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The role of inositol in improving fertility in patients with PCOS. - literature overview

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ABSTRACT

Introduction and purpose

Polycystic ovary syndrome is a common reproductive disorder, accompanied primarily by hyperandrogenism and insulin resistance. Myo-inositol (MI) and D-chiro-inositol (DCI), have emerged as potential therapeutic agents due to their role as insulin sensitizers. This article examines the effects of inositol therapy on fertility in women with PCOS and its role in assisted reproductive technology (ART). Studies suggest that inositols alleviate irregular menstruation, reduce androgen levels and positively affect ovulation rates. MI supplementation has also shown positive effects during controlled ovarian hyperstimulation and IVF procedures, reducing the required FSH dose and cycle length. However, despite positive results on ovulation and menstrual regularity, the article indicates the need for further studies to establish inositol as standard ART therapy in patients with PCOS.

Material and methods

The following review was based on articles from the PubMed and Google Scholar databases. Key search terms included polycystic ovary syndrome; assisted reproductive treatment, insulin resistance, inositols, Myo-inositol, D-chiro-inositol.

Conclusions

Inositols are a promising therapeutic option for women with PCOS. They have been shown to have positive effects on improving insulin sensitivity and fertility. However, despite inositol's safety and easy availability, the ideal dose and timing of use, the appropriate MI/DCI ratio, as well as the potential side effects of excess DCI and the problem of inositol resistance, require further comprehensive studies.

Keywords: Polycystic ovary syndrome; inositols; Myo-inositol; D-chiro-inositol; assisted reproductive technology; insulin resistance

The role of inositol in improving fertility in patients with PCOS. - literature overview

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive condition characterized by chronic anovulation and hyperandrogenism. [1] . It is the most prevalent cause of disorder of ovulation and problems with fertility in females and it affects about 6-10% of women in reproductive age. The pathogenesis of PCOS is still poorly understood, but the most role of insulin in hyperandrogenism is central. Insulin resistance in association with luteinizing hormone has an impact on increasing the production of androgen in theca cells. [2] According to the 2003 Rotterdam criteria, the diagnosis of PCOS should be based on at least two of three criteria, including: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries as identified by ultrasonography, excluding other androgen excess disorders. [3]

In addition to irregular periods, anovulatory infertility, the effects of hyperandrogenism, such as hirsutism, women with PCOS struggle with a number of other comorbidities including psychological (anxiety, depression), metabolic (obesity, insulin resistance, type 2 diabetes), cardiovascular (hypertension, dyslipidemia) increased risk for sleep apnea, endometrial carcinoma, and pregnancy-related complications (gestational diabetes, preeclampsia, pregnancy-induced hypertension, postpartum hemorrhage and infection, preterm delivery, meconium aspiration, stillbirth, operative deliveries, and shoulder dystocia). Obesity or overweight which often exist with PCOS may result in insulin resistance and hyperinsulinemia as an effect. It will exacerbate hyperandrogenism. In addition, adipose tissue produces leptin, which has a direct effect on ovarian function and has an effect on theca cell androgen synthesis, like insulin. [4]

Hyperandrogenism, hyperestrogenemia, insulin resistance and hyperinsulinemia acting on both the ovary and the endometrium, and it is certain that these factors have the biggest impact on the mechanism for the existence of infertility in PCOS. [5] Infertility is an important problem, which affects 40% of women with PCOS. [6] Moreover, about 80% women who suffer from anovulatory infertility have PCOS. [7] Treatment of IR, hyperinsulinemia and hyperandrogenism could return the metabolic and hormonal state to homeostasis, and thereby alleviate ovarian dysfunction, anovulation, and finally infertility. There are several treatment suggestions for hyperinsulinemia, pharmacological (metformin and thiazolidinediones) and non-pharmacological (diet and weight reduction). Both have proved to be beneficial for the

treatment of infertility in women with PCOS [8]. Unfortunately, it isn't perfect pathway to treat insulin resistance and struggle with infertility, because of side effects such as nausea and diarrhea (in the case of metformin) and increased body weight (in case of pioglitazone). In addition to traditional treatments that improve insulin sensitivity (metformin, thiazolidinediones), inositol stereoisomers (Myo-inositol and D-chiro-inositol) may also play a key role in therapy, because of their action as modulators of insulin sensitivity and as gonadotropin second messengers in the ovary. [9] . Various randomized and nonrandomized cohort studies have shown that MI and DCI improve menstrual irregularities and ovarian activity in women with PCOS. [2] Due to their properties, MI and DCI can be effective in supporting ovarian function, ovulation induction. MI has the ability to increase the intracellular calcium ion oscillation. [10] In addition to its effect on insulin resistance, MI plays a role in FSH signaling and therefore in oocyte maturation and embryo development. [2] In this article, we focus on the role of inositol in the treatment of PCOS, and especially on its effect on patients' fertility, including its use to prepare for assisted reproductive techniques.

