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Fertility Treatment in PCOS: Metformin vs. Inositol

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by

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Abstract

The most common endocrine disorder affecting women is polycystic ovary syndrome (PCOS) (Pourghasem, 2019). Metformin is commonly used to decrease insulin resistance and increase fertility in these women. However, it is known to cause many side effects, which are mostly gastrointestinal related. Myoinositol is a B-vitamin that is thought to also decrease insulin resistance and increase fertility with few side effects. The purpose of this literature review is to determine whether myoinositol is a comparable substitute for metformin in patients with PCOS suffering with infertility. This was done by evaluating pregnancy rates, insulin resistance, and side effects of metformin and myoinositol. A literature review was completed and found that both medications had similar pregnancy rates. Neither medication affected insulin resistance. However, myoinositol had few side effects and appeared to reduce the occurrence of ovarian hyperstimulation syndrome (OHSS). In conclusion, both medications had similar efficacy at increasing pregnancy rates, but myoinositol had fewer side effects and provided protection against OHSS.

Introduction

The most common endocrine disorder affecting women is PCOS (Pourghasem, 2019). This is an endocrine condition that leads to hirsutism, irregular menstrual cycles, acne, insulin resistance, and hyperinsulinemia (Morin-Papunen, 2012). Approximately 80% of infertility in women is caused from anovulation secondary to PCOS (Tang and Glanville, 2006). Not only can PCOS affect fertility, but it can also lead to a higher rate of miscarriage, causing three times the rate of pregnancy loss compared to individuals without PCOS (Morin-Papunen, 2012).

The Rotterdam criteria is used to diagnose PCOS. This criteria includes anovulation, oligomenorrhea, and clinical and/or biochemical indications of hyperandrogenism which include the presence 12 or more follicles of 2-9 mm in size on each ovary or increased ovarian volume of over 10 mL per ovary (Emekçi Özay et al., 2017).

Myoinositol is a member of the B vitamins that plays a role in lipid synthesis, cell growth, the structure of the cell membrane, cell cytogenesis and cell morphogenesis. Through these mechanisms, it can improve oocyte maturation, hormone levels, and insulin resistance (Emekçi Özay et al., 2017). Metformin can improve insulin resistance by decreasing gluconeogenesis and increasing the rate of glucose use in the periphery (Sturrock, 2022). This is thought to lead to increased fertility in women with PCOS.

Statement of the Problem

Many women with PCOS have difficulty achieving pregnancy. Metformin has traditionally been the treatment choice to help improve pregnancy rates in this population. More recently, it has also been proposed that myoinositol may be as beneficial at improving pregnancy rates in this population of women while inducing fewer side effects.

Research Question

In patients with PCOS, is myoinositol as effective as metformin in increasing pregnancies?

Research Methods

A literature review was conducted using PubMed, Embase, and CINHAL. Keywords and MESH terms were both utilized to find articles used to assess the use of metformin and myoinositol in patients with infertility and polycystic ovary syndrome. After evaluating these articles, other articles were accessed using the Similar Articles category in PubMed. Only articles less than 18 years old were considered for the review. There was a total of 1,824 articles that evaluated the use of metformin, myoinositol, or both medications for women with PCOS. Several articles were excluded because they did not evaluate the pregnancy rates of women using these medications. Many articles were excluded because they also evaluated the use of other herbal or nutritional supplements which were not evaluated in this review. There was a total of eight studies that met the criteria for this review. Of these, three articles met the criteria for evaluation of metformin use in infertile women with polycystic ovary syndrome, three articles met the criteria for evaluation of myoinositol use in infertile women with polycystic ovary syndrome, and two articles met the criteria for evaluation of the use of metformin plus inositol in infertile women with polycystic ovary syndrome.

Literature Review

Myoinositol in Women with PCOS

Akbari Sene et al. (2019) conducted a double blind randomized clinical trial to determine the embryo quality, oocyte quality, and fertilization rate in patients with PCOS who received myoinositol. The trial was conducted from February 2017 to May 2018 (Akbari Sene et al.,

2019). Fifty women were chosen at random from patients who were referred to the IVF Center at Iran University of Medical Sciences. These patients were previously diagnosed with PCOS using the Rotterdam criteria and suffered from infertility. They were being considered for in-vitro fertilization treatment. According to the study, the demographics, clinic characteristics, and sperm analysis of the patients and their significant others were evaluated and found to be comparable among the patients prior to beginning the trial. Exclusion criteria included other metabolic disorders, diabetes mellitus, BMI (body mass index) over 35 kg/m^2, allergies to inositol, or history of receiving hormone medications in the past three months. Women between the ages of 20 to 35 with partners who produced a normal semen analysis were deemed appropriate for the study. The mean age in the group receiving myoinositol plus folic acid was 31.3 (SD 4.1) while the mean age of the control group was 29.78 (SD 4.5).

Utilizing permuted block randomization, this group was then divided in half. (Akbari Sene et al., 2019). One group received 4 grams of myoinositol plus 400 mg of folic acid daily for one month. The second group was the placebo-controlled group and thus, received only 400 mg of folic acid daily. Both groups received the medication for one month prior to starting the trial until the ovum were retrieved for in-vitro fertilization. At the end of the month, an antagonist cycle of hormone treatment was performed on both groups, and ovum were retrieved for in-vitro fertilization.

The egg quality was assessed using European Society of Human Reproduction and Embryology guidelines. The mean (SD) score for number of retrieved oocytes was 13.8 (7.67) in the group receiving myoinositol, whereas the mean (SD) score for the number of retrieved oocytes was 12.4 (7.67) in the control group (Akbari Sene et al., 2019). The number of oocytes that were retrieved was not statistically significant between the two groups ($p < 0.6$). However,

in comparison to the control, the percentage of oocytes that were in the MII phase ($p < 0.035$) and fertilization rate ($p < 0.03$) both significantly increased. The study also showed that the number of grade I (high quality) embryos was significantly increased ($p = 0.006$), and the percentage of grade III (poor quality) embryos was significantly decreased ($p = 0.029$) in the group receiving myoinositol. The pregnancy rate in those receiving myoinositol was 40% while the pregnancy rate in the control group was 35% ($p = 0.744$).

This study only included fifty patients, which is a small sample of the population. If the study were larger, it may have provided a more accurate representation of the patient population who suffer with infertility secondary to PCOS. There were five patients who dropped out of each group by the end of the study and thus, were not able to be included in the data, making it an even smaller representation of the population (Akbari Sene et al., 2019). It was also a very small-time frame of only one month; therefore, this study may not be an accurate representation of the benefits or adverse effects of the medication over time. Also, the study did not specify its definition of infertility.

The results of the study did indicate that there may be some benefit to the addition of myoinositol for patients with infertility secondary to PCOS (Akbari Sene et al., 2019). However, the study did not definitively prove the benefit of myoinositol due to its small sample size and short time frame.

