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COMMENTARIES

Effects of oral supplementation with Inositols in women with polycystic ovary syndrome undergoing in vitro fertilization: a long and windy road

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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]

A new treatment?

To date, the scientific community is facing a global crisis, due primarily to the extent of irreproducibility of published data. As was previously highlighted (Editorial, 2018), on the one hand this condition may cause the adoption of wrong behaviours in clinical practice due to inadequate conclusions, based on poor methodological quality of the studies/trials and flawed data collection/analysis. On the other hand, and this may be viewed even more dangerous, the tolerance of faulty dominant biological paradigms may lead to enhanced reliance on these misleading pathways.

In this scenario, we read with great interest the paper by Mendoza et al. (Mendoza et al., 2019) recently published in Gynaecological Endocrinology. The study compared reproductive outcomes in women affected by polycystic ovary syndrome (PCOS) undergoing intracytoplasmic sperm injection (ICSI), after treatment with 550 mg of Myo-Inositol (MI) + 150 mg of D-Chiro-Inositol (DCI) twice daily (study group) or 550 mg of MI + 13.8 mg of DCI twice daily (control group) for 12 weeks. In our opinion, this study is particularly important since provides data about the effects of a novel formulation with a MI: DCI ratio (3.6:1), very different from what was previously proposed by the "*International Consensus Conference on myo-inositol and D-chiro-inositol in Obstetrics and Gynecology*" (Bevilacqua et al., 2015). Although we appreciated the accurate methodology of this double-blind, multicentre randomized clinical trial (RCT) with quadruple masking (Participant, Care Provider, Investigator and Outcomes Assessor), we would like to highlight some critical issues that should be taken into account for a proper evaluation. First, authors wrote that the patients were offered the possibility of doing intrauterine inseminations or ICSI. This is hardly understandable, considering that the two techniques have specific and different clinical indications. Furthermore, a growing body of evidence suggests intrauterine insemination as the first line treatment (Bahadur et al.,

2016). Therefore, the inclusion of women undergoing only ICSI (as Mendoza et al. did) could lead to a potential selection bias.

Second, the authors declared that the study was conducted "from February 2016 to April 2017". Nevertheless, we checked the Clinical Trial registration ID (NCT03201601), and this study was first posted on 28 June 2017 (Figure 1), so after the study conclusion (or at least after the completion of patients' enrolment).

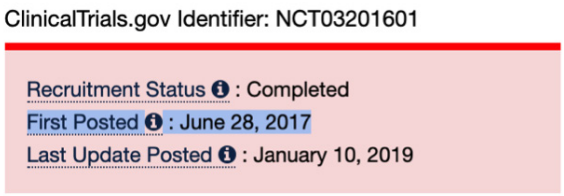

Figure 1: Data about clinical trial registration (NCT03201601), available from ClinicalTrials.gov.

This may clearly raise serious concerns from the ethical point of view. In addition, although we appreciate the transparency in declaring the disclosure according to the most important methodological guidelines (Schünemann et al., 2015), we should acknowledge that 40% of the authors (4/10) are workers for the Biosearch Life, a company that produces DCI from carob fruit. This seems an undisputable conflict of interest.

Finally, the comparison of 40:1 and 3.6:1 ratios did not show significant differences in the metabolic parameters (insulin and glucose levels as well as HOMA-index) and in testosterone levels. The same absence of significance was found in the number of oocytes, the number of good quality oocytes (MII oocyte), while the number of embryos (particularly the number of Embryo A quality) was the same in both groups. The only parameters with a substantial difference were the pregnancy rate and the live birth rate. In the discussion authors suggested that these findings may be due to a positive role of DCI during implantation. However, this statement seems to be purely speculative, without any further experimental confirmation or eventual supporting evidence from previous investigations, since meta-analyses published so far reported conflicting results about this issue (Laganà et al., 2018). Namely, the Authors should have discussed opposite results, recently published by Prapas's team (Ravanos et al, 2017), suggesting that high level of DCI are likely to be detrimental in ensuring a proper ovarian function, as also highlighted by experimental studies (Bevilacqua et al., 2019).

We agree with what was already highlighted by the last Cochrane review (Showell et al., 2018) and, in this scenario, we solicit future studies, with larger cohorts and adequate statistical power, in order to evaluate the effects of treatment with different MI:DCI ratios in PCOS women, both for metabolic/hormonal as well as reproductive outcomes.

This is of paramount importance, considering the accumulating attention about the "reproducibility crisis" in modern science (Ioannidis JP, 2005): in particular, the high rate of non-replication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p-value less than 0.05. It is crystal clear that the lack of replication may lead to robust concerns about the validity of study findings.

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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