or reducing the spontaneous ovulation.

Our speculation, though requiring confirmation, is supported by evidences collected by several authors: Isabella et al. [19] recently observed dose-dependent detrimental effects of inositol supplementation on oocyte quality and ovarian response of non-insulin-resistant PCOS undergoing in vitro fertilization treatment; similar findings are reported by Lisi et al. [20] after inositol supplementation in non PCOS women undergoing assisted reproductive treatments.

In conclusion, we are suggesting that further studies on insulin profile and inositol effects on lean PCOS women are mandatory.

Our intent is to encourage research finalized at improving medical care by reducing empirical treatments and potential unintended adverse effects as a result of inappropriate prescriptions which arise from a partial understanding of the pathogenic mechanisms of the condition we at to cure.

Conflict of interest All authors declare no conflicts of interest.

References

1. Laganà AS, Barbaro L, Pizzo A (2014) Evaluation of ovarian function and metabolic factors in women affected by polycystic ovary syndrome after treatment with D-chiro-inositol. Arch Gynecol Obstet. doi:10.1007/s00404-014-3552-6
2. Iuorno MJ, Jakubowicz DJ, Baillargeon JP, Dillon P, Gunn RD, Allan G, Nestler JE (2002) Effects of D-chiro-inositol in lean women with the polycystic ovary syndrome. Endocr Pract 8(6):417–423
3. Pizzo A, Laganà AS, Barbaro L (2014) Comparison between effects of myo-inositol and D-chiro-inositol on ovarian function and metabolic factors in women with PCOS. Gynecol Endocrinol 30(3):205–208
4. Genazzani AD, Prati A, Santagni S, Ricchieri F, Chierchia E, Rattighieri E, Campedelli A, Simoncini T, Artini PG (2012) Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. Gynecol Endocrinol 28(12):969–973
5. Rondanelli M, Perna S, Faliva M, Monteferrario F, Repaci E, Allieri F (2014) Focus on metabolic and nutritional correlates of polycystic ovary syndrome and update on nutritional management of these critical phenomena. Arch Gynecol Obstet 290(6):1079–1092
6. Baptiste CG, Battista MC, Trottier A, Baillargeon JP (2010) Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol 122(1–3):42–52
7. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G (1999) Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med 340(17):1314–1320
8. Qiao J, Feng HL (2011) Extra- and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence. Hum Reprod Update 17(1):17–33
9. Piomboni P, Focarelli R, Capaldo A, Stendardi A, Cappelli V, Cianci A et al (2014) Protein modification as oxidative stress

marker in follicular fluid from women with polycystic ovary syndrome: the effect of inositol and metformin. J Assist Reprod Genet 31(10):1269–1276
10. Jancar N, Kopitar AN, Ihan A, VirantKlun I, Bokal EV (2007) Effect of apoptosis and reactive oxygen species production in human granulosa cells on oocyte fertilization and blastocyst development. J Assist Reprod Genet 24(2–3):91–97
11. Hennet ML, Yu HY, Combelles CM (2013) Follicular fluid hydrogen peroxide and lipid hydroperoxide in bovine antral follicles of various size, atresia, and dominance status. J Assist Reprod Genet 30(3):333–340
12. Vitagliano A, Noventa M, Gizzo S (2014) Is it time to consider patients suffering from endometriosis-related infertility as "novel candidates" for targeted peri-conceptional D-chiro inositol supplementation? Hypothesis, rationale and some considerations. J Assist Reprod Genet. doi:10.1007/s10815-014-0412-z
13. Nehra D, Le HD, Fallon EM, Carlson SJ, Woods D, White YA, Pan AH, Guo L, Rodig SJ, Tilly JL, Rueda BR, Puder M (2012) Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids. Aging Cell 11(6):1046–1054
14. Huang B, Li Z, Ai J, Zhu L, Li Y, Jin L, Zhang H (2014) Antioxidant capacity of follicular fluid from patients undergoing in vitro fertilization. Int J Clin Exp Pathol 7(5):2273–2282
15. Palini S, Benedetti S, Tagliamonte MC, De Stefani S, Primiterra M, Polli V, Rocchi P, Catalani S, Battistelli S, Canestrari F, Bulletti C (2014) Influence of ovarian stimulation for IVF/ICSI on the antioxidant defence system and relationship to outcome. Reprod Biomed Online 29(1):65–71
16. Gizzo S, Capuzzo D, Zicchina C, Di Gangi S, Coronella ML, Andrisani A, Gangemi M, Nardelli GB (2014) Could empirical low-dose-aspirin administration during IVF cycle affect both the oocytes and embryos quality via COX 1-2 activity inhibition? J Assist Reprod Genet 31(3):261–268
17. Chen L, Xu WM, Zhang D (2014) Association of abdominal obesity, insulin resistance, and oxidative stress in adipose tissue in women with polycystic ovary syndrome. Fertil Steril 102(4):1167–1174.e4
18. Ciotta L, Stracquadanio M, Pagano I, Carbonaro A, Palumbo M, Gulino F (2011) Effects of myo-inositol supplementation on oocyte's quality in PCOS patients: a double blind trial. Eur Rev Med Pharmacol Sci 15(5):509–514
19. Isabella R, Raffone E (2012) Does ovary need D-chiro-inositol? J Ovarian Res 5(1):14
20. Lisi F, Carfagna P, Oliva MM, Rago R, Lisi R, Poverini R, Manna C, Vaquero E, Caserta D, Raparelli V, Marci R, Moscarini M (2012) Pretreatment with myo-inositol in non polycystic ovary syndrome patients undergoing multiple follicular stimulation for IVF: a pilot study. Reprod Biol Endocrinol 23(10):52