Emekçi Özay et al. (2017) conducted a randomized prospective trial to determine the effect that myoinositol has on the pregnancy rates of women with PCOS who also received ovulation induction treatment and intrauterine insemination. The trial was conducted between March 2013 and May 2016 and performed at the Department of Obstetrics and Gynecology (Emekçi Özay et al., 2017). There were a total of 196 women included in the trial who were

between the ages of 18 and 35 years. Inclusion criteria involved women who were diagnosed with PCOS and anovulation with infertility for greater than 12 months. The women were all patients of Dokuz Zeylul University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, and Infertility Outpatient Clinic. The Rotterdam criteria were used to diagnose PCOS. Other endocrine causes of infertility and male factor infertility were ruled out prior to beginning the trial. Patients did not take oral contraceptives, antiandrogens, or medications that could affect hormone metabolism for the previous six months leading up to the trial.

The women were divided into two groups at random (Emekçi Özay et al., 2017). Each group included 98 patients. Group 1 was prescribed 4 grams of myoinositol plus 400 micrograms of folic acid. Both medications were started during the first initial appointment and were taken twice daily for 12 weeks, including during controlled ovarian hyperstimulation and intrauterine insemination. Myoinositol was stopped ten days after intrauterine insemination. Group 2 received 400 micrograms of folic acid daily.

Both groups received recombinant FSH (follicle stimulating hormone) on day three of their menstrual cycle. In those who experienced oligomenorrhea or amenorrhea, menstruation was induced with oral progestin. For both groups, when a dominant follicle was seen on transvaginal ultrasonography, an ovulation trigger of choriogonadotropin alpha was administered and intrauterine insemination was performed 36 hours later (Emekçi Özay et al., 2017). The cycle was canceled if more than five follicles greater than or equal to 18 mm were noted or if the endometrium thickness was less than seven millimeters.

Prior to beginning the trial, height, weight, waist circumference, hip circumference, waist/hip ratio, and BMI were evaluated (Emekçi Özay et al., 2017). All measurements were

taken by the same person. On day two or three of the menstrual cycle, fasting plasma glucose, fasting insulin, FSH, LH (luteinizing hormone), estradiol, prolactin, TSH total and free testosterone, DHEAS (dehydroepiandrosterone-sulfate), and SHBG (sex hormone binding globulin) were measured. Progesterone was measured on day 21 of the cycle.

The primary outcome that was evaluated included clinical pregnancy rate (Emekçi Özay et al., 2017). A pregnancy was defined as cardiac activity after six weeks of gestation seen on transvaginal ultrasound. The data was analyzed with Statistical Program for Social Sciences with a significance level of $p < 0.05$. The HOMA-IR score was evaluated to monitor insulin resistance. A HOMA-IR score of 2.5 and above was considered insulin resistant.

In the group taking myoinositol, serum progesterone levels showed a significant increase after 12 weeks ($p <0.01$) (Emekçi Özay et al., 2017). There was also a decrease in fasting insulin ($p = 0.03$) and fasting glucose ($p = 0.04$). Group 1 had two patients dropped from the trial who did not respond to FSH administration, and one patient canceled due to an elevated risk of ovarian hyperstimulation syndrome. Group 2 had five patients dropped due to no response to FSH and three patients canceled due to elevated risk of ovarian hyperstimulation syndrome.

In group 1, the amount of FSH required to stimulate ovulation ($p = 0.02$) and cycle duration ($p = 0.03$) were significantly lower and rates of clinical pregnancy were higher ($p = 0.02$) (Emekçi Özay et al., 2017). During the initial evaluation of insulin resistance, 47 patients in group 1 and 45 patients in group 2 had insulin resistance. After treatment with myoinositol, the patients in group 1 who originally displayed insulin resistance had a lower FSH dose requirement ($p = 0.02$) and ovulation induction was shorter ($p = 0.02$). However, there was no statistical difference in HOMA-IR evaluation after treatment with myoinositol. Pregnancy rates were higher in group 1 ($p = 0.04$) and the number of canceled cycles were decreased in group 1

($p = 0.0.04$). There was no statistical difference in trigger day endometrial thickness, follicle number greater than 17 mm, or spontaneous abortion rate.

This article only included women who were patients at the same clinic; therefore, it may not be the most accurate representation of the population of women with PCOS (Emekçi Özay et al., 2017). The patients in the trial only took the medication for three months. If the trial were longer, evaluation of the long-term effects of myoinositol could be analyzed. Although there were aspects of the trial that should be improved, when evaluating body composition of the patients, only one person performed the measurements which helped to reduce error and discrepancies.

Pourghasem et al. (2019) conducted a randomized single-blind controlled clinical trial to determine the effectiveness of inositol and metformin in infertile women with polycystic ovary syndrome who were resistant to letrozole. This study was performed in Iran between 2015 and 2016 (Pourghasem et al., 2019). The inclusion criteria consisted of women who were between the ages of 15 to 38 years with a diagnosis of PCOS according to the Rotterdam criteria. Also, infertility for at least one year, absence of tubal abnormalities or male anatomic abnormalities; an intact uterine cavity, and thyroid levels within normal limits. Any patient with hyperprolactinemia or other endocrine disorders was excluded from the trial. Prior to beginning the trial, infertility duration, BMI, type of infertility, triglyceride level, cholesterol, hirsutism, LH/FSH, and menstrual pattern were evaluated.

There was found to be no significant differences in socio-demographic and clinical characteristics among the participants ($p > 0.05$) (Pourghasem et al., 2019). Primary outcomes included ovarian function and rate of pregnancy. Ovarian function was evaluated based on the presence of mature follicles that were greater than or equal to 17 mm over the duration of 12 to

16 menstrual cycles. A clinical pregnancy was defined as presence of gestational sac five weeks after HCG (human chorionic gonadotropin) administration, as seen on ultrasonography.

There were 50 participants in each of the three groups. All patients received 2.5 mg letrozole. Their ovarian follicles and endometrial thickening were monitored via vaginal ultrasonography. When a mature follicle had developed, 10,000 units of HCG were injected. A mature follicle was considered equal to or larger than 17 mm. If a patient did not ovulate with 2.5 mg of letrozole, they were administered 5 mg following the same protocol (Pourghasem et al., 2019). Then, 7 mg of letrozole was administered if the patient still did not ovulate. Patients who did not ovulate even with the highest dose of letrozole were divided into three groups. Group 1 was the control group and received 200 mcg folic acid daily as a placebo. Group 2 received 1500 mg of metformin daily plus 200 mcg of folic acid. Group 3 received 2000 mg myoinositol plus 200 mcg folic acid twice daily for three months.

Descriptive characteristics, Chi-square, ANOVA (Analysis of variance), and Kruskal-Wallis tests were used to analyze the data (Pourghasem et al., 2019). The Scheffe test and statistical software were also utilized. $P < 0.05$ was considered statistically significant for all tests.

