

PCOS: Comparing Inositol Supplementation to Metformin Treatment

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Abstract

The purpose of this literature review is to compare the viability of inositol versus metformin for the treatment of polycystic ovarian syndrome (PCOS). The research outlines the criteria for diagnosis and the many symptoms associated with the condition. The aim is to discover if inositol should be recommended for PCOS symptoms as a replacement for metformin. It was found that safety and popularity of the two options were important factors for physicians and patients to consider before choosing a treatment. Within these scopes, adverse effects, costs, regulation, and belief of treatment were compared. Findings indicated that inositol supplementation may possibly be an alternative to the prescription medication, as there were many similarities within these scopes such as GI disturbances. However, differences between the two were apparent such as the policies governing the substances' regulations and the belief between prescription medication versus dietary supplementation. Additionally, ethical considerations for clinical research included debates on the inclusion of minors and pregnant women for which there were no conclusive solutions.

Key Words: Polycystic Ovarian Syndrome (PCOS), Inositol, Metformin, Popularity, Safety, Medical Literature Review

PCOS: Comparing Inositol Supplementation to Metformin Treatment

There is a significant lack of information and trials for biologically female-specific conditions such as polycystic ovarian syndrome (PCOS) and its treatments. Women's health has historically been misinterpreted and underrepresented in medical professions throughout the world. Medical research studies had traditionally utilized male subjects in clinical trials, leaving a significant gap of data between men and women. In the United States, significant call to action about this issue was not seen until the 1990s when the FDA and National Institutes of Health (NIH) then "encouraged the participation of women in early-phase drug trials, required women be included in efficacy studies, and mandated the analysis of trial data to identify sex differences" (Sosinsky et al., 2022). Presently, there is an increase in female participation in research trials, however, there remains the need for more data collection. This is the case for conditions in which both men and women share, pharmaceutical trials, and reproductive trials. Especially in the case of reproductive conditions, women have been excluded from participation due to concern of reproductive capabilities or changes. One such condition is PCOS.

PCOS is defined as both a chronic endocrine and metabolic disorder "associated with infertility; miscarriage; adverse pregnancy outcomes; and cardiovascular, metabolic, psychological and neoplastic risk" (Dason et al., 2024). This means the disorder affects the endocrine system due to hormonal imbalance and affects the metabolic system through insulin irregularities. Although there are many representations of PCOS, the most current criteria for diagnosing the disorder include "the presence and degree of three major features: irregular menstruation, hyperandrogenism, and polycystic ovarian morphology (PCOM)" (Islam et al., 2022). These criteria are called the Rotterdam criteria.

Using the Rotterdam criteria is most common among physicians when diagnosing PCOS. Using this criteria requires that 2 of the 3 distinguishing characteristics be present with the

exclusion of other diagnoses. Irregular menstruation is normally self-reported by the client and is a common cause of initial concern. Rotterdam criteria describes irregular menstruations as greater than 3 years since having a menarche, greater than 35 days apart or less than 21 days apart, less than 8 menstrual cycles per year; or greater than 90 days for any 1 menstrual cycle (Dason et al., 2024). It is recommended that upon self-reported irregular menses, PCOS should be considered by physicians.

Hyperandrogenism is defined as excess androgen hormones and is present in “60% of patients with PCOS and can be assessed using total testosterone, calculated free testosterone, dehydroepiandrosterone sulfate (DHEA-S) and androstenedione” (Dason et al., 2024). As testosterone is the most common androgen hormone, it is common practice to draw labs for testosterone to assess for hyperandrogenism. This imbalance can manifest in multiple ways. Clinically, hyperandrogenism presents itself with “hirsutism, acne, or alopecia usually represents low-to-average levels of androgen excess” (Islam et al., 2022). Hirsutism refers to terminal hair growth found on chins, upper lips, chest, and other areas associated with androgenic hair growth. Among hyperandrogenic conditions, comedonal acne is the most common type of acne seen especially among adolescent female patients. Alternatively, presentation of alopecia is not common with “22% of women displaying male-like hair loss were discovered during PCOS diagnosis” (Islam et al., 2022). Not all symptoms of hyperandrogenism are seen in PCOS presentation.

