**PICO Search Assignment Worksheet Name: Sierra Teegarden**

**Brief description of patient problem/setting (summarize the case very briefly):**

A 26 y/o female with a past medical history of Polycystic Ovarian Syndrome (PCOS) presents to the clinic for fertility management. She was previously found to have anovulation secondary to her PCOS. She was counseled on the standard therapies for subfertility and ovulation dysfunction secondary to PCOS. After her visit, the Physician Assistant discussed a promising new area of research regarding Inositol(s) to improve ovulation in this setting but stated they were unsure if it was effective. Based on this clinical conversation, I decided to see if current evidence argued for or against the recommendation of Inositol for subfertility and ovarian failure from PCOS.

**Search Question**:

Does Inositol improve ovulation compared to placebo in women with polycystic ovarian syndrome?

**Question Type:** What kind of question is this?

Prevalence Screening Diagnosis

Prognosis Treatment Harms

I plan to set my search to include meta-analysis, systematic reviews, and randomized control trials initially. If the yielded results are sparse, I will further expand my search criteria to include retrospective studies related to my question. To make sure that the data is relevant, I will set my filters to search within the last 10 years. Additionally, I will give higher priority to U.S. based studies and only use studies outside of the U.S. if there are not similar or better U.S. studies available. My search terms will initially include the population and intervention terms and I will broaden or narrow these terms as necessary pending the results yielded.

**PICO search terms:**

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| **P** | **I** | **C** | **O** |
| PCOS | Inositol | placebo | Restore ovulation |
| Polycystic ovarian syndrome | Myo-inositol | No intervention | Improve fertility |
| Recurrent urinary tract infection | D-chiro-inositol |  | Improve ovulation |

**Search tools and strategy used:**

**Filters/limits applied:**

1. Full text
2. Publication date: Within 12 years
3. Language: English
4. Article Type: Meta-Analysis, Systematic review, Randomized Control Trial, Randomized Control Study, Retrospective Study
5. Age: None selected

**Databases used:**

1. PubMed
2. Google Scholar
3. Science Direct
4. Wiley Online Library

**Results found:**

**Number of articles returned once relevant limits are added**

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| **Database** | **Filter** | **Terms Searched** | **Articles Returned** |
| **PubMed** | Full text/English/Meta-analysis/Systematic Review/Randomized control trial/Randomized control study/Sort by relevance | PCOS inositol | 22 |
| Inositol polycystic | 24 |
| **Google Scholar** | 2010-2022/Include citations/All in title | Inositol PCOS | 91 |
| **ScienceDirect** | English/2012-2022/Research Articles/Medicine & Dentistry/Sort by relevance | Inositol PCOS | 172 |
| **Wiley Online Library** | English/Anywhere/Published 2010-2022/Journals/Open access content/Sorted by Relevance | Inositol PCOS | 13 |

I oscillated between using the terms “PCOS” and “Polycystic ovarian syndrome” in my search but found that the results yielded most of the same articles so I then chose to keep “PCOS” as the search term for the remainder of the online databases. The number of results per search was relatively low despite removing search filters and only including the intervention and population terms. Additionally, many of the high-quality studies were conducted outside of the United States, but I still considered selecting these articles for my PICO results since there were not better alternative choices. While Science direct yielded the highest number of articles, many were not of relevancy and the same was true of google scholar. On PubMed there was only a handful of articles that looked at ovarian function as an outcome for the use of Inositol for PCOS, making many of the search results irrelevant to answering my question. However, when looking through all of the databases I was able to find enough relevant studies to help answer this PICO question.