It was only considered a clinical pregnancy if a gestational sac was visible via ultrasonography after five weeks post HCG injection. The pregnancy rate was not statistically significant ($p = 0.56$). In group 1, which received letrozole and folic acid, there were 16 patients who achieved pregnancy. In group 2, which received letrozole, metformin, and folic acid, the pregnancy incidence was 19 patients. In group 3, which received letrozole, myoinositol, and folic acid, the pregnancy rate was 14 patients. The group receiving myoinositol had a lower pregnancy incidence compared to the groups receiving placebo or metformin; however, it was not

statistically significant ($p = 0.56$) (Pourghasem et al., 2019). There were no side effects in the control group or the group taking myoinositol; however, the group taking metformin had an incidence of gastrointestinal side effects of 42%.

Ovarian function was then evaluated by assessing infertility over time. There was no significant difference among the three groups in terms of ovarian function ($p>0.56$); however, ovarian function was slightly lower in the group taking letrozole, folic acid, and inositol. There were 31 patients showing normal ovarian function in group taking inositol compared to the group taking metformin with 33 patients who had normal ovarian function (Pourghasem et al., 2019).

Fertility duration was statistically significant ($p = 0.001$), with 20 patients who continued to experience infertility after two to five years after the trial began and only four patients who continued to experience infertility after six to nine years in group 1 (Pourghasem et al., 2019). In group 2, 23 patients continued to experience infertility after two to five years and 10 patients experienced infertility after six to nine years. In group 3 (letrozole, myoinositol, and folic acid), 15 patients continued to experience infertility after two to five years and 16 patients continued to experience infertility after six to nine years.

BMI was also assessed during the process of evaluating ovarian function and showed a statistically significant improvement ($p=0.002$). In group 1, BMI was lowered to a normal range of 18.5 kg/m^2 to 24.9 kg/m^2 in 10 of the patients (Pourghasem et al., 2019). Group 2 had three patients and group 3 had 18 patients who had a BMI that was lowered to this normal range. In the myoinositol and folic acid group, ovarian function was increased when BMI decreased, and ovarian function decreased when BMI increased. In the group taking metformin and folic acid, ovarian function was increased even when BMI was high.

In review of the data, the study showed that the addition of inositol and metformin in patients with letrozole resistance improved ovarian function, but the improvement was not significant (Pourghasem et al., 2019). Metformin had a higher rate of side effects compared to the myoinositol and control groups who had no side effects. The data showed that myoinositol led to a decrease in pregnancy rates after 12 weeks when compared to the control group and the group receiving metformin, but there was no statistical significance. It was concluded that ovarian function improvement in the inositol group when BMI was between 18.5 kg/m^2 to 24.9 kg/m^2 was due to decrease in insulin resistance due to a higher BMI.

Although it is beneficial that the trial evaluated fertility for up to six to nine years, the study group was small with only 150 patients. A larger group would allow for a more realistic representation of the population of women who suffer with PCOS and infertility who are resistant to letrozole. Including a control group allowed for more accuracy in the data analysis. This study also evaluated fertility in multiple ways which allowed for a more accurate evaluation of the benefits of the medications.

Metformin in women with PCOS

Sturrock et al. (2022) conducted a randomized placebo controlled double-blind crossover study to determine if a pretreatment of metformin has benefits for patients who are infertile and resistant to clomiphene (Sturrock et al., 2022). The trial included 26 women who were then divided into two groups. One group received a placebo medication while the other received metformin.

The ages ranged between 28.3 and 31.8, with the mean age 30.1 (Sturrock et al., 2022). The average BMI was 33.3 and ranged between 30.2 and 36.6. Chemistry data were also evaluated for each individual. Inclusion criteria included amenorrhea, chronic oligomenorrhea

with a cycle greater than 40 days for at least six months; serum progesterone of equal to or less than 10 nmol 1^{-1} on day 20 to 22. It was also required that persistent anovulation was seen on ultrasound, as evidenced by endometrial thickness of less than or equal to 5 mm and the absence of an ovarian follicle greater than or equal to 14 mm after clomiphene citrate 100 mg was administered for five days (Sturrock et al., 2022). A baseline physical to include blood pressure, Ferriman Gallwey hirsutism score, and ovarian ultrasound was also performed prior to beginning the trial. Insulin resistance and free androgen index were also evaluated.

The metformin/placebo dose was started at a low dose, then increased over a period of three weeks to decrease side effects. During the first week, the patients received 500 mg daily with the main meal for one week, then 500 mg twice daily during week two, then increased to 500 mg three times daily moving forward (Sturrock et al., 2022). The medication was given for a 12-week period. After 12 weeks, menstruation frequency and ovulation were evaluated by assessing serial ovarian scans and luteal phase progesterone estimates. At this time, if a regular menstrual cycle was induced, the patient continued the metformin/placebo for 3 more months. If normal menstruation had not occurred, it was induced with medroxyprogesterone 5 mg daily for five days. If after 12 months, ovulation did not occur, metformin/placebo were continued with the addition of clomiphene citrate 50 mg daily on days two through six of the cycle. It was then increased to 100 mg if ovulation again, did not occur. No more than three cycles of clomiphene were given.

Primary outcomes evaluated in this trial included pregnancy, spontaneous menses, and spontaneous and clomiphene-induced ovulation (Sturrock et al., 2022). Biochemical changes were evaluated as secondary outcomes including estradiol, testosterone, LH, FSH, prolactin, sex hormone binding globulin, insulin, progesterone, fasting glucose, insulin resistance using

HOMA-IR equations, beta cell function, and free androgen index. The significance level was set at less than 0.05. Data was analyzed using unpaired t-test and contingency tables as well as the statistical software Stat 100 (Sturrock et al., 2022).

Of the 12 women in the metformin group, spontaneous menstruation occurred in five women, while six of the 14 women in the placebo category experienced spontaneous menstruation. However, this was not statistically significant ($p = 0.63$). There were no women in the metformin category that spontaneously ovulated. One woman in the placebo group spontaneously ovulated ($p = 0.30$) (Sturrock et al., 2022). The efficacy of the clomiphene was the same between both groups. Ovulation was induced with clomiphene in five of the patients in the metformin group and four patients in the placebo group ($p = 0.63$). Three of the 12 women in the metformin group became pregnant, while two of the 14 women in the placebo group became pregnant ($p = 0.59$). The mean live birth rate beyond 24 weeks was statistically significant, with a mean of 37.8 live birth rates in the metformin group and a mean of 14.3 in the placebo group ($p=0.025$). There was no significant difference in weight, BMI, or blood pressure between the metformin group and the placebo group, not including the women who became pregnant (Sturrock et al., 2022). There was also no significant difference in fasting glucose, fasting insulin, insulin resistance, testosterone, sex hormone binding globulin, free androgen index, LH, FSH, prolactin, 17-Hydroxyprogesterone, or estradiol.

Due to the long duration of the trial, there were two women who dropped out of the metformin group (Sturrock et al., 2022). Of these two women, both denied dropping out due to side effects, but instead, intended to move forward with in vitro fertilization therapy. Metformin did not appear to affect spontaneous menstruation, spontaneous ovulation, or androgen concentrations in comparison to placebo.