The third Rotterdam criteria is the presence of polycystic ovarian morphology (PCOM), or the structural variants in polycystic ovaries. Normally visualized through a transvaginal ultrasound, there are debates on the evaluation of this criteria. It was initially distinguished by “a value of 12 or more Follicle Number Per Ovary (FNPO), measuring between the size of 2–9 mm

or, an ovary with a volume of 10 cm³” (Islam et al., 2022). However, there are variants to this diagnostic criteria. Advancements in the visualization technology can change the evaluation data to “FNPO value of 20 or more of the same-sized follicles (2–9 mm) and an ovary volume of 10 cm³ for adult women” (Islam et al., 2022). For PCOS, these “string-of-pearls” follicles can affect ovulatory ability, however, the PCOM “may be present in as many as 25% of healthy females and is considered a variant of normal” (Dason et al., 2024). As women have historically been underrepresented in medical research, it proves difficult to definitely diagnose PCOS.

The presenting symptoms of PCOS can vary from patient to patient and are dependent on which factors influenced the condition. Many common symptoms include hirsutism, acne, and irregular periods due to hyperandrogenism; however other symptoms may occur if there are preexisting conditions in addition to PCOS such as thyroid or metabolic disorder. There is an correlation between the condition and the presence of comorbidities like “cardiovascular disease (CVD) risk factors including diabetes, obesity, metabolic syndrome, adverse pregnancy outcomes such as pre-eclampsia and psychosocial distress including depression” (Benham et al., 2024). Therefore, patients have increased mortality rate of cardiovascular disease and diabetes type 2 if left unmanaged.

Treatment of PCOS is dependent on symptoms and the intent of the treatment. First line treatment for almost all symptoms includes a diet and lifestyle change. One option a gynecologist may consider administrating for patients in child-bearing years is combined hormonal birth control which “are first-line medical treatment options for cycle regulation and hirsutism or acne” (Dason et al., 2024). This is not an option for all patients as some may be trying to get pregnant or are pregnant or are unable to receive hormonal medications. The most common non hormonal medication for PCOS its many symptoms is Metformin also known as

Glucophage, however there are studies that advocate for the use of other medications, such as inositol, instead.

Metformin is sometimes considered the “gold standard” of PCOS treatment. While it is marketed as a diabetic medication, it was the “first insulin sensitising drug (ISD) to be used in PCOS to investigate the role of insulin resistance in the pathogenesis of the syndrome” (Lashen, 2010). Being an insulin sensitizing drug, metformin works to reduce the amount of circulating insulin by increasing the tissue and cells sensitivity to receive the insulin. Doing so helps reduce blood sugar levels by allowing insulin to effectively break down the glucose. For the treatment of PCOS, studies have shown evidence that metformin helps in “restoring ovulation, reducing weight, reducing circulating androgen levels, reducing the risk of miscarriage and reducing the risk of gestational diabetes mellitus (GDM)” (Lashen, 2010). Despite the reported symptom improvements, metformin is still debated as an appropriate medication for PCOS symptoms.

Another debated non-hormonal treatment is inositol which is considered a supplement rather than a prescribed medication. Inositol, sometimes referred to as vitamin B8, is a sugar alcohol found naturally in some carbohydrates, fruits, and legumes. It is an over-the-counter supplement that functions “in many signalling cascades, including downstream of FSH and insulin [and] it may have a role in improving insulin sensitivity” (Dason et al., 2024). While the pathway is different to metformin, there are some studies that indicate the inositol may perform actions similar to metformin in regard to metabolic and endocrine control.

There remains room for investigation in women’s health, especially for the treatment of reproductive disorders such as PCOS. Although metformin is a common drug, it was not approved in the United States until the 1990s, indicating that it is still new, and it is not even marketed for the treatment of PCOS symptoms. Therefore, other avenues of treatment need to be

researched for better clinical outcomes. There is evidence that inositol may function similarly to metformin, but it is unclear whether inositol could be used as a substitute for the diabetic drug.

An important factor in this discussion would be the safety of administration for both metformin and inositol. As with most prescription drugs, metformin can come with side effects and is contraindicated with other drugs. With inositol being marketed as a supplement, there are not extensive studies on the interactions between it and other supplements or pharmaceuticals. Additionally, it is unknown if inositol would have the same popularity as metformin within the medical field. As the United States gains more of an interest in more natural treatments versus pharmacy drugs, inositol has the potential to be recommended by medical professionals. However, this remains unseen as there are several aspects that may affect the popularity of inositol over metformin. With regards to the safety and the popularity of inositol as a comparable treatment for PCOS, it will be important to determine the ethical considerations of this research. As with all research, ethics should be considered to protect the safety of the research subjects and protect the researcher from the public's concerns. The research for the treatment of PCOS using metformin versus inositol should be safe, viable, and ethical.

