Letter to the Editor
Myo-inositol and dominant follicle

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Dear Editor,

the physiological mechanisms that are behind recruitment and selection of antral follicles in human ovaries remain incompletely understood. One hypothesis is that the follicle, destined to become dominant in a cohort of growing follicles and which will ovulate at mid-cycle, may contain a greater number of granulosa cells and a higher density of FSH receptors. Thus, the dominant follicle acquires greater responsiveness to FSH in comparison with the remaining preantral follicles that instead undergo atresia[1]. The phosphatidylinositol 3-kinase (PI3K)/AKT (protein kinase B) pathway is a pivotal signaling corridor necessary for transducing the FSH signal. As known, PI3K phosphorylates the 3-position hydroxyl group of the phosphatidylinositol ring. Protein kinase A (PKA) mediates the actions of FSH by signaling through multiple targets to activate PI3K/AKT[2]. PKA uses a route that promotes phosphorylation of insulin receptor substrate-1 (IRS-1) on Tyr 989, a canonical binding site for the 85-kDa regulatory subunit of PI3K that allosterically activates the catalytic subunit[2]. Protein kinase C (PKC) is another signaling molecule of the G-protein coupled receptors (including the FSH receptor). PKC activation by the ligand/receptor interaction increases the intracytoplasmic levels of inositol triphosphate (IP3), which is a second messenger for FSH and other hormones.

Noteworthy, Myo-inositol (MI) is a precursor of both IP3 and cell membrane-associated phosphatidylinositols.

MI is a cis-1,2,3,5-trans-4,6-cyclohexanehexol and constitutes the most prominent form of nine possible stereoisomers of the carbohydrate inositol. An insulin-dependent epimerase converts irreversibly myo-inositol into the stereoisomer D-chiro-inositol (DCI). The physiological MI: DCI ratio differs from tissue to tissue, reflecting the dissimilar local activity of the insulin-dependent epimerase. Clearly, the activity of this epimerase is variably reduced depending on the extent of insulin resistance of a given tissue in disorders associated with insulin resistance, but it will be variably increased if the tissue is unaffected by such resistance, as in the case of ovarian tissue of women with polycystic ovary syndrome (PCOS), a well-known anovulatory disorder associated with insulin resistance-related hyperinsulinemia. Therefore, it was hypothesized that women with PCOS have an enhanced intraovarian MI to DCI epimerization, leading to MI deficiency. In turn, MI deficiency impairs FSH signaling, resulting in reduced oocyte quality[3]. It was found that the MI: DCI ratio is 0.2:1 in PCOS women, and 100:1 in control women (a 500-fold difference)[3].

In cultured theca cells from follicles of women undergoing hysterectomy, the intracellular MI:DCI ratio decreases by about 5-fold and the epimerase activity increases by 3-fold[4]. Remarkable, in PCOS women MI and DCI behave as insulin-sensitizing agents[5], and indeed they are precursors of the cell-membrane associated phosphatidylinositols, which transduce insulin signaling. MI administration to PCOS women improves insulin sensitivity, restores ovulatory cycles and, in Assisted Reproductive Technologies (ART), allows to collect oocytes of greater quality[5]. The smaller number of FSH injections to induce ovulation in ART demonstrates the improvement of FSH signaling[5].

Returning to the issue of our incomplete understanding of recruitment and selection of antral follicles, we can hypothesize that a follicle becomes dom-

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inant owing to a greater content of MI, though we cannot state whether this enrichment originates from enhanced synthesis *de novo* and/or from decreased activity of epimerase. Therefore, the other follicles become atresic because they are MI deficient, and such deficiency makes them unable to transduce the FSH signaling. A similar MI deficit might apply to women with FSH-resistant amenorrhea and with premature menopause, both with follicular atresia associated with elevated serum levels of FSH.

The implications are that MI supplementation might be beneficial to these subsets of women.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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