The trial only included 26 women, which is a small reflection of the population of women with PCOS. Although the trial was small, it was a long study, with women receiving metformin or placebo for six months (Sturrock et al., 2022). This allowed the for medication to work to its fullest extent compared to other trials where the patients only received the medication for a brief period, often only one to two months. It was also placebo-controlled and double-blinded, which helped to reduce biases that may interfere with the results of the study.

Tang and Glanville et al. (2006) completed a randomized, placebo-controlled, double-blind study over the course of three years. The goal of this study was to analyze how metformin affected fertility in patients receiving IVF treatment. Ninety-four women were included in the trial. Metformin was administered during 52 of the treatment cycles while a placebo was administered to 49 of the treatment cycles (Tang and Glanville et al., 2006). The mean age in the group receiving metformin was 31.3 (4.0 SD). The mean age in the group receiving the placebo was 31.1 (4.0 SD) (p-value = 0.850). The mean BMI of the metformin group was 27.9 kg/m^2 (5.6 SD), while the mean BMI of the placebo group was 26.9 kg/m^2 (4.8 SD) (p-value = 0.330). The length of infertility prior to the trial in the metformin group was 4.5 years and 4 years in the placebo group. A p-value of less than or equal to 0.05 was considered significant.

This study diagnosed PCOS by the visualization of 10 or more cysts that had a diameter of six to eight millimeters seen on transvaginal ultrasound, and additionally with either oligomenorrhea/amenorrhea or hyperandrogenism. Women with a BMI of 30 kg/m^2 or greater were advised to lose weight in the 6 to 12 months leading up to the trial. Inclusion criteria also included serum testosterone <5.0 nmol/l, normal prolactin concentration, thyroid, renal, and hematological indices. It was also required that participants had not received metformin in the three months leading up to the trial. If a patient had received hormone therapy in the previous six

weeks leading up to the trial, they were excluded from the trial. Additionally, if a patient had a chronic disease that might hinder the pharmacokinetics of metformin, including renal or liver disease, the patient was excluded from the trial as well (Tang and Glanville et al., 2006). Any patient who experienced irregular menstrual cycles was assessed to rule out causes other than PCOS.

A transvaginal ultrasound was completed one month prior to the clinical trial as well as baseline fasting glucose and insulin, sex hormone binding globulin, and testosterone levels (Tang and Glanville, 2006). All patients were administered a five-day course of 10 mg of Provera (medroxyprogesterone), then two weeks of combined oral contraception starting on the second day of their menstrual cycle. The patients were then given GnRH for two to three weeks. After this, the patients were randomly split into two groups, in which half received metformin and half received a placebo pill. These treatments remained blind until the last patient finished the regimen. The patients were instructed to take one tablet every 12 hours from the first day of GnRH until the egg retrieval was performed. From there, the patients all followed the same fertility regimen of monitoring follicular growth and increased FSH based on the response.

If there were less than two lead follicles by day 14, the treatment was abandoned, and the patient was done with the trial. Lead follicles were characterized as over 17 mm (Tang and Glanville et al., 2006). A clinical pregnancy was defined as 12 weeks of gestation, while a pregnancy of 24 weeks of gestation or greater was considered a live birth.

From the beginning of the clinical trial to the day of oocyte retrieval, there were no significant changes in fasting glucose levels. Metformin did, however, lower fasting insulin levels after four weeks when compared to the placebo ($p = 0.05$) (Tang and Glanville et al., 2006). Metformin also reduced estradiol levels at the time of HCG administration during the IVF

protocol. There were no increases in testosterone levels in those patients taking the metformin, which included a baseline of 1.99 nmol/l to a rise of 1.97 nmol/l; however, there was an increase in the placebo group ($p = 0.040$) with a rise from 2.06 nmol/l to 2.52 nmol.

The cycles that achieved conception had a lower free androgen index (2.33 nmol/l) compared to those cycles that did not achieve conception (3.0 nmol/l) ($p = 0.024$) (Tang and Glanville et al., 2006). The patients in the metformin group experienced lower vascular endothelial growth factor ($p = 0.048$). Due to poor response to the IVF medications, five cycles in the metformin group were dropped and two cycles of placebo group were dropped, but the difference was not significant ($p = 0.487$).

This study resulted in an improvement in the pregnancy outcomes and reduced risk of ovarian hyperstimulation syndrome after 28 days of metformin in combination with an IVF cycle. However, it did not enhance the rates of fertilization or response to the stimulation medications utilized during the IVF cycle. A pregnancy rate of 38.5% in the women receiving metformin and 16.3% in the women receiving placebo ($p = 0.023$) was reported. Metformin reduced serum androgen, estradiol, fasting insulin, and vascular endothelial growth factor, but was unable to prove that metformin increases fertilization, cleavage rate, embryo quality, or number of retrieved eggs (Tang and Glanville et al., 2006).

The study only included 94 patients, which is a small clinical trial. If there were a larger number of patients, the study would have more accurately represented the population. The trial also only lasted twenty-eight days. It included only one menstrual cycle and only one cycle of in-vitro fertilization. A longer trial where the patients received a longer course of metformin might have shown different data and response rates of the metformin. Although the trial was short, over 95 percent of the clinical procedures were carried out by only one researcher, which helps reduce

the differences in technique among individual researchers, and thereby reduces the number of variables (Tang and Glanville et al., 2006).

Requesting that women with a BMI of 30 kg/m^2 or greater lose weight prior to the trial may have changed the results. Because they lost weight prior to the trial, it is difficult to know if the weight loss affected their hormone production and fertility. The trial results did not include whether those who had lost weight also had increased fertility during the trial, so it is unknown if the healthier lifestyle contributed to the results, or if the results were due to the medication. The trial information also did not include how many women were required to lose weight from each category.

Morin-Papunen et al. (2012) conducted a multicenter, double-blind, placebo-controlled, randomized trial to determine if metformin decreases early miscarriage rates and improves pregnancy and live birth rates in women who suffer with PCOS. The study included 300 women who were diagnosed with PCOS and referred to one of three different clinics for anovulatory infertility (Morin-Papunen et al., 2012). The trial took place between January 2003 and December 2009.

Those included in the trial were between the ages of 18 to 39 years with a BMI greater than 19 kg/m^2 with a diagnosis of PCOS based on Rotterdam criteria (Morin-Papunen et al., 2012). All patients had polycystic ovaries seen on ultrasound prior to the trial and most had oligomenorrhea, hyperandrogenism, or hirsutism. The two groups in the trial had similar characteristics. Tubal patency and male fertility were confirmed prior to beginning the trial. A baseline metabolic, clinic, and hormonal parameter was established at baseline, three months after treatment began, and as needed.

The patients all suffered from infertility for a minimum of six months prior to the trial start date, with at least three months since any infertility treatments were administered. Patients were not included in the trial if they were diagnosed with type 2 diabetes mellitus, liver disease, or a history of cardiac or renal failure (Morin-Papunen et al., 2012). Patients were also not included if they currently used hormone medications, tobacco, or alcohol.

