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Inositol - why should it be in the spotlight for women in a reproductive age?

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Summary:

Introduction and purpose: Inositol exists in the form of nine isomers, two of which are dominant - myo-inositol (MI) and D-chiro-inositol (DCI). It is a naturally occuring sugar involved in many biological pathways. Due to its insulin-sensitizing, anti-inflammatory and antioxidant properties, inositol has been suggested as a novel treatment agent in prevention and treatment of reproductive disorders. The paper presents currently available data regarding the impact of oral supplementation of inositol for fertility of women and men, reproductive outcomes among subfertile women with polycystic ovarian syndrome (PCOS) and its effectiveness on preventing and treating gestational diabetes mellitus (GDM).

Material and methods of research: The search was conducted using PubMed and Google Scholarship databases available to November 2023.

Results: Although the evidence is still insufficient, it is suggested that inositol may be beneficial for subfertile women, also those undergoing assisted reproductive techniques and in vitro fertilization. Moreover inositol can positively influence sperm quality. Myoinositol supplementation was also effective and safe for pregnant women with GDM and their children. In these women lower HOMA-IR (Homeostatic Model Assessment – Insulin Resistance) and reduction of fetal macrosomia were observed. Myoinositol also seems to be favorable for overweight or obese women in GDM prevention and treatment. Current findings indicate the positive impact for hormonal changes and restoration in menstrual cyclicity in women with PCOS, improving reproductive disorders in these patients.

Conclusions: Overall, although findings are encouraging, further trials for this promising intervention are still required to support oral supplementation of inositol.

Key words: inositol; pregnancy; fertility

1. Introduction

Inositol is a sugar found in the form of nine isomers, of which myo-inositol (MI) and D-chiro-inositol (DCI), dominant in nature, attract the greatest attention of scientists. Although the body can synthesize inositol, most of it is obtained through food.

In the human body, inositol participates in numerous biochemical processes. It builds phosphatidylinositol (PI), which plays an important role in regulatory processes at the cellular level. After transformation, secondary messengers are formed, such as inositol trisphosphate (IP3) and diacylglycerol (DAG), which constitute an element of the phosphoinositol pathway. They regulate, among other things, the concentration of Ca2+ ions in the cell. Inositol also affects the functioning of cell receptors, regulates hemostasis, enzyme secretion and nerve conduction [1].

It is worth emphasizing that inositol acts as an antioxidant, has anti-inflammatory properties, and also regulates sugar levels at the cellular level as an intracellular transmitter for insulin, increasing the sensitivity of cells to its action. All these properties have made inositol and its derivatives of interest to researchers in recent years, especially due to their potentially positive effect on fertility in women, especially those with polycystic ovary syndrome

(PCOS), and men [2]. In this paper, we tried to summarize the latest scientific research on the effect of inositol on fertility.

2.1 The effect of inositol supplementation on fertility in women and men

Despite the increased number of studies on inositol in recent years, there is still an insufficient amount of research regarding its impact on fertility in both women and men. Inositol is an antioxidant, and it is precisely in this mechanism that a potential positive effect on fertility is sought.

In a meta-analysis from 2020, authors described the impact of antioxidant use in women with subfertility, defined as the inability to conceive within a 12-month period. One of the antioxidants considered in this meta-analysis was inositol. The authors compiled data from 63 clinical trials involving a total of 7760 women. In the summary, they concluded that the intake of antioxidants may benefit subfertile women, but the evidence is very weak [3].

In a randomized, double-blind controlled trial conducted by Chan SY et al. with 1729 women aged 18-38 randomly assigned to two groups, the supplementation of MI, probiotics, and other micronutrients (vitamins B2, B6, B12, D, zinc) and its effect on the time to natural conception and clinical pregnancy rates were compared. No statistically significant impact of supplementation was observed in this study. However, based on the results, the authors suggest that supplementation could have a favorable effect on fertility in obese women. This statement requires further confirmation in subsequent studies [4].