Methodology

The following review was based on articles from the PubMed and Google Scholar databases. Key search terms included polycystic ovary syndrome; anovulation; assisted reproductive treatment, insulin resistance, inositols, Myo-inositol, D-chiro-inositol.

State of knowledge

Treatment of PCOS should be individualized for every patient, depending on their reproductive desire and most bothersome symptoms. The first part of the treatment should be based on lifestyle changing, losing weight and reducing BMI. [11] The main purpose is a low-calorie diet, limit the intake of simple sugars and refined carbohydrates, as well as foods with a low glycemic index. [12] In addition, a lot of pharmacological treatment options exist, for example selective estrogen receptor modulators (clomiphene citrate, tamoxifen), metformin, aromatase inhibitors (letrozole), low dose follicle-stimulating hormone stimulation and inositol, which is the main focus of this article. The mainstream treatments of anovulatory infertility, that accompanies PCOS therefore aim to tilt the balance of intraovarian steroid synthesis away form an LH-insulin-leptin-driven excessive androgen synthesis resulting in follicular atresia, toward FSH-driven final development of a dominant follicle. [4]

Biological character and functions of inositol

Inositols are hexahydroxycyclohexanes and include nine stereoisomers. [5] In cells inositols exist as free form and as components of membrane phosphoinositides (in this form, inositols

have
a function in membrane integrity and in intracellular signaling). Phospholipase C is involved in the hydrolysis of phosphatidylinositol and phosphatidylinositol diphosphate (PIP2) (formed from phosphatidylinositol), resulting in the formation of inositol 1,4,5-triphosphate, which is involved in the signaling of many hormones and neurotransmitters as a second messenger. [13] Two of isomers: myo-inositol (MI) and D-chiro-inositol (DCI) are of greatest importance in PCOS treatment, because of their post-receptor effects of insulin. The biggest sources of inositols are fruits, beans, corn and nuts. [5]; [14]. MI and DCI differ in action and location of occurrence. MI is responsible for the metabolism, transport and breakdown of glucose and its conversion to glycogen, while the great role of DCI is to participate in the insulin signaling pathway and in the stimulation of enzymes regulating glucose metabolism. [13] Moreover, DCI glycans can stimulate insulin secretion in pancreas. [15] MI and DCI play a significant role in ovarian follicle development. MI is responsible for FSH signaling as a second messenger, while DCI is involved in androgen synthesis as an aromatase inhibitor. An adequate ratio of MI to DCI (physiologically it is equal to 100:1 in follicular fluid and 40:1 in plasma) is necessary for proper ovarian function. In PCOS and insulin resistance it is changed due to increased epimerase activity, converting MI to DCI. [13] In PCOS, the MI/DCI ratio is 0.2:1, which probably interferes with FSH signaling. Hence, restoring proper intercourse is crucial in treatment. [16]

Inositol and fertility in PCOS

The HOMA index is used to assess insulin resistance. It is the reduction in the value of this index that we can observe after taking inositol. A number of studies conducted among women with PCOS treated with inositol preparations have shown its effect on decreasing the HOMA index, as well as improving ovulatory function and reducing serum androgen levels. In addition to this, inositol has also shown a positive effect on reducing blood pressure and plasma triglyceride levels, which reduces the cardiovascular risk faced by PCOS patients. [17] A recent study that compared the drugs used in PCOS (metformin and COC) and inositol therapy showed significant improvements in insulin resistance and lipid profile after inositol, while treatment with conventional contraceptive drugs worsened insulin resistance, cholesterol and triglyceride levels, and there was a decrease in ovarian hormone levels. [18] As mentioned earlier, inositol isomers also have a positive effect on reducing androgen levels, making them effective in treating hirsutism, as well as causing a reduction in total androgen levels. [5] In a review of studies comparing inositol treatment and the use of placebo and metformin, there was a significant increase in the likelihood of spontaneous ovulation and an increase in the frequency of menstrual cycles with inositol. By regulating menstrual cycles, inositol may also