The patients were then divided into two groups which included obese and non-obese patients (Morin-Papunen et al., 2012). These two groups were then randomized using random blocks of ten with computer-generated lists. There was a total of 160 women in the group receiving metformin, with 70 of those women from the obese category and 90 in the non-obese category. There was also a total of 160 women in the placebo category, with 73 in the obese category and 87 in the non-obese category.

Both the metformin and the placebo pills were prepackaged in identical packaging. All patients and personnel involved in the study were blind to the drug and dosing being prescribed to each patient. One tablet of metformin or placebo was administered daily for one week and then increased by one tablet every week until the non-obese group was taking three tablets daily and the obese group was taking four tablets daily (Morin-Papunen et al., 2012). The medications were continued for a minimum of three months and a maximum of nine months. If a woman became pregnant, she continued the medication up until week 12 of gestation. A smaller dose of metformin was used in non-obese women in attempt to minimize side effects and dropouts while simultaneously providing ovulation restoration.

After three months of the medication, if pregnancy did not occur, ovulation was induced using clomiphene for up to four to six cycles (Morin-Papunen et al., 2012). If pregnancy still did not occur, gonadotrophins or aromatase inhibitors were then used to stimulate ovulation. If a

male was also found to have subfertility during the pre-trial evaluations, intrauterine insemination or in vitro fertilization was also utilized.

If a woman received a positive pregnancy test, it was considered a clinical pregnancy. A first trimester miscarriage was defined as a lack of cardiac activity prior to 12 weeks of gestation, as evidenced on ultrasonography after pregnancy was confirmed with a pregnancy test. The definition of birth was considered a live pregnancy after 22 weeks of gestation or an infant that weighed 500 grams or more. A monthly urine pregnancy test was obtained. There was a similar dropout rate between the metformin (16.8%) and placebo (21.2%) groups, which was not significantly different; however, more women who received metformin (34.6%) experienced side effects when compared to the placebo (7.1%) group ($p < 0.001$) and thus discontinued treatment (Morin-Papunen et al., 2012).

Of the patients receiving metformin, both weight and BMI had a statistically significant decrease after three months ($p < 0.001$). The miscarriage rate of the metformin group was 15.2% compared to the placebo group, which was 17.8% which was not significant ($p = 0.7$) (Morin-Papunen et al., 2012). Throughout the study, there were a total of 135 pregnancies. Of those, 79 pregnancies (53.6%) were in the metformin group. Of the pregnancies in the metformin group, there were 48 pregnancies in the non-obese group and 31 pregnancies in the obese group. There were 56 pregnancies (40.4%) in the placebo group. Of those, there were 19 pregnancies in the obese group and 37 in the non-obese group.

Overall, the metformin group had a significant increase in pregnancy rates ($p = 0.006$). In the non-obese women who received metformin, the pregnancy rate increase was not significant ($p = 0.09$). In the obese group, there was a significant increase in pregnancy rates in those who received metformin ($p = 0.04$). Using Cox regression analysis, the study showed there was an

increased possibility of achieving pregnancy with metformin in standard fertility treatment with a 95% confidence interval. The longer a person experienced infertility, the less likely they were to achieve pregnancy, but this was not significant ($p = 0.058$). There was no difference in average time to achieve pregnancy between the metformin and placebo groups ($p = 0.9$). Not including the patients who received IVF, 58% of the women in the group receiving metformin and 39.4% of the patients receiving the placebo were able to achieve pregnancy ($p = 0.008$) (Morin-Papunen et al., 2012).

The percentage of live birth rates were significantly increased in the group receiving metformin (41.9%) compared to the placebo group (28.8%) ($p = 0.014$). The difference between the obese and non-obese groups was not significant. The number of live birth rates remained elevated in the metformin group after excluding those receiving IVF ($p = 0.03$). Again, the difference between obese and non-obese groups was not significant (Morin-Papunen et al., 2012).

Although there were some aspects of the trial that needed improvement, there were some aspects of the trial that were carried out well. Both the patients and staff were blind to the drug codes, medications, and dosing that each patient was prescribed to help eliminate pre-conceived ideas of trial outcomes. The dropout rates were also low and similar between the metformin and placebo groups. This trial included obese and non-obese patients, which allowed for representation of patients with either body type who suffered from PCOS.

There were also some aspects of the trial that could have been improved. The trial used polycystic ovaries as a criteria, but did not describe what they considered to be polycystic ovaries. The results of the trial may have been affected by the fact that some patients with male factor subfertility automatically received intrauterine insemination or in-vitro fertilization, which

may have falsely increased pregnancy rates. Another weakness of the trial was the smaller dose of metformin utilized by the non-obese group, which may have resulted in a lower pregnancy rate and live births.

Metformin plus myoinositol

Prabhakar et al. (2021) conducted a randomized control study to evaluate the impact of myoinositol with metformin and myoinositol alone in women with polycystic ovary syndrome who were infertile and undergoing ovulation induction cycles. The Rotterdam criteria were used to diagnose PCOS. The primary outcome of the study was to evaluate clinical pregnancy rates after six months of treatment. The secondary outcomes included metabolic and endocrine function, ongoing pregnancy, abortion, and multiple pregnancy rates (Prabhakar et al., 2021).

There were 130 women who were screened and a total of 116 women accepted into the trial. The inclusion criteria included women aged 20 to 38 years who failed to conceive for more than 12 months, BMI less than 30 kg/m^2, and patent fallopian tubes, as evidenced by hysterosalpingography or laparoscopy, and mild or no male factor infertility (Prabhakar et al., 2021). Patients then underwent a detailed history and physical exam to include their history of infertility and PCOS, BMI, hip circumference, waist circumference, hirsutism scoring using the modified Ferriman-Gallwey scoring, and secondary sex characteristics.

Baseline lab evaluation was then performed on days two to three of the cycle before the trial began. This included a lipid panel, fasting blood sugar, fasting serum insulin, Homeostatic Model Assessment of insulin resistance, serum FSH, LH, TSH, prolactin, testosterone, sex hormone binding globulin, and anti-mullerian hormone. On day two to five of the cycle leading up to the trial, ovarian reserve and ovarian volume was evaluated (Prabhakar et al., 2021).

The patients were split into two groups using a computer-generated randomization table. Group 1 received 1500 mg of metformin plus 4 g of myoinositol per day. The metformin was divided into three doses of 500 mg daily, while the myoinositol was divided into two doses of 2 g daily. Group 2 received 4 g of myoinositol per day only. This was divided into two doses of 2 g daily (Prabhakar et al., 2021). The patients in both groups continued with this treatment for six months and kept a record of menstrual cycles and weight. They were encouraged to attempt natural conception.

Patients underwent follow-up at one month of treatment and three months of treatment. After three months, clinical parameters were repeated including weight, BMI, waist and hip ratio, and metabolic and endocrine parameters. Anyone who had conceived naturally was documented and excluded from the following analysis. The remaining patients continued the same regimen and were administered ovulation induction to include letrozole, HCG injections, and purified gonadotropin injections. If a patient had a positive pregnancy test, they continued their original regimen for the first three months of pregnancy, and then stopped. The patients with a negative pregnancy test performed up to two more cycles of ovulation induction (Prabhakar et al., 2021).