Safety

Metformin Side Effects

Adverse effects of pharmaceutical drugs are one of the main reasons why a patient may stop usage either due to safety or noncompliance. Metformin has a variety of reported side effects that resulted in a discontinued prescription. The most reported side effects are “the gastrointestinal symptoms of nausea, diarrhoea, flatulence, bloating, anorexia, metallic taste and abdominal pain” (Lashen, 2010). Among patients, the GI effects are most commonly discussed and reported. The less common side effects include “chest discomfort, headache, diaphoresis,

hypoglycemia, weakness, and rhinitis while taking metformin” (Corcoran & Jacobs, 2023). Long term use of metformin has also been associated with vitamin B12 deficiency. Additionally, metformin does have a black box warning which indicates that the FDA declared a warning for the potential of severe injury or death for the drug. For metformin, the black box warns against “lactic acidosis, an infrequent yet severe adverse effect with an incidence rate of approximately 1 in 30,000 patients” (Corcoran & Jacobs, 2023).

Because side effects can be a cause for patients to be noncompliant with medications, it is important to know how many people are affected. Due to the type of research and parameters, studies often yield different results. A study on the adverse effects of metformin with Japanese patients with diabetes mellitus 2 found their results retrospectively. Okayasu et al. (2012) found that “diarrhea was most frequently occurred during metformin use (26.7% of patients) although the symptom of diarrhea was mild in most cases and disappeared within 3d after the initial use.” Diarrhea was present in 27 out of 101 patients as seen in the table titled Figure 1 and the risk for adverse effects increased with the presence of their identified risk factors. Figure 2 indicates the six risk-factors: “age ≤ 65 , female, BMI ≥ 25 , initial daily dose of 750mg, ALT ≥ 30 IU/L and ALP ≥ 27 ” (Okayasu et al., 2012). For PCOS patients, many begin presenting symptoms within a few years after starting their menstruation. Therefore, there is a number of those women that are less than or equal to 65 years of age and have a larger BMI that’s greater than or equal to 25 for which the incidence of these adverse effects greatly increases.

Figure 1.

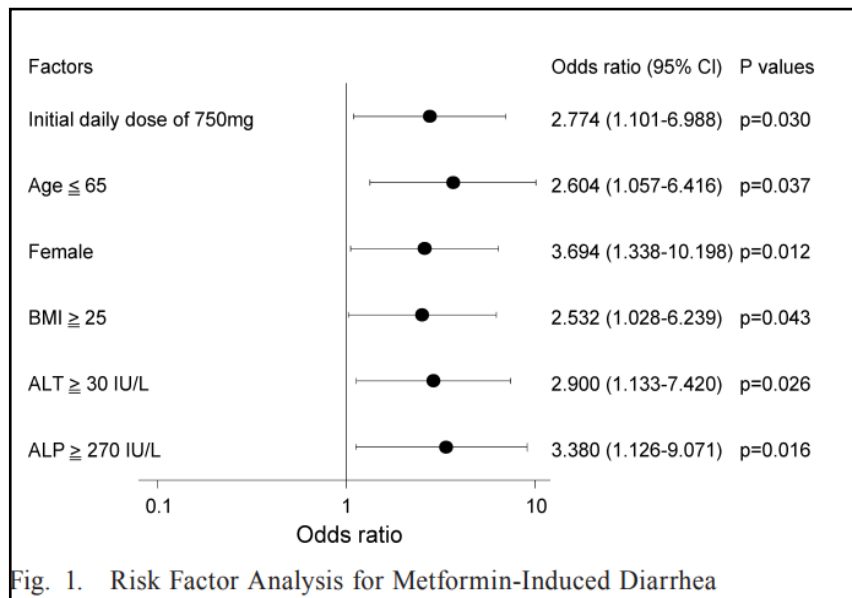
Table 3. The Incidence of ADRs of Metformin (N=101)

ADRs	Number of patients (%)
Diarrhea ^{a)}	27 (26.7%)
Anorexia ^{a,b)}	3 (3.0%)
Nausea ^{a)}	0 (0%)
Vomiting ^{a)}	0 (0%)
Hepatic dysfunctions ^{c,d)}	0 (0%)
Renal dysfunctions ^{e)}	0 (0%)

ADRs were monitored during the hospitalization (up to 7d after metformin treatment). *a)* We counted the number of patients who developed diarrhea, anorexia, nausea and vomiting as more than G0. *b)* No patients with anorexia occurred diarrhea during metformin use. *c)* Values of AST and ALT 3 times above ULN (*i.e.* G1) considered being hepatic dysfunction after metformin use. *d)* One patient who had high ALT (G1) before metformin use together with unchanged ALT after metformin use was excluded from the analysis. This patient caused diarrhea after metformin use for 3 d. *e)* Values of serum creatinine 1.5 times above ULN (*i.e.* G1) considered being renal dysfunction after metformin use.