**Results found:**

**Article 1**

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| **Citation**: Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of Inositol(s) in Women with PCOS: A Systematic Review of Randomized Controlled Trials. *Int J Endocrinol*. 2016;2016:1849162. doi:10.1155/2016/1849162 |
| **Type of Study: Systematic Review** |
| **Abstract**: Polycystic ovary syndrome (PCOS) is a common endocrine disorder, with complex etiology and pathophysiology, which remains poorly understood. It affects about 5–10% of women of reproductive age who typically suffer from obesity, hyperandrogenism, ovarian dysfunction, and menstrual irregularity. Indeed, PCOS is the most common cause of anovulatory infertility in industrialized nations, and it is associated with insulin resistance, type 2 diabetes mellitus, and increased cardiovascular risk. Although insulin resistance is not included as a criterion for diagnosis, it is a critical pathological condition of PCOS. The purpose of this systematic review is the analysis of recent randomized clinical trials of inositol(s) in PCOS, in particular myo- and D-chiro-inositol, in order to better elucidate their physiological involvement in PCOS and potential therapeutic use, alone and in conjunction with assisted reproductive technologies, in the clinical treatment of women with PCOS. |
| **Reason for Selection:** I chose this systematic review because it evaluates 12 RCTs over a long period of time (1999-2016) to determine the efficacy of Inositols on ovarian function in women with PCOS. The main outcomes of this study help to answer my PICO question which include glucose and insulin sensitivity, sex hormones, stimulation days, oocyte quality, embryo quality, biochemical pregnancies, and pregnancy rate. |
| **Key Points:**   * Oral administration of Myo-Inositols alone or in combination with D-chiro-Inositols are capable of restoring spontaneous ovulation and improving fertility in women with PCOS * Myo-inositols appear to reduce insulin resistance * Myo-inositols also appeared to decrease body weight and circulating leptin and increase HDL compared with placebo indicating that they may also reduce cardiovascular diseases related to PCOS * Treatment with Myo-Inositols with D-chiro-Inositols in a 40:1 ratio improves the endocrine profile and insulin resistance of obese women with PCOS |