There were 11 patients who were dropped from the trial leaving a total of 105 patients. Of the patients who remained, there were 50 patients in group 1 and 55 patients in group 2 (Prabhakar et al., 2021). Those who conceived in the initial three months were not evaluated in the secondary outcome of metabolic and hormonal parameters.

For the analysis, a two-sided probability of less than 0.05 was considered statistically significant. After three months of the trial, there was no significant difference between group 1 and group 2 in the metabolic study parameters. There was a statistical improvement of BMI,

LH/FSH ratio, AMH, HOMA-IR, total cholesterol, triglyceride, and HDL in both groups after three months with a 95% confidence interval. There was no significant change in waist/hip ratio, testosterone, or VLDL in either group after three months. The clinical pregnancy rate in group 1 was 42.0 % and 45.5% in group 2. The relative risk was not statistically significant ($p > 0.05$) (Prabhakar et al., 2021).

The ongoing pregnancy rate and live birth rate in group 1 were 40% and 41.8% in group 2 ($p = 0.849$). Spontaneous conceptions during the first three months of the trial were 28% in group 1 and 27% in group 2 ($p = 0.939$) (Prabhakar et al., 2021). During the first ovulation induction cycle, 2.80% conceived in group 1 while 10.00% conceived in group 2 ($p = 0.362$). During the second cycle, 11.43% conceived in group 1 while 8.33% conceived in group 2 ($p = 0.710$). During the first cycle, 6.45% conceived in group 1 and 9.09% conceived in group 2 ($p = 0.990$).

This study also monitored for side effects of the medication. Group 1 reported higher adverse events (84.2%) compared to group 2 (18.7%). This is believed to be due to the metformin regimen (Prabhakar et al., 2021). One patient even dropped out of the trial due to her severe side effects including nausea, vomiting, epigastric pain, bloating, and flatulence which did not respond to anti-histaminic/proton pump inhibitor medications.

During this study, the results were comparable between the group that received metformin alone and the group that received metformin plus myoinositol. There was no advantage to consuming both medications together in relation to BMI, menstrual irregularities, or metabolic or endocrine function. The conclusion of this study illustrated that the use of myoinositol alone in infertile women with PCOS may exclude the need for metformin; therefore, decreasing the risk of adverse side effects that are often caused by metformin (Prabhakar et al.,

2021). Both medications may increase fertility among this population; however, there is no benefit to the administration of both medications simultaneously.

This study had a small sample size which again, does not represent the entire population of infertile women with PCOS. Although it was small, the trial lasted for six months, which allows for a more accurate depiction of how the medications may affect a patient over time. This trial did not include a control group. Including a control group may have provided a more accurate overview of how the medications affected the fertility of the patients. Without the control group, it is difficult to determine if the pregnancies were due to the ovulation induction cycles or the metformin/myoinositol after the first three months. There was also no discussion or evaluation of socio-demographics which can play a role in compliance of treatment and may have changed results.

Agrawal et al. (2019) conducted a randomized control trial from January 2016 to May 2017 to determine if metformin and myoinositol together can provide more benefit to reproduction compared to metformin alone in women with PCOS while receiving ovulation induction treatment. There were a total of 120 women included in the trial who were chosen from the current patients at an infertility clinic. Inclusion criteria consisted of women who were diagnosed with PCOS using the Rotterdam criteria who were between the ages of 20 and 38 years, had patent tubes as evidenced on hysterosalpingography or laparoscopy, and BMI greater than 30 kg/m^2. Any couples with male factor infertility or thyroid disease were not included in the trial (Agrawal et al., 2019).

The primary outcome evaluated was the rate of live births (Agrawal et al., 2019). The secondary outcomes evaluated were pregnancy rate, abortion rate, number of multiple

pregnancies, ovarian hyperstimulation syndrome, and parameters of clinical, hormonal, and metabolic changes.

The patients were divided into two groups using a randomization table generated from a computer. The average duration of infertility in group 1 was 3.75 years, while the average duration of infertility in group 2 was 4.75 years (Agrawal et al., 2019). Prior to beginning the trial, a history of the patient's PCOS and infertility was retrieved along with a physical exam and evaluation of height, weight, BMI, hip circumference, waste circumference, hirsutism score using modified Ferriman-Galway, acne scoring using Global Acne Grading system, and secondary sex characteristics. Labs were also evaluated including complete blood count, liver function tests, kidney function tests, lipid profile, fasting blood sugar, fasting serum insulin, Homeostatic Model Assessment of insulin resistant, FSH, LH, TSH, prolactin, testosterone, sex hormone binding globulin, anti-mullerian hormone. Antral follicle count was also used to assess ovarian reserve and volume.

Group 1 received three daily doses of metformin 500 mg plus myoinositol 600 mg for six months. Group 2 received three daily doses of metformin 500 mg for six months (Agrawal et al., 2019). The patients were also instructed to track their menstrual cycles and weight and attempt to conceive naturally. After three months of treatment, all labs and measurements were reassessed. Anyone who conceived was excluded from the following analysis. Anyone who did not ovulate continued with the medication and received ovulation induction with Clomiphene citrate and gonadotropins injections. If during the first cycle of this treatment, a patient did not ovulate, they were then administered 5000 IU of HCG followed by intrauterine insemination. This treatment was performed for no more than three cycles.

Results were evaluated using STATA software. Data results with a p-value of less than 0.05 were considered statistically significant. In group 1, there was a statistically significant resumption of menstrual length ($p = 0.03$) and bleeding days ($p = 0.01$) compared to group 2. A presumptive sign of ovulation was resumption of a menstrual cycle as progesterone was not evaluated. During the three-month evaluation of the modified Ferriman-Gallwey score for Hirsutism, BMI, and hormone and biochemical parameters, the groups were comparable. In the first three months, there were 14 patients who conceived spontaneously in group 1 and eight in group 2; however, this was not significant ($p = 0.15$) (Agrawal et al., 2019).

There was a total of 63 ovulation induction cycles in group 1 and 70 ovulation induction cycles in group 2. After three cycles of ovulation induction, the clinical pregnancy rate was significantly higher in group 1 in comparison to group 2 ($p = 0.001$). At the end of the trial, the total pregnancy rate of group 1 was 63.3% while the total pregnancy rate in group 2 was 33.3%, which was statistically significant ($p = 0.001$) (Agrawal et al., 2019). The live birth rate in group 1 was 55% while the live birth rate in group 2 was 26.67%, which was statistically significant ($p = 0.002$). Hypertension and diabetes mellitus were comparable and not significant between the groups.

In group 1, there were five patients who endured ovarian hyperstimulation syndrome (Agrawal et al., 2019). Of these, one case was due to the exogenous HCG trigger for ovulation induction, while the other four cases were due to endogenous HCG during pregnancy. There were no cases of ovarian hyperstimulation syndrome in group 2 (Agrawal et al., 2019).

