

Editorial – Update on Inositol(s)

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Over the past few decades, the use of inositol(s) in the clinical practice is attracting ever-growing interest. After successfully launching the special issue of “Inositol(s) from Bench to Bedside in Endocrinology and Gynecology”, we introduce this new special issue on Update on Inositol(s). Inositol is a polyol naturally occurring in fruits, beans, grains, nuts as well as animals. The most common of its 9 different stereoisomers is myo-inositol, followed by D-chiro-inositol. Myo-inositol is found in phospholipids which exert a function as cellular mediators of signal transduction, in metabolic regulation, and cell growth¹. Given its action as an insulin-sensitizing molecule, myo-inositol has shown positive effects on the treatment of polycystic ovary syndrome (PCOS)², type II diabetes³ and gestational diabetes mellitus (GDM)⁴. Myo-inositol, as a dietary supplement, exhibits also promising benefits for promoting female and male fertility⁵, restoring thyroid function⁶, as well as reducing metabolic syndrome⁷ and anxiety. The aim of this special issue is to endorse the continuing research on inositol(s) and its beneficial effect in different therapeutic fields. The studies are mainly focused on the role of three essential molecules myo-inositol, D-chiro-inositol, and inositol hexakisphosphate (InsP₆), a metabolite of myo-inositol. The articles cover 6 thematic areas: PCOS, infertility, GDM, thyroid disorders, and oncology including basic and clinical research, as well as reviews.

- a) **PCOS:** A lot has been said about the positive correlation between myo-inositol and PCOS, so far. Indeed, the specific role of myo-inositol in mediating different actions of insulin has shown profound benefit for the treatment of PCOS. Cochrane and systematic reviews available in the literature, strongly affirm the effectiveness of this molecule alone or combined with D-chiro-inositol in restoring spontaneous ovulation and improving fertility in women with PCOS. PCOS women have altered metabolic parameters and a reduced availability of inositol in the ovaries, which may cause insulin resistance and hyperinsulinemia. Hence, the use of myo-inositol as insulin sensitizing agent for the regulation of metabolism and promotion of ovulation has been considered a valuable therapeutic approach for PCOS. For this special issue, De Leo's group⁸ has reviewed all types of treatment, including natural molecules, for hyperandrogenism and metabolic disorders in PCOS women. Rolland et al⁹ have shown that supplementation of myo-inositol improved sensitivity to clomiphene citrate rising ovulation and pregnancy rates in PCOS subjects. As metformin is considered one of the first approaches to PCOS, Nas and Tüü¹⁰ have investigated the therapeutic role of this oral drug compared to myo-inositol in insulin-resistant patients. Very intriguing findings were observed, demonstrating that myo-inositol is a valuable alternative of metformin as insulin-resistance treatment. Orrù et al¹¹ have highlighted the importance of pharmacokinetics (PK) analysis prior drug design and development. In particular, it was shown that the optimal therapeutic approach for PCOS is 2 g of myo-ins twice a day. This double administration guarantees almost 24-hour coverage and the absence of side-effects. This is a very interesting topic, as a poor oral bioavailability may impair drug efficacy. Indeed, the pharmacological interaction between molecules and their bioavailability after consumption are critical parameters to understand and identify the preferable therapeutic approach. Thus, the identification of their mechanism of action and PK properties are critical steps to support the effectiveness of treatment.
- b) **Infertility:** It is a fairly common problem. Worldwide about a third of the time, infertility can be traced to the man. Reduction of number and motility of spermatozoa as well as a sperm morphology changes are parameters mainly characterizing oligoasthenoteratospermia (OAT). Drugs, assisted re-

productive technology, and surgery are common treatments for male infertility. Following the papers in this special issue can be seen that myo-inositol, either oral or incubated with semen, improves sperm quality and assisted reproductive technology outcomes, thus increasing the possible achievement of spontaneous pregnancies¹²⁻¹⁶.

- c) **GDM:** During the first trimester of pregnancy, the onset of glucose intolerance and insulin resistance can represent a risk factor for GDM. It is the most common medical complication of pregnancy, associated with maternal and fetal adverse outcomes. Myo-inositol has been tested for preventing and treating gestational diabetes in a number of clinical trials. High dosage of myo-inositol has been reported to induce occasionally minor side effects such as nausea and diarrhea; however, a case report by Costabile and Unfer¹⁷ has shown a safe profile of this molecule even at high concentration (4 g of myo-inositol, 3 times per day for 3 weeks). Furthermore, it has been demonstrated its effectiveness in lowering blood glucose levels in a faster and steady way. These findings highlight new insights on the use of myo-inositol for the treatment of GDM.
- d) **Thyroid disorders:** Hashimoto's thyroiditis is the most common autoimmune disorder worldwide affecting more than 10% of females and 2% of males. The quality of life is often impaired by symptoms occurring in such disease. However, a specific therapy for autoimmune thyroiditis has not been defined yet. Whence the interest of finding a valuable approach for this pathology. In this special issue, two studies investigated the effect of a combination with myo-inositol and selenium, for 6 months in Hashimoto's patients with subclinical hypothyroidism¹⁸ or patients with euthyroid chronic autoimmune thyroiditis¹⁹. The findings of these two studies are in agreement, showing a reduction of thyroid-stimulating hormone (TSH) and autoantibodies levels after treatment with myo-inositol in association with selenium. Nordio et al¹⁸ evaluated also the quality of life in the patients showing a significant subjective symptomatology amelioration in all of them. The immune-modulatory effect of myo-inositol in association with selenium was instead assessed by Ferrari et al¹⁹, highlighting a risk-reduction of developing overt hypothyroidism. Therefore, these results not only corroborate earlier findings but also indicate the supplementation of myo-inositol and selenium as a beneficial therapy for autoimmune thyroiditis.
- e) **Oncology:** In the past few years, a number of preliminary studies^{20,21} have drawn attention to the involvement of inositol(s) in carcinogenesis and its adjuvant action in cancer treatment. Indeed, myo-inositol and InsP₆ are considered safe chemopreventive agents by exerting antioxidant and anti-inflammatory activities. Proietti et al²² have demonstrated the anticancer effect of the conventional chemotherapy exerted by topical InsP₆. In particular, it was shown the effectiveness of InsP₆ treatment in preventing and/or mitigating chemotherapy-induced side effects and ameliorating the quality of life in women with ductal breast cancer.

Conclusions

This special issue draws attention to the ongoing research on the use of inositol(s) in the clinical practice. It covers many areas showing progress and novel therapeutic approaches in the gynecology, endocrinology and oncology fields.

Competing Interests

Vittorio Unfer is employee at LO.LI. Pharma, Rome, Italy. The other author declares that has no conflict of interests regarding the publication of this paper.

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