Letter to the Editor

Critical considerations about the generalized use of n-3 polyunsaturated fatty acids in patients with Polycystic Ovary Syndrome

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I've read with great interest the review recently published by Yuan *et al.* (1) about the efficacy of omega-3 polyunsaturated fatty acids (n-3 PUFAs) on hormonal, oxidative and inflammatory parameters in women with polycystic ovary syndrome (PCOS). The authors conducted a systematic review and a meta-analysis, finding that n-3 PUFA administration significantly improved (I) inflammatory and oxidative state, as indicated by the levels of C-Reactive Protein (CRP), Malondialdehyde (MDA) and Total Antioxidant Capacity (TAC), (II) and the hormonal profile, as reported by the levels of Luteinizing Hormone (LH), Total Testosterone (TT) and Sex Hormone Binding Protein (SHBG). However, the n-3 PUFA supplementation failed to improve other inflammatory, hormonal and oxidative factors in PCOS women, including Glutathione (GSH), Dehydroepiandrosterone Sulphate (DHEAS), Free Androgen Index (FAI) and Follicle-stimulating hormone (FSH). Indeed, the overall effects of n-3 PUFAs on the hormonal profile, oxidative stress, and inflammation in PCOS patients are still conflicting in the scientific literature.

Furthermore, the authors report in their discussion that some limitations to their work exist. First, the analysis included few eligible studies: in particular, among the 314 studies initially identified, only 10 met the eligible criteria and were included. Second, there is a wide heterogeneity among the identified studies, with increased risk of bias.

The authors conclude the analysis proposing the supplementation with n-3 PUFAs as a low-risk and add-on therapy for patients with PCOS, without discussing crucial critical points. Based on current evidence, I strongly believe that the use of n-3 PUFAs in PCOS management needs deeper assessments regarding the effectiveness and the limitations concerning their application throughout women's life and their high cost.

EPA and DHA are two essential n-3 PUFAs, commonly used as dietary supplements for improving pathological cardiovascular parameters and inflammatory processes. Specifically, their use at different ratios and dosages correlates with different therapeutic benefits. The recommended minimum dosage for supplementation is 500 mg/day, reaching 2,000–4,000 mg/day in patients who have experienced myocardial infarction or altered blood triglycerides levels in the recent past. Therefore, considering such dosages and the high current cost associated to n-3 PUFAs (2), their use should be carefully assessed and reserved only to specific patients who may derive actual benefits from the treatment.

PCOS women exhibit heterogenous pathological features, besides the common diagnostic criteria of Rotterdam (oligo or amenorrhea, polycystic ovary, hyperandrogenism). Such syndrome indeed spans women's life, and menstrual and fertility problems evolve into metabolic complications as age advances (3). In particular, women after 40 years of age may commonly experience cardiovascular problems related to metabolic alterations

including insulin resistance and obesity, dyslipidaemia, diabetes, hypertension. For this reason, the use of n-3 PUFAs should be limited to women over 40 years of age that have already experienced cardiovascular and inflammatory symptoms related to PCOS, while the generalized use in all types of PCOS patients seems unnecessary if not unadvisable.

Moreover, scientific evidence is still controversial about the beneficial effects of n-3 PUFAs on metabolic parameters. Some studies demonstrated that n-3 PUFA supplementation failed to improve symptoms related to PCOS, like body weight and hip circumference, fasting blood sugar, number of ovarian follicles, size of ovary, menstrual bleeding, and hirsutism score (4), as well as serum levels of total cholesterol (TC), LDL, HDL (4). On the contrary, other studies indicated positive effects only on TC and LDL, without affecting HDL and TG. In addition, a meta-analysis of randomized controlled clinical trials, conducted by Sadeghi and colleagues, revealed that supplementation with n-3 PUFAs may have not positive effects in improving insulin resistance in women with PCOS (4), corroborating the conflicting evidence.

On the other hand, the use of n-3 PUFAs deserves a proper attention in younger women with PCOS since guidelines recommend avoiding EPA administration during pregnancy (5). Indeed, EPA competes with arachidonic acid for the enzymes responsible for the formation of eicosanoids (cyclooxygenase, lipoxygenase), which are crucial for neural foetal development. In addition, like all other fatty acids, n-3 PUFAs exhibit a higher calorific value compared to other dietary supplements, and they should be taken with care in obese PCOS women.

Finally, I should point out that the use of n-3 PUFAs may have side effects that need to be monitored during the assumption, including gastrointestinal symptoms, like heartburn and nausea. Based on available information, supplementation with n-3 PUFAs in PCOS patients deserves a proper attention and it should be avoided in younger patients and in those with obesity, for which it seems unnecessary (6). On the contrary, widely recommended treatments for PCOS women are based on myo-inositol and D-chiro-inositol, which exhibit a lower calorific value than fatty acids, and well-established positive effects on hyperandrogenism and metabolic profile. Specifically, myo-inositol supplementation, by recovering the FSH signalling, counteracts the ovarian depletion, which determines menstrual irregularities and reduced fertility in PCOS women. Noteworthy, some studies conducted on different cellular systems reported that the stimulation with n-3 PUFAs may negatively modulate inositol trisphosphate pathway, also reducing its release as second messenger (7-9). A research group further hypothesized that *in vitro* stimulation with DHA may induce in cells of *Saccharomyces Cerevisiae* a depletion of intracellular inositol levels even stronger than valproic acid (10). Therefore, considering that women with PCOS exhibit a compromised inositol pathway, further studies are encouraged to make the clinical use of n-3 PUFAs in PCOS patients clearer.

In conclusion, we must always keep in mind that the management of PCOS aims to alleviate the symptoms and it may vary depending on patients' age and needs. On these bases, considering the nutritional characteristics and their cost, n-3 PUFA supplementation should not be generally recommended to all PCOS patients, but likely limited to those over 40 years with cardiometabolic disturbances.

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