This study showed that the combination of metformin and myoinositol results in a significantly higher birth rate compared to metformin alone; however, it did not affect the metabolic and hormonal parameters (Agrawal et al., 2019). Although this study evaluated

menstruation cycles as a sign of ovulation, it did not evaluate progesterone or obtain a transvaginal ultrasound to determine whether patients were truly ovulating. Because of this, it is not truly known whether patients who experienced menstrual bleeding actually ovulated because bleeding can occur without ovulation. Although it was randomized, there was no placebo which allowed for the possibility of false effects from the medication. It was also not blinded, which would have helped to reduce the possibility of measurement bias during the evaluation of the results. Although there were some aspects of the trial that could have used improvement, the study lasted for six months, which allowed time for the medication to its full effects.

Discussion

Metformin is a medication that is traditionally used to improve insulin resistance and pregnancy rates in women with PCOS, though it is often accompanied by many side effects. Myoinositol has been used in place of metformin more recently due to its potential for similar outcomes while causing fewer side effects. Metformin was compared to myoinositol, reviewing the difference in pregnancy rates, insulin resistance, and medication adverse effects.

Pregnancy rates

PCOS is thought to lead to infertility. These studies evaluated how metformin and myoinositol can contribute to increased pregnancy rates in women suffering with this disease. Ozay et al. (2017) reported a clinical pregnancy rate of 18.6% percent in the group receiving myoinositol compared to 12.2% in the group who received placebo ($p = 0.02$). Sene et al. (2019) reported a statistically significant higher quality of oocytes and embryos after treatment with myoinositol, but no increase in pregnancy rates. It is postulated that this is because of the small number of subjects in the trial, which included only 50 women. A larger study may be beneficial in order to better evaluate the effect of pregnancy rates after treatment with myoinositol. The study conducted by Ozay et al. (2017) included 196 patients, which may account for the difference in results.

Sturrock et al. (2022) reported a pregnancy rate of 25% in the metformin group and 14% in the group receiving placebo ($p = 0.59$). Tang and Glanville et al. (2006) reported a pregnancy rate of 38.5% in the women receiving metformin and 16.3% in the women receiving placebo ($p = 0.023$). This trial was only 28 days which could account for the different outcome compared to the study performed by Sturrock et al. (2022) which was 3 months in duration. Sturrock et al. (2022) also reported that previous studies reviewing metformin in women with PCOS evaluated women with a higher BMI and fasting insulin as well as few menstrual irregularities and lower androstenedione levels compared to this study. It noted that the study completed by Sturrock et al. (2022) included women who had more similarities with patients who did not respond to metformin in other trials which may contribute to the lack of response in the Sturrock et al. (2022) trial.

Another study reported a total of 135 pregnancies in the duration of their study (Morin-Papunen et al., 2012). This study compared obese versus non-obese women. In the obese category, 49.0% of women taking metformin achieved pregnancy while 41.4% receiving a placebo achieved pregnancy ($p = 0.04$). In the non-obese category, the pregnancy rate was 58.6% in the group receiving metformin and 47.7% in the group receiving placebo ($p = 0.09$). In the obese and non-obese categories combined, pregnancy rate was 53.6% in the metformin group and 40.4% in the non-obese category ($p = 0.006$). The obese group received 1000 mg of metformin compared to the non-obese group who received only 500 mg of metformin, which may have accounted for a statistically significant higher pregnancy rate in the obese group. During this trial, a step-wise approach was taken toward achieving pregnancy. If a woman did not become pregnant on metformin alone, ovulation induction was performed. If a couple experienced male subfertility, IVF was used. Because some couples were treated differently throughout the trial, the results may have had some biases. It is reassuring that the pregnancy rate was still higher in the metformin group after removing the results of those who received IVF. However, the patients receiving ovulation induction were still included in this evaluation and thus, may have still been biased. This was one of the longer trials evaluated in this literature review. Metformin was administered for 3 months before stimulation was started. This may also contribute to the difference in results, as many of the trials were much shorter.

Pourghasem et al. (2019) reported that 32% of women receiving the control, 38% of women receiving metformin, and 28% of women receiving myoinositol achieved pregnancy ($p = 0.56$). This study showed that myoinositol actually lowered pregnancy rates when compared to placebo and metformin, though this was not statistically significant. It compared the effectiveness of metformin and myoinositol in conjunction with letrozole in women who were

resistant to letrozole. Perhaps the study would have provided contrasting results if a different ovulation induction or non-letrozole resistant women were used.

Agrawal et al. (2019) reported a pregnancy rate of 63.3% in the group receiving metformin and myoinositol compared to 33.3% in the group receiving metformin after six months of treatment ($p = 0.001$). This study was rather long, with treatment administered for 3 months prior to stimulation induction, making the results more reliable compared to other much shorter studies. However, this study was very small, with only 14 women in the placebo group and 12 women in the metformin group, making the data less reliable. Similar to the trial by Agrawal (2019), this study lasted for a minimum of 12 weeks. The difference in sample size could lead to the difference between the trial results.

Prabhakar et al. (2021) reported no statistically significant increase in pregnancy rate. The first group received 4 G myoinositol and 1500 mg metformin twice per day. The second group received 4 G myoinositol per day. The medications were administered in similar quantities as the study by Agrawal et al. (2019) which administered 1500 mg metformin plus 1800 mg myoinositol daily for the first group. The second group received 1500 mg metformin daily. The study groups were similar in size. Both studies administered ovulation induction after 3 months of spontaneous conception had not occurred. Neither study included a placebo which may have allowed for biases. This could explain the difference in results despite similar medications and doses.

Insulin Resistance

Insulin resistance is thought to contribute to infertility in women with PCOS. Several of the studies reviewed evaluated how metformin and myoinositol affected insulin resistance. Tang and Glanville et al. (2006) reported no difference in fasting serum glucose levels after treatment

with metformin, but did not directly evaluate a HOMA-IR score. Another study reported there was no improvement of HOMA-IR indices of insulin resistance after treatment with metformin (Sturrock et al.,2022). Ozay et al. (2017) reported that there was no statistical difference in HOMA-IR evaluation after treatment with myoinositol. Agrawal et al. (2019) reported no statistically significant improvement in the HOMA-IR index after three months of receiving metformin plus myoinositol. Additionally, Prabhakar et al. (2021) reported no difference in HOMA-IR between groups. Given these results, it is reasonable to conclude that neither metformin nor myoinositol improved insulin resistance in this population.