have a positive effect on reducing the risk of endometrial hyperplasia and malignancies. [19] However, there was a need to further investigate the effect of inositol on the rate of spontaneous clinical pregnancies, without the use of assisted reproductive techniques, as well as the rate of live births. Studies conducted to date comparing inositol, metformin and placebo have not yielded significant differences in terms of pregnancy rates. The data obtained in the studies are promising but have too little power. If this issue is further investigated, it is possible that inositol isomers will become the first line of fertility support in women with PCOS. [9] It was confirmed that inositol, compared to metformin, showed greater efficacy in improving pregnancy rates after stimulation. In subsequent years, the positive effect of inositol on restoring ovulation, regular menstrual cycles, and thus improving fertility and pregnancy rates in women with PCOS was again confirmed. [20] While it has been confirmed that the 40:1 ratio was best at restoring ovulation in PCOS patients, recent studies offer new insights. It was shown that taking inositol preparts 2 times a day in a 3:1 MI/DCI ratio resulted in higher rates of pregnancies and live births compared to using them in a 40:1 ratio, as previously proven. In an even more recent study, even a 2:1 ratio was shown to give even better results in terms of pregnancy rates. However, it should be kept in mind that high doses of DCI can negatively affect the treatment process of patients, due to MI resistance and decreased MI absorption caused by competition between DCI and MI for the transporter.[5] During studies conducted on mouse models, it appeared that MI may be responsible for stimulating the progression of oocytes to fertilizable eggs. In addition, MI accelerates the transport of oocytes through the fallopian tube and may also increase the production of anti-Müllerian hormone. Meanwhile, already during pregnancy, MI also appears to play a key role in the proper development of the embryo and prevents oxidative stress-induced damage to both mother and fetus during pregnancy. [21]

The role of inositol in assisted reproductive techniques (ART).

The most common cause of IVF failure in patients with PCOS is insufficient quality of oocytes and embryos. Therefore, the greatest focus should be on improving their quality. MI improves oocyte quality and plays a significant role in increasing pregnancy rates due to its ability to sensitize cells to insulin. [2] Although there is not enough strong evidence for direct improvements in fertility with inositol alone, significantly better outcomes have been shown in patients undergoing assisted reproductive technologies who received inositol supplementation during preparation, compared to those who did not. Among other things, it was shown that the use of MI in combination with clomiphene citrate (CC), used as a first-line drug for ovulation induction, significantly increased ovulation rates. In addition, patients' resistance to CC decreased and pregnancy rates improved. The use of MI during in vitro fertilization also has

positive effects, as it reduces the amount of recombinant FSH administered, as well as the ovulation induction time. [16] During subsequent studies, it has been observed that the use of myo-inositol in women with PCOS undergoing controlled ovarian hyperstimulation with rFSH and intrauterine insemination reduces the dose of rFSH administered and also the length of the cycle. In addition, the pregnancy rate increased compared to the control group. Other studies have observed that MI supplementation is able to reduce the amount of FSH in women undergoing IVF, both those with and without PCOS. The use of MI has also been shown to have a positive effect on ART in women with poor ovarian response, improving the conception rate or ovarian sensitivity index, as evidenced by the lower amount of FSH used. [22] Although there is ample evidence of the positive impact of MI during ART procedures, the role of DCI is controversial in this case. When DCI was administered to non-obese women with PCOS and normal insulin sensitivity undergoing IVF, oocyte quality and ovarian response were shown to deteriorate with increasing doses of DCI. This is most likely due to the fact that an adequate MI:DCI ratio is required for normal ovarian function, hence supplementation with DCI alone is not appropriate. [9] The role of MI in the process of preparation for assisted reproductive techniques has been studied since the 1990s. It has been shown that a high level of MI in follicular fluid correlates with high oocyte quality and thus increases the chance of a successful pregnancy after in vitro fertilization. It has been shown that MI significantly improves the quality of oocytes and thus increases the chances of successfully completing the in vitro fertilization procedure in women with PCOS, which was confirmed in the following years during a number of subsequent studies. [23] Improvement in oocyte quality and pregnancy rates by inositol is achieved by lowering estradiol levels on the day ovulation is triggered and reducing the number of medium-sized follicles and increasing the number of large follicles. [14] The formation of large follicles is possible because MI stimulates the progression of folliculogenesis. Thus, it contributes to reducing the risk of ovarian hyperstimulation. [20]

