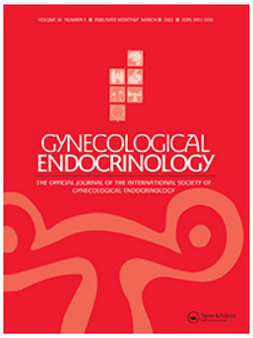

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REVIEW

Strategy to improve the female fertility in the general gynecologist's office: use of a nutritional supplement based on myo-inositol/D-chiro-inositol and antioxidants

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ABSTRACT

Subfertility is more than a quality-of-life problem as it has a substantial negative public health impact. Polycystic ovary syndrome (PCOS) is one of the most common causes of subfertility, affecting one out of 10 women in reproductive age. Among PCOS women undergoing assisted reproductive technology, treatment based on myo-inositol and high doses of D-chiro-inositol has been shown to increase pregnancy rate and number of live births, reduce ovarian hyperstimulation syndrome and improve oocyte quality. A preparation based on myo-inositol and high doses of D-chiro-inositol, together with antioxidants, vitamins, and minerals, could have beneficial effects and be an optimal strategy to improve female fertility in the general gynecologist's office. The aim of this review is to highlight the role of inositol and its isomers in improving fertility of women with PCOS.

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Introduction

Subfertility is the inability to achieve spontaneous pregnancy in a period of time above of the population mean. As a rule, subfertility is regarded to be more than a quality-of-life problem, having considerable public health consequences including psychological stress, social stigmatization and financial burden. It has been estimated that more than 70 million couples have fertility problems. In Western countries, subfertility affects 15% of the population of reproductive age, that is, one out of six couples [1].

Preparing to have a child after marriage is common in most societies, and even in developed countries, having a child of your own is considered a significant achievement. Therefore, subfertility could be considered as a crisis in couples' lives, due to the real or unreal perception of feeling rejected by society, with possible major psychological and emotional impacts [2].

Subfertility is perceived differently by women and men. For many women who undergo repeat abortions or in whom assisted reproductive techniques fail, subfertility is experienced as a stigma associated with a feeling of shame, or as a sense of mourning of loss. Men, on the other hand, perceive subfertility as putting their masculinity into question [2].

The availability of, access to, and quality of interventions to address subfertility continue to pose a challenge in many countries. Often, the diagnosis and treatment of subfertility are not prioritized in national health policies and are rarely covered through public health systems. Thus, although assisted reproductive techniques have been available for more than three decades now, they are largely inaccessible in many parts of the world, but they are also unaffordable for many couples in developed countries, where access to these techniques is highly dependent on individual economic capacity [3].

Subfertility may have male, female, or mixed causes. In almost a third of cases, there are two or more causes of subfertility. Among males, subfertility is most caused by problems with semen ejection, absence or low levels of spermatozoa, or abnormal sperm morphology or motility. Among women, subfertility may be caused by a variety of abnormalities of the ovaries, uterus, fallopian tubes, and endocrine system. Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine abnormalities [3]. Moreover, subfertility increases with female age, some toxic habits (mainly smoking), obesity, psychological stress, and various drugs.

The aim of this review is to highlight the role of inositol and its isomers on the improvement of fertility in women with PCOS.

Polycystic ovary syndrome (PCOS)

PCOS is one of the most common causes of chronic anovulation and affects one in every 10 women of reproductive age. Women with PCOS have an adverse reproductive profile, which includes a high risk of pregnancy-induced hypertension, preeclampsia, and gestational diabetes mellitus [4]. Patients with PCOS present not only a higher prevalence of classic cardiovascular risk factors, such as hypertension, dyslipidemia, and type-2 diabetes mellitus, but also of nonclassic cardiovascular risk factors, including mood disorders, such as depression and anxiety [5]. Furthermore, women with PCOS show a greater risk of endometrial cancer compared to healthy women without the syndrome, particularly during the premenopausal period [6].

PCOS involves highly heterogeneous symptoms and seems to be very complicated to treat. However, although a small percentage of women with PCOS present numerous symptoms and complications that can render diagnosis and treatment difficult, in most cases PCOS can be treated in the general gynecological office, with no need of being referred to fertility units.

