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Letter to the Editor

Myo-inositol: with or without

Dear Sir;

An innovative study by Heimark *et al*. [1] gives us the opportunity to clarify the debated role of myo-inositol (MI) and D-chiro-inositol (DCI) in Polycystic ovary syndrome (PCOS), an endocrine disorder in women (5 to 12%) and a leading cause of infertility. We integrate their findings with the study by Unfer *et al*. [2] focused on the same topic.

Hyperinsulinemia plays one of the roles in the pathogenesis of PCOS. Therefore, insulin-sensitizing drugs such as metformin [3] and thiazolidines are therapeutic options, although some side effects limit their use for PCOS patients [4].

Inositol is an insulin-sensitizing agent recently posited for the treatment of PCOS. Myo-inositol (MI) and D-chiro-inositol (DCI) are two stereoisomers precursors of signalling molecules such as phosphoinositides (PtdIns) and inositol phosphoglycans (I-PGs), being the latter insulin second messengers and mediators of the insulin action [5]. Noteworthy, it has been shown that MI-PG and DCI-PG mediate different actions of insulin: MI-PG is involved in cellular glucose uptake, whereas DCI-PG is involved in glycogen synthesis, and there is evidence that reduced inositol(s) availability impairs hormonal signalling [5].

In tissues, an insulin-dependent epimerase regulates the conversion of MI to DCI, and their ratio, in a different proportion, depending on the specific function of each tissue [5]. In ovary the predominant inositol is MI [1].

We are carrying out a trial to evaluate the MI/DCI ratio in the follicular fluid in PCOS women, treated and untreated with MI, to correlate these levels with oocyte and embryo quality.

A specific deficiency of MI in the ovary of PCOS women might be responsible for poor oocyte quality and impaired follicle-stimulating hormone (FSH) signalling [5]. Unlike other tissues, the ovaries of PCOS women are not insulin-resistant. The theory of the "DCI paradox" speculates that, in patients with PCOS, hyperinsulinemia stimulates intraovarian epimerization of MI to DCI, resulting in an overproduction of DCI and a depletion of MI [5].

The new findings [1-2] support this theory at two different levels. Larner *et al*. assessed the activity of the epimerase in theca cells from normal cycling women and from women with PCOS [1]. Epimerase activity was increased in the theca cells from PCOS women compared to normal women. The ratio of MI to DCI was decreased due to an absolute reduction of MI.

Unfer *et al.* [2] found that the concentration of MI, and the ratio of MI to DCI, decrease in the follicular fluid of PCOS women, as compared with the same fluid from normal cycling women. Thus, these studies confirm the occurrence of an imbalance between MI and DCI levels in the follicular fluid of PCOS patients.

According to these innovative results, the ovarian "FSH resistance" may be caused by intraovarian depletion of MI. To further support this hypothesis, oral administration of MI to PCOS women in controlled ovarian hyperstimulation reduces the units of FSH required, lowers the risk of ovarian hyperstimulation syndrome (OHSS), and improves oocyte and embryo quality [5].

Taking into consideration that MI supplementation is well tolerated, these results suggest that pre-treating PCOS women with MI supplementation before controlled ovarian hyperstimulation may improve oocyte and embryo quality and decrease "FSH resistance," making the ovary more sensitive to FSH.

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