The application of inositol supplementation in in vitro fertilization (IVF) is also being investigated, gaining popularity in recent years. In a study conducted by Lisi et al. the supplementation of myo-inositol and its effect on ovarian response, oocyte quality, and embryo quality were examined in women without PCOS undergoing multiple follicular stimulation for IVF. It was observed that, compared to the control group, the number of retrieved oocytes was significantly reduced. Moreover, in women not supplemented with MI, a higher amount of gonadotropins was required [5]. Similar results were obtained in a study by Francesca Caprio et al. in 2015. Women who supplemented with MI for 3 months before IVF showed better ovarian sensitivity to gonadotropins compared to non-supplemented patients [6]. Sahar Mohammadi et al. observed that the ovarian sensitivity index and significantly reduced required units of gonadotropin were better in patients undergoing assisted reproductive techniques (ART) compared to the control group [7]. However, none of the studies demonstrated that inositol supplementation preceding ART statistically increased

pregnancy rates. The impact of inositol isomers' concentration in follicular fluid and blastocyst quality was also observed in women undergoing IVF [8].

The influence of inositol on sperm quality is also being studied in the context of fertility. One of the mechanisms that may reduce sperm quality is DNA fragmentation, which can be caused by oxidative stress. In addition to DNA fragmentation, the antioxidative action also involves reducing lipid peroxidation, protein oxidation, and mitochondrial dysfunction, which can affect sperm viability, sperm motility, oocyte fertilization, embryo implantation and embryo quality. This mechanism is considered a positive role of inositol action on male fertility [9,10]. Studies indicate that MI supplementation improves sperm quality and motility in fresh and frozen-thawed semen. Despite this data, it is still unknown how this effect affects fertility and whether couples struggling with infertility would benefit from inositol supplementation [11]. A study involving 109 men with asthenozoospermia showed that supplementation with MI for 3 months improved sperm motility, which returned to normal results in 85.32% of patients [12]. Similarly, in other studies investigating supplementation with MI, alpha-lipoic acid, folic acid, betaine and vitamins, it was demonstrated that a 3-month supplementation positively influences sperm quality, improving its parameters in subfertile men [13]. Another study confirmed the improvement in sperm quality after MI supplementation in men with oligoasthenospermia and in men without fertility problems [14].

2.2 The effect of inositol supplementation on fertility in women with polycystic ovary syndrome (PCOS)

PCOS is a common endocrine metabolic dysfunction associated with reproductive abnormalities. It is characterized by polycystic ovaries, ovulatory dysfunction, insulin resistance, obesity, hyperandrogenemia or hyperandrogenic changes. That leads to menstrual irregularities, infertility, pregnancy complications and prenatal programming of the offspring [15]. Infertility, which is an important clinical manifestation of PCOS, accounts for more than 75% of cases of anovulatory infertility [16].

Biochemically this disorder is characterized by excessive early follicular growth with interrupted progression to a dominant follicle. The increased production of androgens leads to the excess of follicles and the elevation of serum estradiol levels. This hyperandrogenism is caused by the surplus of luteinizing hormone (LH) and by hyperinsulinism [17].

Studies have shown that myo-inositol has a positive impact on insulin sensitivity, decreases hyperandrogenism and improves the menstrual cycle, thus it has been proposed as a potential therapeutic option for PCOS [18].

Unfer et al. have conducted the search of 12 studies and suggested that MI (with or without DCI) improves oocyte maturation, pregnancy rates and hormonal parameters such as LH, LH:FSH ratio, testosterone, androstenedione, insulinaemia and HOMA-IR (Homeostatic Model Assessment – Insulin Resistance) in women with PCOS [19]. In another study after 12 weeks of MI administration in 50 overweight women with PCOS hormonal changes and restoration in menstrual cyclicity in amenorrheic and oligomenorrheic subjects were also observed. These results indicate that MI intake may improve reproductive axis functioning in patients diagnosed with PCOS by reducing the hyperinsulinemic state [20]. Moreover Kamenov et al. evidenced that intake of 2 g per day of MI leads to improvement of ovulation and higher rates of pregnancy and delivery [21]. Similar findings were presented in some meta-analyses which have also found that MI alone or combined with DCI may be effective in women with PCOS [22,23,24,25]. The results especially highlight the beneficial effect of MI in metabolic profile improvement and reduction in hyperandrogenism.