Medication adverse effects

Medication side effects have been posed to be an issue with metformin as many patients taking it, have reported gastrointestinal side effects. Tang and Glanville et al. (2006) reported that 45.1% of patients in the metformin group and 8.2% of patients in the placebo group experienced side effects ($p < 0.001$). Of these, 3.8% in the metformin group and 20.4% in the placebo group required hospitalization due to severe ovarian hyperstimulation syndrome (OHSS) ($p = 0.023$). Morin-Papunen et al. (2012) reported that of the patients receiving metformin, 34.6% suffered from side effects leading to treatment discontinuation, while only 7.1% receiving placebo suffered such severe side effects ($p < 0.001$). The study does not report the type of symptoms. Sturrock et al. (2022) slowly increased the dose of metformin to decrease side effects; thus, there were no patient-reported side effects. Prabhakar et al. (2021) reported the group receiving metformin plus myoinositol suffered from a significantly higher side effect rate compared to the group receiving myoinositol. The trials administered different doses of metformin; however, the two trials that did not slowly increase the dose experienced a high rate

of side effects. It is reasonable to conclude that metformin causes many side effects, but increasing the dose slowly can help to reduce those side effects leading to more compliance.

Pourghasem et al. (2019) reported there were no side effects in the group receiving myoinositol. However, 42% of patients receiving metformin reported side effects. Ozay et al. (2017) reported one patient receiving myoinositol dropped from the trial due to OHSS. There were three patients receiving a placebo who dropped from the trial due to risk for OHSS. The results from both of these trials could indicate that myoinositol actually provides protection against OHSS versus no myoinositol. However, Agrawal et al. (2019) reported five patients who experienced OHSS in the group receiving both metformin and myoinositol and no reported cases of OHSS in the group receiving metformin alone. If myoinositol were protective against OHSS, then the group receiving both metformin and myoinositol should have had fewer cases of OHSS compared to the group receiving metformin without myoinositol. This difference could be due to the difference in dosing. Agrawal et al. (2019) only administered 600 mg of myoinositol, while Ozay et al. (2017) administered 4 G of myoinositol and Proughasem et al. (2019) administered 2 G of myoinositol. This could indicate that a higher dose of myoinositol could provide protection from OHSS.

Conclusion

The current research does not provide a clear answer as to whether metformin or myoinositol is more effective at increasing pregnancy rates in women with PCOS. Some studies show that metformin is effective, while other studies show that it is not effective in increasing fertility in this population. The same results have been shown with myoinositol. Neither metformin nor myoinositol improved insulin resistance, which is thought to be one of the mechanisms behind infertility in this population. Overall, it does not appear that one medication

is more effective than the other; however, metformin has many side effects, even causing some women to discontinue the medication due to such side effects. Myoinositol has not been shown to cause any adverse side effects. Based on this review, both medications may provide similar efficacy. However, myoinositol may be a beneficial alternative medication used to control insulin resistance and thereby increase fertility in those women who are not able to tolerate metformin. Myoinositol may also provide protective properties against OHSS during ovulation stimulation for IUI and IVF.

Applicability to Clinical Practice

Polycystic ovary syndrome is a prevalent disease in the population of women of child-bearing age. It is common for women with this disease to experience infertility. The applicability of this data is relatively useful in providing an alternative medication to metformin for these patients. Previously, metformin was the medication of choice to help improve insulin resistance, which may contribute to infertility. With its fewer side effects and cost efficiency, myoinositol may provide benefits as an alternative to metformin.

There are other options for fertility treatment in women who battle infertility, including IUI and IVF; however, these treatment options alone do not address the insulin resistance and hyperinsulinemia caused by PCOS. Therefore, metformin is often used in addition to IUI or IVF as seen in the studies above. Though it has previously been the option of choice for these patients, metformin is often accompanied by many side effects causing women to discontinue the medication, putting their chances at achieving pregnancy at risk. With few side effects and equal efficacy at improving pregnancy rates, myoinositol may be an alternative treatment option to metformin in helping those who desire to experience motherhood despite their diagnosis of PCOS.

REFERENCES

Agrawal, Mahey, R., Kachhawa, G., Khadgawat, R., Vanamail, P., & Kriplani, A. (2019). Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial. *Gynecological Endocrinology: The Official Journal of the International Society of Gynecological Endocrinology.*, *35*(6), 511–514. https://doi.org/10.1080/09513590.2018.1549656

Akbari Sene, A., Tabatabaie, A., Nikniaz, H., Alizadeh, A., Sheibani, K., Mortezapour Alisaraie, M., Tabatabaie, M., Ashrafi, M., & Amjadi, F. (2019). The Myo-inositol effect on the oocyte quality and fertilization rate among women with polycystic ovary syndrome undergoing assisted reproductive technology cycles: A randomized clinical trial. *Archives of Gynecology and Obstetrics*, *299*(6), 1701–1707. https://doi.org/10.1007/s00404-019-05111-1

Emekçi Özay, Ö., Özay, A. C., Çağlıyan, E., Okyay, R. E., & Gülekli, B. (2017). Myo-inositol administration positively effects ovulation induction and intrauterine insemination in patients with polycystic ovary syndrome: a prospective, controlled, randomized trial. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology*, 33(7), 524–528. https://doi-org.ezproxylr.med.und.edu/10.1080/09513590.2017.1296127

Misra S. (2012). Randomized double blind placebo control studies, the "Gold Standard" in intervention based studies. *Indian journal of sexually transmitted diseases and AIDS*, 33(2), 131–134. https://doi.org/10.4103/0253-7184.102130

Morin-Papunen, L., Rantala, A. S., Unkila-Kallio, L., Tiitinen, A., Hippeläinen, M., Perheentupa, A., Tinkanen, H., Bloigu, R., Puukka, K., Ruokonen, A., & Tapanainen, J. S. (2012). Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *The Journal of clinical endocrinology and metabolism*, 97(5), 1492–1500. https://doi-org.ezproxylr.med.und.edu/10.1210/jc.2011-3061

Pourghasem, S., Bazarganipour, F., Taghavi, S. A., & Kutenaee, M. A. (2019). The effectiveness of inositol and metformin on infertile polycystic ovary syndrome women with resistant to letrozole. *Archives of gynecology and obstetrics*., 299(4), 1193–1199. https://doi.org/10.1007/s00404-019-05064-5

Prabhakar, P., Mahey, R., Gupta, M., Khadgawat, R., Kachhawa, G., Sharma, J. B., Vanamail, P., Kumari, R., & Bhatla, N. (2021). Impact of myoinositol with metformin and myoinositol alone in infertile PCOS women undergoing ovulation induction cycles - randomized controlled trial. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology*, *37*(4), 332–336. https://doi-org.ezproxylr.med.und.edu/10.1080/09513590.2020.1810657

Sturrock, N. D., Lannon, B., & Fay, T. N. (2002). Metformin does not enhance ovulation induction in clomiphene resistant polycystic ovary syndrome in clinical practice. *British journal of clinical pharmacology*, *53*(5), 469–473. https://doi-org.ezproxylr.med.und.edu/10.1046/j.1365-2125.2002.01575.x

Tang, T., Glanville, J., Orsi, N., Barth, J. H., & Balen, A. H. (2006). The use of metformin for women with PCOS undergoing IVF treatment. *Human reproduction (Oxford, England)*, *21*(6), 1416–1425. https://doi-org.ezproxylr.med.und.edu/10.1093/humrep/del025