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PCOS is a multifactorial process, a classic example of the interaction of fertility and energy metabolism, in which insulin resistance appears to play a fundamental pathophysiological role. Although in recent years no major progress has been made in genetic code that relates PCOS and insulin resistance/diabetes, both are known to be polygenic entities that are highly influenced by the epigenetic, more specifically in the intrauterine environment where the female fetus is developed, which due to epigenetic reasons will express the genes that predispose to PCOS or diabetes [7,8].

There is a direct link between PCOS endocrine disturbances and carbohydrate metabolism disorder. Thus, insulin acts directly in the ovary, stimulating the testosterone production in the cells of the internal theca of the ovarian follicles, causing hirsutism, oligomenorrhea, acne, chronic anovulation and other characteristic features of the PCOS; however, there are substances such as inositols and alpha lipoic acid, that improve the response to both insulin and testosterone [7–9]. Some published studies suggest that up to 50% of women with PCOS have hyperinsulinemia and peripheral insulin resistance in skeletal muscle, adipose tissue, although ovarian theca and granulosa cells are also known to be extremely sensitive to insulin and are not resistant insulin-resistant. There would, therefore, exist a dichotomy between the insolent resistance of peripheral tissue insulin resistance and ovarian insulin sensitivity [10].

Treatment of PCOS

Treatment for women with PCOS should be individualized, depending on reproductive desire and symptoms (subfertility related to ovulatory dysfunction, menstrual disorders or hyperandrogenism-related symptoms). Irrespective of the strategy chosen, changes in lifestyle (diet and exercise) are always part of the treatment, and the benefits of lifestyle interventions with regard to free androgen index, weight, and body mass index (BMI) have been demonstrated [11,12]. The main objective of nutritional therapy in these patients must be to attain specific goals such as improving insulin resistance, metabolic and reproductive functions, which will be rendered by the design of a low-calorie diet in order to achieve weight loss or maintain a healthy weight, limit the intake of simple sugars and refined carbohydrates, as well as foods with a low glycemic index, reduce saturated and trans fatty acids and pay attention to possible deficiencies of certain nutrients, such as vitamin D, chromium and omega-3 [12,13].

Currently, there are several published systematic reviews and meta-analyses on the use of different nutritional supplements, such as antioxidants such as polyphenols, vitamin E, resveratrol and lipoic acid - which has shown to be play an important role in glucose uptake through and thus of insulin sensitivity [9], as well as vitamin D, melatonin and inositol, among other, in order to improve female, male or mixed fertility. All of these articles coincide that the studies are highly heterogeneous and usually include small sample size, and while their results suggest a beneficial effect of these compounds on fertility there is no high-quality evidence [14–18]. However, it should be remembered that these studies have individually evaluated a single compound, making it difficult to detect a consistent effect, whereas combined use could reveal a more evident benefit.

Importance of inositol and its isomers

In women with PCOS, a defect in tissue bioavailability or in inositol metabolism may contribute to the development and maintenance of insulin resistance. Inositol and its isomers, myo-inositol (MYO) and D-chiro-inositol (DCI), act by increasing insulin sensitivity and reducing hyperandrogenism. Women with PCOS present very low levels of DCI, which may be due to a deficiency of epimerase, the enzyme that allows the transformation of MYO into DCI [19]. DCI is regarded as an insulin sensitizer, whereby, when DCI levels are diminished, insulin resistance is increased, in turn leading to the metabolic complications of hyperinsulinemia [18].

In addition, MYO and its transformation into DCI are also known to participate in oocyte maturation, meaning that not only are they intermediaries of insulin in the theca cell but they probably also bring an influence to bear upon oocyte quality [20]. MYO supplementation has been seen to improve the metabolic profile and hyperandrogenism in women with PCOS, besides increasing the clinical pregnancy rate in subfertile women undergoing ovulation induction by means of intracytoplasmic sperm injection (ICSI) or *in vitro* fertilization and embryo transfer (IVF-ET), probably improving embryos quality number of inadequate oocytes [15,17].

Despite this, recent systematic reviews have shown that MYO supplementation is not sufficient to improve oocyte maturation, embryo quality, or pregnancy rate [21,22]. The existence of tissue-specific MYO/DCI ratios in the ovary has led researchers to develop a treatment based on both molecules in the ratio of 40 (MYO) to 1 (DCI). This ratio has proven to be effective in improving endocrine and metabolic parameters in obese women with PCOS; although, based on the available data, it was not possible to establish a specific MYO:DCI ratio that should be administered to patients with PCOS [23].