**Article 2:**

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| **Citation**: Showell MG, Mackenzie-Proctor R, Jordan V, Hodgson R, Farquhar C. Inositol for subfertile women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2018;12(12):CD012378. Published 2018 Dec 20. doi:10.1002/14651858.CD012378.pub2 |
| **Type of Study: Systematic Review** |
| **Abstract:** **Background:** Subfertile women are highly motivated to try different adjunctive therapies to have a baby, and the widespread perception is that dietary supplements such as myo‐inositol (MI) and D‐chiro‐insoitol (DCI) are associated with only benefit, and not with harm. Many fertility clinicians currently prescribe MI for subfertile women with polycystic ovary syndrome (PCOS) as pre‐treatment to in vitro fertilisation (IVF) or for ovulation induction; however no high‐quality evidence is available to support this practice. This review assessed the evidence for the effectiveness of inositol in subfertile women with a diagnosis of PCOS.**Objectives:** To evaluate the effectiveness and safety of oral supplementation of inositol for reproductive outcomes among subfertile women with PCOS who are trying to conceive.**Search methods:** We searched the following databases (to July 2018): Cochrane Gynaecology and Fertility Group (CGFG) Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, and AMED. We also checked reference lists and searched the clinical trials registries.**Selection criteria:** We included randomised controlled trials (RCTs) that compared any type, dose, or combination of oral inositol versus placebo, no treatment/standard treatment, or treatment with another antioxidant, or with a fertility agent, or with another type of inositol, among subfertile women with PCOS.**Data collection and analysis:** Two review authors independently selected eligible studies, extracted data, and assessed risk of bias. The primary outcomes were live birth and adverse effects; secondary outcomes included clinical pregnancy rates and ovulation rates. We pooled studies using a fixed‐effect model, and we calculated odds ratios (ORs) with 95% confidence intervals (CIs). We assessed the overall quality of the evidence by applying GRADE criteria.**Main results:** We included 13 trials involving 1472 subfertile women with PCOS who were receiving myo‐inositol as pre‐treatment to IVF (11 trials), or during ovulation induction (two trials). These studies compared MI versus placebo, no treatment/standard, melatonin, metformin, clomiphene citrate, or DCI. The evidence was of 'low' to 'very low' quality. The main limitations were serious risk of bias due to poor reporting of methods, inconsistency, and lack of reporting of clinically relevant outcomes such as live birth and adverse events. We are uncertain whether MI improves live birth rates when compared to standard treatment among women undergoing IVF (OR 2.42, 95% CI 0.75 to 7.83; P = 0.14; 2 RCTs; 84 women; I² = 0%). Very low‐quality evidence suggests that for subfertile women with PCOS undergoing pre‐treatment to IVF who have an expected live birth rate of 12%, the rate among women using MI would be between 9% and 51%.  We are uncertain whether MI may be associated with a decrease in miscarriage rate when compared to standard treatment (OR 0.40, 95% CI 0.19 to 0.86; P = 0.02; 4 RCTs; 535 women; I² = 66%; very low‐quality evidence). This suggests that among subfertile women with PCOS with an expected miscarriage rate of 9% who are undergoing pre‐treatment to IVF, the rate among women using MI would be between 2% and 8%; however this meta‐analysis is based primarily on one study, which reported an unusually high miscarriage rate in the control group, and this has resulted in very high heterogeneity. When we removed this trial from the sensitivity analysis, we no longer saw the effect, and we noted no conclusive differences between MI and standard treatment.  Low‐quality evidence suggests that MI may be associated with little or no difference in multiple pregnancy rates when compared with standard treatment (OR 1.04, 95% CI 0.63 to 1.71; P = 0.89; 2 RCTs; 425 women). This suggests that among subfertile women with PCOS who are undergoing pre‐treatment to IVF, with an expected multiple pregnancy rate of 18%, the rate among women using inositol would be between 12% and 27%.  We are uncertain whether MI may be associated with an increased clinical pregnancy rate when compared to standard treatment (OR 1.27, 95% CI 0.87 to 1.85; P = 0.22; 4 RCTs; 535 women; I² = 0%; very low‐quality evidence). This suggests that among subfertile women with PCOS who are undergoing pre‐treatment to IVF, with an expected clinical pregnancy rate of 26%, the rate among women using MI would be between 24% and 40%. Ovulation rates were not reported for this comparison.  Other comparisons included only one trial in each, so for the comparisons MI versus antioxidant, MI versus an insulin‐sensitising agent, MI versus an ovulation induction agent, and MI versus another DCI, meta‐analysis was not possible.  No pooled evidence was available for women with PCOS undergoing ovulation induction, as only single trials performed comparison of the insulin‐sensitising agent and the ovulation induction agent. **Authors' conclusions:** In light of available evidence of very low quality, we are uncertain whether MI improves live birth rate or clinical pregnancy rate in subfertile women with PCOS undergoing IVF pre‐treatment taking MI compared to standard treatment. We are also uncertain whether MI decreases miscarriage rates or multiple pregnancy rates for these same women taking MI compared to standard treatment. No pooled evidence is available for use of MI versus placebo, another antioxidant, insulin‐sensitising agents, ovulation induction agents, or another type of inositol for women with PCOS undergoing pre‐treatment to IVF. No pooled evidence is available for use of MI in women undergoing ovulation induction. |
| **Reason for Selection:**I chose this systematic review because it evaluated whether women with subfertility from PCOS benefited from taking inositol supplements which relates to increased ovarian function which helps to answer my PICO question. The systematic review had a relatively large sample size of 13 trials with 1472 participants. |
| **Key Points:**   * It is uncertain whether Myo-Inositol improves live birth rate or clinical pregnancy rate in subfertile women with PCOS compared to standard treatment * It is uncertain whether Myo-Inositol decreases miscarriage rates or multiple pregnancy rates compared to standard treatment * There is no evidence available for the use of MI versus placebo * The evidence presented was low-quality |