A study of women with PCOS undergoing intracytoplasmic sperm injection (ICSI) showed a significantly higher number of pregnancies in women who received folic acid (200 μg) combined with MI (2g) twice daily 3 months before the procedure, compared with women who received only folic acid (200 μg twice daily). [24] Similar evidence was obtained in an IVF clinical trial on women with PCOS. Here, too, there was an increased number of mature oocytes in the group that received 1g of MI and 400 μg of folic acid compared to the group treated with folic acid in combination with cyanocobalamin. [22] In addition to studies that have yielded very promising results regarding the role of inositol in PCOS patients, there have been a plethora of studies whose results were not statistically significant or yielded less than satisfactory results. In 2019, a review of data was published on the effect of treatment with

myo-inositol (MI)/di-chiroinositol (DCI) compared to no treatment, placebo or other treatment of ovarian reserve markers in women with PCOS and assessing the effect of these therapies on reproductive outcomes in women with PCOS undergoing an IVF/ICSI procedure. This is precisely one review according to which the efficacy of inositol in preparation for IFV/ICSI procedures cannot yet be unanimously confirmed, and there is a need for furthermore thorough studies. The review accurately points out the inconsistency of the study results obtained, which may be due to the significant heterogeneity of the patient population, as well as the lack of equal doses and timing of inositol use. In addition, it was pointed out that inositols may only be effective in women with PCOS who exhibit insulin resistance, hence the inclusion of all PCOS patients, regardless of their insulin sensitivity, may result in inconsistent results from the studies conducted. [25] Therefore, there is still a need for larger, more thorough studies on the role of inositol in ART treatments. The 2023 international evidence-based guidelines for the evaluation and treatment of PCOS still consider inositol an experimental therapy. However, despite this, numerous studies show the positive effects of inositol on improving ovarian activity, oocyte quality, reducing the risk of hyperstimulation and increasing the rate of successful pregnancy termination, especially when inositol is also supplemented during pregnancy. [26]

Possible problems during inositol treatment.

MI is a natural molecule used as a dietary supplement and has been included on the list of compounds generally recognized as safe (GRAS). No side effects were observed when using MI and DCI, even in combination. However, it is important to note that in order for inositol to fulfill its biological functions, an adequate ratio of MI to DCI must be maintained in the organ. This is because it has been shown that excess DCI can have a negative impact on blastocyst quality. The reason for this may be that DCI inhibits aromatase, which converts androgens to estrogens. Hence, once it is inhibited, androgen levels may be higher, which will impair the quality of the blastocyst. It has also been shown that administering too much DCI can reduce intestinal absorption of MI, as DCI and MI will compete for the SMIT2 transporter, to which DCI has a slightly higher affinity. Some patients may also experience inositol resistance, the mechanism of which is not yet fully known. It is speculated that the lack of inositol's effects may be due to problems with its absorption, such as obesity or dysbiosis. [21] For this reason, a technique has been developed to promote MI absorption through the simultaneous administration of alpha-lactalbumin, which aids passage through biological barriers. [27]

Conclusions.

Inositol is an effective and safe treatment option for PCOS. Its use is not associated with side effects like other traditional treatment methods. In addition, it is a preparation easily available to patients. Myo-inositol, as a second messenger of gonadotropins and insulin, supports the proper development of oocytes and the progress of embryogenesis. It also turned out to be helpful in inducing ovulation and restoring normal menstrual cycles, improving the quality of oocytes and ovarian function, as well as reducing the risk of ovarian hyperstimulation syndrome, to which patients with PCOS are particularly vulnerable. These properties are also helpful in improving fertility and preparing patients for IVF/ICSI treatments. At the same time, DCI levels above a certain threshold may adversely affect ovarian function, hence, over the years it has been proven that to maintain proper ovarian function it is necessary to maintain an appropriate MI/DCI ratio, but there is still a need to investigate whether the previously established 40:1 ratio is the most optimal. There is also a need to conduct larger studies that would further clarify the effect of inositol on fertility, spontaneous ovarian cycles, clinical pregnancy rates and live birth rates in ART, as the data available in the literature so far often report statistically insignificant results, or there are studies that due to some limiting factors, such as a small study population or heterogeneity of the patient population, as well as different doses and duration of inositol use, do not provide clearly satisfactory results. It is also necessary to develop precise treatment regimens and adjust the doses of the preparation, depending on the phenotype of the disease presented by the patients. To sum up, a number of studies have proven the effectiveness of inositol in the treatment of patients with PCOS.

It improves insulin sensitivity and oocyte quality, which is the main goal in the treatment of infertility in these women. Additionally, MI has been shown to be helpful in successfully performing ART treatments and improving pregnancy and birth rates, especially when supplemented during pregnancy as well. These data prove that inositol has a chance to become the first choice in the treatment of women with PCOS and improving their fertility, as long as more and more detailed studies are developed that provide reliable, statistically significant results confirming the validity of its use.

Author's contribution

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