The D-*chiro*-inositol paradox in the ovary

The D-*chiro*-inositol–to–*myo*-inositol ratio is regulated by an insulin-dependent epimerase. Enzyme activity varies among tissues, likely owing to the specific needs of the two different molecules. We hypothesize that in the ovaries of polycystic ovary syndrome patients, epimerase activity is enhanced, leading to a local *myo*-inositol deficiency which in turn is responsible for the poor oocyte quality. (Fertil Steril® 2011;■:■–■. ©2011 by American Society for Reproductive Medicine.)

Key Words: Myo-inositol, D-chiro-inositol, PCOS, oocyte quality, FSH

Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935 (1), and several aspects of this syndrome, such as diagnosis and treatments, are still debated. Currently, the diagnosis is based on the outcome of a consensus meeting held in Rotterdam in 2003 sponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine.

The outcome of the meeting defined that PCOS diagnosis should be based on three different factors: 1) oligoanovulation; 2) hyperandrogenism (clinical or biochemical); and 3) the presence of $\geq$12 follicles in each ovary measuring 2 $\pm$ 9 mm in diameter and/or increased ovarian volume (>10 mL) (2, 3). Although 16% to 80% of PCOS patients show insulin resistance (IR), the consensus meeting decided to exclude IR from the diagnostic criteria (4).

Among the treatments routinely used in clinical practice, the most promising ones are insulin-sensitizing agents (5), including inositol. Inositol is a polyalchol existing as nine different stereoisomers, two of which have been shown to be insulin mediators: *myo*-inositol (MI) and D-*chiro*-inositol (DCI) (6).

In vivo, DCI is synthetized by an epimerase that converts MI into DCI and, depending on the specific needs of the two different molecules, each tissue has a typical conversion rate (6, 7). In particular, it was shown that the ratio of these two insulin mediators was itself insulin dependent. Indeed, in subjects with type 2 diabetes, the DCI/MI ratio was reduced and less DCI was synthetized, owing to a reduction in the epimerase activity (7–10).

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In 1999 Nestler et al. used DCI in the treatment of PCOS (11). In their study, 19 out of 22 obese hyperinsulinemic PCOS patients treated with 1.2 g/d DCI showed restored ovulation compared with the placebo group. Furthermore, an improvement of the hormonal profile was observed in the DCI group. Recent studies showed that 4 g/d MI, besides improving hormonal profile and restoring ovulation, is able to induce regular menses in both lean and obese PCOS patients (12–15).

Furthermore, a direct correlation of MI concentration in the follicular fluid and high oocyte quality has been found (16). Additional studies also showed that MI supplementation is able to improve oocyte quality (17), and in a recent study we showed that MI rather than DCI is able to improve both oocyte and embryo quality (18). Interestingly, in both studies reductions of the amount of recombinant FSH (rFSH) administered and the number of canceled cycles were observed (17, 18).

Unlike tissues such as muscle and liver, ovaries never become insulin resistant (19–21). Therefore, we could speculate that PCOS patients with hyperinsulinemia likely present an enhanced MI to DCI epimerization in the ovary; this would result in an increased DCI/MI ratio (i.e., overproduction of DCI), which in turn would lead to an MI deficiency in the ovary. This MI depletion could eventually be responsible for the poor oocyte quality observed in these patients (22).

Furthermore, because MI supplementation reduces the rFSH IU administrated during IVF cycles (17, 18), it is likely that the putative MI deficiency in the ovary would also impair the FSH signaling, resulting in an increased risk of ovarian hyperstimulation syndrome for PCOS patients.

Therefore, we could speak of a "DCI paradox": indeed, although DCI is useful in the treatment of PCOS patients to reduce IR, it has no effect at ovarian level.

We hope that the present letter will be used as a starting point for further research to unravel the precise role played by MI and DCI at the ovarian level.

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