**Article 3:**

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| **Citation**: Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. *Reprod Health*. 2021;18(1):171. Published 2021 Aug 18. doi:10.1186/s12978-021-01207-7 |
| **Type of Study: Meta-analysis** |
| **Abstract:**  **Background:**Multiple oral insulin-sensitizing agents, such as metformin, thiazolidinediones, inositols, and berberine, have been proven safe and efficacious in improving the endocrine, metabolic, and reproductive abnormalities seen in polycystic ovary syndrome (PCOS), providing more options for healthcare providers and patients. These oral insulin sensitizers are more convenient, practical, and economic than agents that need to be injected. A comparison of the clinical effectiveness of the four different classes of oral insulin sensitizers in PCOS has not been explored, leading to clinical uncertainty about the optimal treatment pathway. The present study aims to compare the effects of oral insulin sensitizers on endocrine and metabolic profiles in women with PCOS.  **Methods:**We identified randomized controlled trials for PCOS from a variety of databases, published from January 2005 to October 2020. Outcomes included changes in menstrual frequency, improvements in hyperandrogenism and glucolipid metabolism and adverse side effects. A random-effects network meta-analysis was performed.  **Results:**Twenty-two trials comprising 1079 patients with PCOS were included in this study. Compared with metformin, treatment with myo-inositol + D-chiro-inositol was associated with a greater improvement in menstrual frequency (odds ratio 14.70 [95% confidence interval (CI) 2.31-93.58]). Myo-inositol + D-chiro-inositol and metformin + thiazolidinediones combination therapies were superior to respective monotherapies in reducing total testosterone levels. Thiazolidinediones, metformin + thiazolidinediones, and myo-inositol + D-chiro-inositol were associated with a lower insulin resistance index (HOMA-IR) compared with that in metformin alone (mean differences: - 0.72 [95% CI (- 1.11)-(- 0.34)] to - 0.89 [95% CI (- 1.460)-(- 0.32)]). Metformin + thiazolidinediones treatment was associated with lower triglyceride levels compared with that in metformin and thiazolidinediones monotherapy, while thiazolidinediones was superior to metformin in increasing high-density lipoprotein cholesterol and decreasing fasting plasma glucose, triglycerides, low-density lipoprotein cholesterol, and gastrointestinal adverse events.  **Conclusions:**Ours is the first study to report that for women with PCOS, myo-inositol combined with D-chiro-inositol and metformin combined with thiazolidinediones appear superior to metformin alone in improving insulin resistance and decreasing total testosterone. Myo-inositol combined with D-chiro-inositol is particularly efficacious in menstrual recovery. Thiazolidinediones and metformin combined with thiazolidinediones improve lipid metabolism better than metformin alone. Trial registration PROSPERO CRD42020211524. |
| **Reason for Selection:**I chose this meta-analysis because it has a relatively large sample size of 22 studies and 1079 participants which is comparable to the size of article 2. The outcomes focused on menstrual frequency, improvement in hyperandrogenism and glucolipid metabolism, and adverse side effects which help answer my PICO question about ovulatory recovery. |
| **Key Points:**   * Myo-inositol combined with D-chiro-inositol is superior to metformin alone in improving insulin resistance and decreasing total testosterone * Myo-inositol combined with D-chiro-inositol is effective in menstrual recovery * Compared with metformin, treatment with myo-inositol and D-chiro-inositol was associated with greater improvement in menstrual frequency |

**Article 4:**

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| **Citation**: Azizi Kutenaei M, Hosseini Teshnizi S, Ghaemmaghami P, Eini F, Roozbeh N. The effects of myo-inositol vs. metformin on the ovarian function in the polycystic ovary syndrome: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2021;25(7):3105-3115. doi:10.26355/eurrev\_202104\_25565 |
| **Type of Study: Systematic Review and Meta-analysis** |
| **Abstract:**  **Objective:**Recent studies have revealed that myo-inositol could be more influential in patients with polycystic ovary syndrome (PCOS). This study was aimed to determine and compare the effects of myo-inositol and metformin on hormonal and metabolic profiles and fertility outcomes.  **Materials and methods:**A comprehensive search was carried out among the English-language databases, including PubMed, Scopus, Cochrane Library, Google Scholar, and Web of Science, and the articles published from April 2010 to February 2019 were tracked down. The fixed and random-effects meta-analysis was used to estimate the pooled effect size. The meta-analysis was performed in Stata Version 14.0.  **Results:**Nine studies with 331 patients treated with metformin and 307 patients treated with myo-inositol groups were included in the analysis. The research groups did not diverge significantly in terms of the basic characteristics, such as age and Body Mass Index (BMI). In the myo-inositol group, the levels of Luteinizing Hormone (LH) [12.55% (95% I: 11.41-13.68%)], S. testosterone [44.38% (95% CI: 38.09-50.67%)] and prolactin [7.97% (95% CI: 6.58- 9.37%)] were significantly higher than those recorded, i.e., LH [7.97% (95% CI: 6.58- 9.37%)], S. testosterone [8.48% (95% CI: 3.14-13.83%)] and prolactin [7.14% (95% CI: 1.50-14.79%)] for the metformin group (p<0.001).  **Conclusions:**Due to the dearth of related research and the high heterogeneity of the Randomized Clinical Trials (RCTs) included in other studies, the present systematic review could not establish any differences between metformin and myo-inositol concerning the hormonal profile and the ovarian function. However, the findings indicated that myo-inositol could improve fertility outcomes by modulating hyperandrogenism. Randomized trials are required to understand the mechanistic actions of myo-inositol in comparison with those of metformin regarding oocyte and embryo quality, fertilization, pregnancy, and live birth rates. |
| **Reason for Selection:**I chose to include this SR/Meta-analysis because it compared the effects of myo-inositol vs metformin on hormonal and metabolic profiles and fertility outcomes in women with PCOS which directly answers my PICO question. Although the sample size is smaller than the previous articles (331 participants and 9 studies) the studies appear to be of acceptable quality and all had similar basic characteristics. |
| **Key Points:**   * No difference could be established between metformin and myo-inositol concerning the hormonal profile and ovarian function * Findings suggest myo-inositol could improve fertility outcomes by modulating hyperandrogenism * Both metformin and inositols appeared to improve fasting blood sugar, fasting insulin, HOMA index, estradiol, and SHBG. * Ovarian volume was not significantly different in PCOS patients treated with myo-inositol vs metformin * A significant decrease in DHEA and testosterone levels were observed in those receiving myo-inositol compared with metformin * LH and LH/FSH ratio and prolactin levels were improved only in the metformin group and not in the myo-inositol group. |