This insulin-sensitizer was also used to improve reproductive dysfunctions in patients with PCOS who had undergone either ART or spontaneous ovulation [23]. The search for the existing literature conducted by Showell et al. aimed to assess the effectiveness of receiving myo-inositol as pre-treatment to IVF (11 trials) or during ovulation induction (2 trials) in subfertile women with PCOS. Unfortunately in light of the evidence of low to very low quality authors were uncertain whether MI may improve live birth rate or cause an increased clinical pregnancy rate in subfertile women with PCOS undergoing IVF pre-treatment taking MI in comparison with standard treatment. There is also no certainty if receiving MI reduces miscarriage rates or multiple pregnancy rates compared to standard treatment [26]. However, also in 2018 Lagana et al. performed the systematic review of randomized controlled trials in which evaluated whether MI supplementation is able to reduce the amount of gonadotropins and the length of controlled ovarian hyperstimulation in both PCOS and non-PCOS women undergoing IVF. The findings indicate that during IVF, MI is effective in both PCOS and non-PCOS women in saving gonadotropins, but efficient reduction in hyperstimulation was observed only in PCOS women. In this mechanism oral MI supplementation may be beneficial especially in women with PCOS undergoing in vitro fertilization [24].

In other systematic review and meta-analysis authors compared the effects of MI vs. another insulin sensitizer drug - metformin on hormonal and metabolic profiles and fertility outcomes

in patients with PCOS diagnosis. Both of them affect hyperinsulinemia and hyperandrogenism in metabolic disorders. Kutenaei et al. suggest that MI would probably be an alternative therapeutic option for women with PCOS receiving conventional drug treatments. As it was mentioned MI modulates hyperandrogenism and in this mechanism can improve fertility outcomes, but still randomized trials are needed to compare MI and metformin action on oocyte and embryo quality, fertilization, pregnancy and live birth rates [23].

There is also a study regarding the second inositol's stereoisomer - D-chiro-inositol, in which ovulation was restored in 86% of patients receiving DCI vs only 27% on the placebo group. Authors suggested that MI combined with DCI contributes significantly in restoring the regularity of the menstrual cycle and weight loss. What is important, losing weight is crucial in treating women with PCOS, because obesity can affect oocyte development, fertilization rate and embryo quality, leading to pregnancy failure [27].

2.3 The effect of inositol supplementation during pregnancy on prevention and treatment of GDM

Pregnancy is physiologically associated with increased insulin resistance. This condition should be under detailed control as it can further lead to diabetes and could also cause a negative impact on the fetus. Therefore, there is ongoing research towards the substances that could moderate or prevent this condition. One of the matters that scientists pin their hopes on is inositol.

A randomized, controlled, open-label study conducted on 84 pregnant women affected by GDM (gestational diabetes mellitus) which was treated with appropriate diet changes evaluated the effects of MI supplementation on insulin resistance parameters. Research group showed a significantly bigger decline in HOMA-IR, insulin and fasting plasma glucose levels in comparison to the control group. Adiponectin raised in the myoinositol group and decreased in the control group. Both groups were obliged to maintain a specific diet so it is justified to exclude possible profitable diet effects. Such changes were noticed after 8 weeks of supplementation with 4 g of MI supplementation [28].

