

## Reproducibility crisis. Impact on uncontrolled release of nutraceutical preparations

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### Commentary on

Mendoza et al., 2019, "Comparison of the effect of two combinations of myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial", *Gynecological Endocrinology*, doi: 10.1080/09513590.2019.1576620. [Epub ahead of print].

### 1. How to waste a good opportunity

In the last decade, natural integrative treatments of Polycystic Ovary Syndrome (PCOS) – a complex ovarian syndrome characterized by anovulation/androgenism/cystic ovaries – gained momentum, given that a plethora of nutraceuticals flooded into the market. Namely, two inositol isomers - myo-inositol (myo-Ins) and D-chiro-inositol (D-Chiro-Ins) have been proven to be effective in PCOS treatment, by improving insulin resistance, serum androgen levels and many features of the metabolic syndrome. However, DCI alone, mostly when it is administered at high dosage, negatively affects oocyte quality. On the contrary, the association myo-Ins/D-Chiro-Ins in a combination reproducing the plasma physiological ratio (40:1) – as claimed by a Consensus Conference (Bevilacqua et al., 2015) and confirmed by a recent clinical pilot study (Nordio, 2019) - represents, up to now, the most promising alternative in achieving better clinical results, by counteracting PCOS at both systemic and ovary level. Honestly, we still lacking a compelling clinical vindication of that assumption, the

outstanding experimental results performed in animals notwithstanding (Bevilacqua et al., 2019). However, data gathered suggest that the two inositol should be administered according to a physiological ratio, which would mirror the concentrations found in the blood (Bizzarri et al., 2016), or in the ovarian follicle (Chiu et al., 2002). However, only few, pivotal studies based on these correct physiological premises have been performed so far. It is staggering. As a result, a good opportunity – treatment of a complex syndrome through natural and safe compounds – risks to be wasted.

### 2. Lack of scientific evidence

Moreover, it is unconceivable – and even amazing – that an overwhelming number of commercial nutraceutical formulas for the inositol-based treatment of PCOS, are including a wide range of concentrations (Tab. I), in which myo-Ins/D-Chiro-Ins ratio varies implausibly from 1: 1 to 104:1!

Ratio Myo-Ins vs D-Chiro-Ins	COMPOSITION
5 :1	2 g myo-Ins + 400 mg D-chiro-Ins + 400 mcg folic acid + 10 mg Mn
5:1	1 g myo-inositol + 200 mg D-chiro-Ins + 200 µg folic acid + 5 mg Mn
40:1	2 g myo-Ins + 50 mg D-chiro-Ins + 5mcg Vitamin D
7:1	875 mg myo-Ins + 125 mg D-chiro-Ins + 2 g glucomannan
1:2,5	200 mg myo-Ins + 500 mg D-chiro-Ins + 500 mg α-lipoic acid + 80 mg monacolin/polygonum extract+ 200 µg folic acid + 5 mg Mn + 12,5 µg Vitamin D + Revifast® 80mg + resveratrol (?)
1:1,25	200 mg myo-Ins + 250 mg D-chiro-Ins + 80 mg Vitamin C + 12 µg Vitamin E + 400 µg folic acid + 11,25 mg zinc + 12 mg L-glutathione
7:1	1750 mg myo-Ins + 250 mg D-Chiro-Ins + 400 µg Folate + glucosamine salt (?) + 100mg metil-sulphonyl-methane + 12,5 mg Zinc pidolate + Vitamin C (?)
104:1	1980 mg myo-Ins + 19 mg D-Chiro-Ins + 200 mg folic acid + 150 mg NAC + 30 mg L-arginin + 7,5 mg Zinc + 41,5 µg Selenium + 1,5 µg Vitamin B12
5:1	2 g myo-Ins + 400 mg D-chiro-Ins + 300 mg Agnocastus + 200 mg Humulus l. + Salacia r. 100 mg + verbena 100 mg 200 µg Folic acid

**Tab. 1:** Composition in myo-Ins/D-Chiro-Ins of some different nutraceutical commercial formulas.

Indeed, in the majority of such cases, there is no rational or any credible hypothesis which can support this kind of bizarre compositions. In other words, those nutraceutical supports are deprived of any scientific evidence. We would also ask if it is ethical to permit that such “drugs”, while deceiving the incognizant consumer, should invade the market, baffling both the Regulatory Agency’s control, as well as common sense. We reasonably repute that something should be done to counteract this unacceptable state of affairs.

### 3. Inadequacy cannot pass over in silence

It seems also that scientific journals – at least sometimes - fail in duty to inform correctly. ORGANISMS publishes in this issue a commentary by Laganà and Aragona, regarding a clinical pilot study with inositols in PCOS, in which several technical and ethical (conflict of interest!) biases have been found. Surprisingly, the article was refused by other journals, alleging weak and inconsistent justifications. We are delighted hosting this

contribution, as it provides further support in revealing the “epidemic” of controversial/irreproducible/false results that plague current clinical research, as pointed out by Ioannidis (Ioannidis, 2005) and recently recalled in an Editorial of Organisms (Editorial, 2018). Allowing the diffusion of clinical data with no sufficient evidence and deprived of robust scientific rationale, highlights the deficiencies of how the scientific and medical enterprise are currently managed, thus asking for a quick intervention. Reliability and trustiness of medical science need to be re-established.

### Conflict of Interest

The Authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The Authors alone are responsible for the content and writing of the paper.

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