**Weighing the evidence**

Of the four articles selected for this PICO search, articles 2 & 3 hold the most weight. Article 3 is weighted slightly more than article 2 because it is also a meta-analysis in addition to being a systematic review and the individual RCTs appear to be of higher quality than that of article 2. In addition to both articles being systematic reviews, they also each have over 1000 participants and multiple studies included. Although article 1 is also a systematic review, it has a much lower participant pool around ~500 which is less than half the sample size of articles 2 & 3. Similarly, article 4 is both a systematic review and meta-analysis but has a small participant pool of 331 patients and it also is the least specific in answering my PICO question when considering the outcomes evaluated. Now that we have considered the weight of each article presented, the key points of each can be considered. Article 3 found that the use of inositols is superior to metformin for improving insulin resistance, decreasing total testosterone, and improving menstrual recovery. Article 2 was uncertain as to whether myo-inositol was superior to standard treatment for improving subfertility in women with PCOS and there was no data on myo-inositol vs placebo. Article 1 found that inositols can store spontaneous ovulation and improving fertility in women with PCOS in addition to reducing insulin resistance, body weight, and circulating leptin. Article 4 was able to draw a conclusion about the use of inositols vs metformin for ovarian function, but it did find that myo-inositols could improve fertility outcomes and decrease DHEA & testosterone hormones. Most importantly, none of the articles found inositols to be ineffective in the treatment of ovarian function or fertility for women with PCOS.

**What is the clinical “bottom line” derived from these articles in answer to your question?**

The clinical bottom line is that none of the studies found inositols to be ineffective in restoring ovarian function and fertility for women with PCOS and most studies found myo-inositol and D-chiro-inositol either alone or in combination with each other to be just as effective or more effective than Metformin and other standard treatments in the restoration. Therefore, I would recommend inositols to my patients as a primary treatment in conjunction with standard therapies for the improvement of ovarian function and fertility for PCOS. More U.S. based research is needed to be done before concluding that inositols can be used as monotherapy without the addition of current standard therapies and if foods containing inositols can be recommended to patients in addition to standard dosing. Additionally, more research is needed to concluded what combination of myo-inositol and d-chiro-inositol is most effective.

**Links:**

**Article 1**

Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of Inositol(s) in Women with PCOS: A Systematic Review of Randomized Controlled Trials. *Int J Endocrinol*. 2016;2016:1849162. doi:10.1155/2016/1849162

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5097808/

**Article 2**

Showell MG, Mackenzie-Proctor R, Jordan V, Hodgson R, Farquhar C. Inositol for subfertile women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2018;12(12):CD012378. Published 2018 Dec 20. doi:10.1002/14651858.CD012378.pub2

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6516980/

**Article 3**

Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. *Reprod Health*. 2021;18(1):171. Published 2021 Aug 18. doi:10.1186/s12978-021-01207-7

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8371888/

**Article 4**

Azizi Kutenaei M, Hosseini Teshnizi S, Ghaemmaghami P, Eini F, Roozbeh N. The effects of myo-inositol vs. metformin on the ovarian function in the polycystic ovary syndrome: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2021;25(7):3105-3115. doi:10.26355/eurrev\_202104\_25565

Link: https://pubmed.ncbi.nlm.nih.gov/33877679/