Another open-label, randomized, controlled trial validated the positive effects of inositol on pregnant women affected by GDM. Women were obliged to intake daily either folic acid (control group), MI (4g) with folic acid or DCI (500 mg) plus folic acid or myo/D-chiro-inositol (respectively 1100 mg and 27.6 mg) with folic acid. The group that was treated with

MI and MI combined with DCI noticed positive effects - they needed less intensive insulin treatment. Additionally, the group with MI at the end of the treatment had lower HOMA-IR index when compared to the control group. It is worth mentioning that women who applied inositol to their daily habits had newborns with lower birth weight in comparison to the control group [29].

Efficacy of MI was also evidenced among the women that had the family history of type 2 diabetes. Two year long study showed that MI significantly reduced the prevalence of GDM. A statistically significant reduction of fetal macrosomia in the MI group was also highlighted together with a significant reduction in mean fetal weight at delivery. The dose of MI administered during the study was 2 g daily [30].

Myo-inositol seems to be also effective in women that do not have the correct body mass index (BMI) level. A study on women with overweight [31] and obesity [32] showed that intake of MI diminished the possibility of GDM incidence. The dosing method was also 2 g per day.

Another randomized trial also suggests that inositol could be considered as an adjunctive therapy for women affected with GDM. Matarelli et al. evaluated the effect of MI on women with high risk of GDM. It turned out that women that supplemented it needed less intensive insulin therapy, had lower risk of premature birth and also neonatal complications [33]. Celentano et al. had similar findings in their research and also exhibited that the MI form had the widest spectrum of advantages [34].

Trends towards inositol efficacy in improving glycemic parameters find confirmation in the metaanalysis conducted by Guo et al. These paper that included four random controlled trials with 586 patients failed to point out that inositol significantly contributes to lower BMI in newborns which previously were mentioned as occurring in the clinical trials. It also did not indicate any other side effects related to inositol which [35].

D-chiro-inositol even though shows less promising results than MI still has some research on its efficiency, but the results are not unambiguous. Di Biase et al. concluded that women with GDM which added 1 g of DCI had lower capillary glucose level after 8 weeks of treatment. Inositol also resulted in lower insulin demand [36].

In contrast to this paper, Fraticell et al in their research compared different forms of inositols in terms of their efficacy on women with GDM. It turned out that DCI had no positive response [29].

The possibility of additional benefits of usage of different forms of inositol was also searched. Malvasi et al. in their pilot study aimed at evaluating the effects of a supplement that

consisted of MI, DCI, folic acid and manganese on healthy women in their second trimester of pregnancy. As a result women in the research group had better glycemic parameters at the end of the study although the limit of the study is the lack of a group that would supplement only MI therefore there is still more data needed to determine which version would have better impact on pregnant women [37].

While MI appears to be a profitable factor in the course of the treatment for women at risk of GDM, the Cochrane review conducted in 2016 acknowledged previous data as still considered insufficient to paradigm shift in the treatment of this condition [38].

4. Conclusions

Our paper which presents the data from the trials and metaanalysis proves that inositol seems to be a safe and effective addition for the clinical management of different conditions assessed with pregnancy.

To date, there is much more data on the efficacy of MI while the effectiveness of the other stereoisomers still has many knowledge gaps and its impact seems to be less significant.

It is yet to be evaluated if inositol could show superiority in regard to concurrent treatments of the conditions which we described in our work or it should be rather considered as the support to the foregoing basis.

To sum up, inositol should be considered as valuable support to women with the risk or the history of diabetes as studies indicate its beneficial impact yet there is still more research needed to bring up unambiguous conclusions.

Author Contributions:

Conceptualization S.T. and M.W.; methodology K.W; software S.T.; check M.W., K.W. and S.T.; formal analysis M.W.; investigation S.T.; resources K.W.; data curation S.T.; writing - rough preparation, S.T., K.W. and M.W.; writing - review and editing, K.W., S.T and M.W.; visualization M.W.; supervision K.W.; project administration S.T.

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Conflicts of Interest

The author declares no conflict of interest.

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