In order to verify the efficacy of administering DCI, a double-blind, randomized, multicenter clinical trial was carried out, in which five Spanish centers participated, to compare the effect of two doses of DCI (13.8 mg vs. 150 mg) in combination with MYO for 12 weeks in 60 PCOS women undergoing ICSI. Patients were randomized to receive soft oral gelatin capsules of 550 mg MYO ± 150 mg DCI twice daily (3.6:1; study group) or 550 mg MYO ± 13.8 mg DCI twice-daily (40:1; control group) for 12 weeks until ovarian drilling. Other compounds, such as vitamin D or melatonin, which also appear to be beneficial, were not allowed so as not to mask the effects of the MYO/DCI combination. The results were clearly superior in women treated with the high dose of DCI: pregnancy rate of 65.5% vs. 25.9%; number of live births 16 versus 4, and an ovarian hyperstimulation syndrome rate of 3.4% versus 18.5% [24].

The retrospective analysis of oocytes of the women from one of the participating sites showed that those who had been given the high doses of DCI presented better oocyte quality, and most significantly, greater oocyte cytoplasmatic quality. These data are consistent with the assumption that severe cytoplasmic changes, such as the presence of granular cytoplasmic granulations centrally located, smooth endoplasmic reticulum aggregates, or excessive vacuolization could affect embryonic development and the implantation potential [25]. These results justify the use of DCI in high doses and have already been reproduced in other studies, which found benefits in terms of oocyte quality in women with PCOS [26,27].

Nutritional supplementation to improve fertility

Based on the results obtained with MYO/DCI and other compounds for improving female fertility, this compound was developed, a food supplement containing innovative and patented

ingredients with proven clinical evidence: DCI and MYO, folic acid, pomegranate extract, melatonin, vitamin D3, vitamin E and B vitamins, zinc and other minerals. Besides 550 mg of MYO + 150 mg of DCI, it contains 5-methyltetrahydrofolate, which is the active form of folic acid which does not need to be metabolized to exert its activity. It is indicated in women who have a defect in its transformation, such as those with congenital thrombophilia or a deficiency of the methyltetrahydrofolate reductase enzyme (MTHFR), which besides being a thrombotic risk factor also increases the risk of miscarriage. 5-MTHF contributes to tissue growth during pregnancy, the cell division process, and to normal homocysteine metabolism. Thanks to its properties, it reduces the likelihood of an early miscarriage, a frequent event among women with fertility problems [28].

It also contains pomegranate extract, a powerful antioxidant rich in polyphenols, which prevents oxidative damage to the follicular fluid and favors the maintenance of blood pressure in normal ranges; melatonin 1.9 mg, at the maximum doses allowed for a product to be deemed nutritional and not pharmacological, vitamin D_3 and other vitamins and minerals, which can assist in embryo implantation and in a successful pregnancy outcome.

Oxidative stress is a state of imbalance between pro-oxidants (reactive oxygen species and reactive nitrogen species) and antioxidant defenses, and it plays a key role in subfertility problems. Subfertility and some pregnancy complications, such as spontaneous miscarriage, pre-eclampsia, gestational diabetes, ruptured membranes, and intrauterine growth restriction, are also associated with oxidative stress. Therefore, maintaining the oxidant-antioxidant balance is important in favor to avert unfavorable maternal-fetal outcomes [29,30], and can provide benefit in women with subfertility [31]. Taking all this evidence into account, a nutritional supplement including MYO and DCI at high doses, as well as antioxidants, such as this compound, may have beneficial effects and be a good strategy for improving female fertility in the general gynecologist's office.

Conclusions

Subfertility is a relatively common condition, with a major medical, psychological, and financial impact. Irrespective of whether pharmacological treatments are used to address the medical entity associated with subfertility, such as PCOS, or assisted reproductive techniques, it is advisable to include lifestyle improvements in order to optimize natural fertility or boost the effectiveness of subfertility treatments. Nutritional supplements that include compounds with clinically proven beneficial effects on fertility are an effective, safe, and accessible tool for improving these patients' health, and increase their likelihood of a successful pregnancy.

In conclusion, in our results, combination of MYO with high doses of DCI improved oocyte cytoplasm quality in women with PCOS.

Disclosure statement

Mendoza, N. participated in the clinical study described in the manuscript, funded by Procare Health Spain; Losa, F. participated in the clinical study described in the manuscript, funded by Procare Health Spain; Palacios, S. has no conflict of interest.

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