(Okayasu et al., 2012)

Figure 2.



(Okayasu et al., 2012)

It is important to note that there are some drug interactions or contraindications for metformin. According to Corcoran & Jacobs (2023), it is “contraindicated in patients with severe renal dysfunction, which is defined as a GFR >30 mL/min/1.73²” and is also contraindicated for

those with “serum creatinine (SCr) levels greater than or equal to 1.5 in men and 1.4 in women or with abnormal creatinine clearance (CrCl).” To prevent adverse effects such as impaired renal function or lactic acidosis, regular monitoring lab values and symptoms should be implemented.

Despite the adverse effects reported, metformin is generally considered by physicians to be safe. However, many metformin studies revolve around the treatment of diabetes with metformin, not the treatment of PCOS and associated symptoms. There are studies that indicate that metformin is generally well-tolerated in those with PCOS symptoms, but studies tend to exclude associated conditions or comorbidities. PCOS is associated with conditions such as obesity, non-alcoholic fatty liver syndrome, and insulin resistance meaning that some patients are at a higher risk for the incidence of side effects or more serious adverse effects.

Inositol Side Effects

Inositol refers to a sugar-alcohol which is naturally formed within the body but can also be taken as a supplement. The most common forms are called Myo-inositol and D-Chiro-Inositol. Being a supplement, there are less studies on the efficacy of this supplementation for the treatment of PCOS symptoms and the concept of using inositol for these symptoms is still fairly new. With the available studies, there are variances in the reporting of side effects associated with inositol.

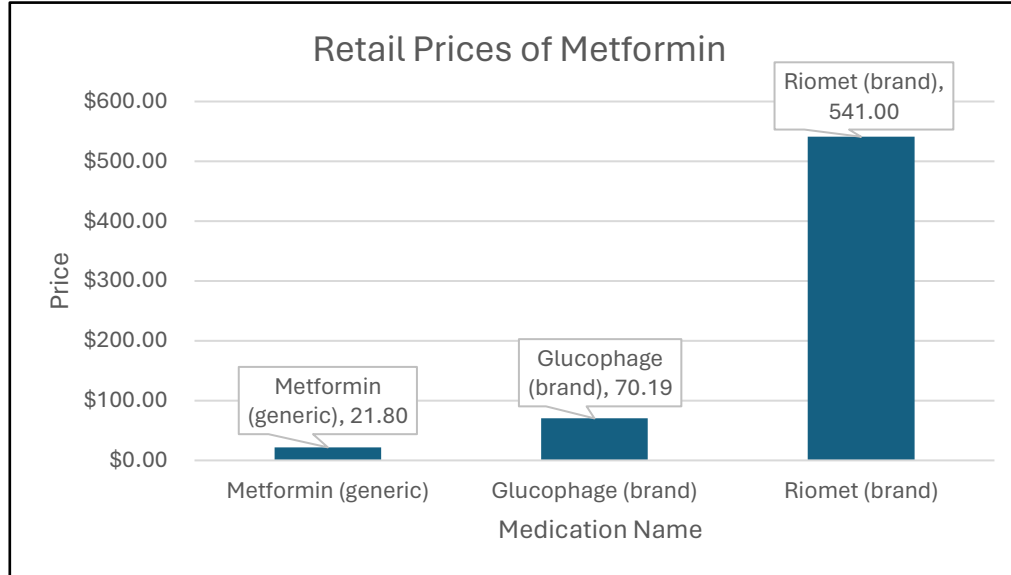
A study by Carlomagno & Unfer (2011), reviewed the clinical evidence of the safety of inositol use. Their research discovered that the “highest dose of myo-inositol (12 g/day) induced mild gastrointestinal side effects such as nausea, flatus and diarrhea” and these results did not change with dosage amounts (Carlomagno & Unfer, 2011). Gastrointestinal side effects were the most reported adverse effects of inositol; however, some studies showed a lack of reported adverse effects. In a systemic review by Unfer et al. (2016), the clinical effects of Myo-inositol

and D-Chiro-inositol gathered data that may contradict the previous study. One control presented evidence that “that no relevant side effects were recorded during combined therapy with Myo-Ins and D-chiro-Ins, providing further evidence of the safety of the usage of these two stereoisomers in combination” (Unfer et al., 2016). With conflicting data, metformin’s long term side effects remain unseen and need further research to determine the safety of administration of the supplement.

Popularity

Metformin Cost

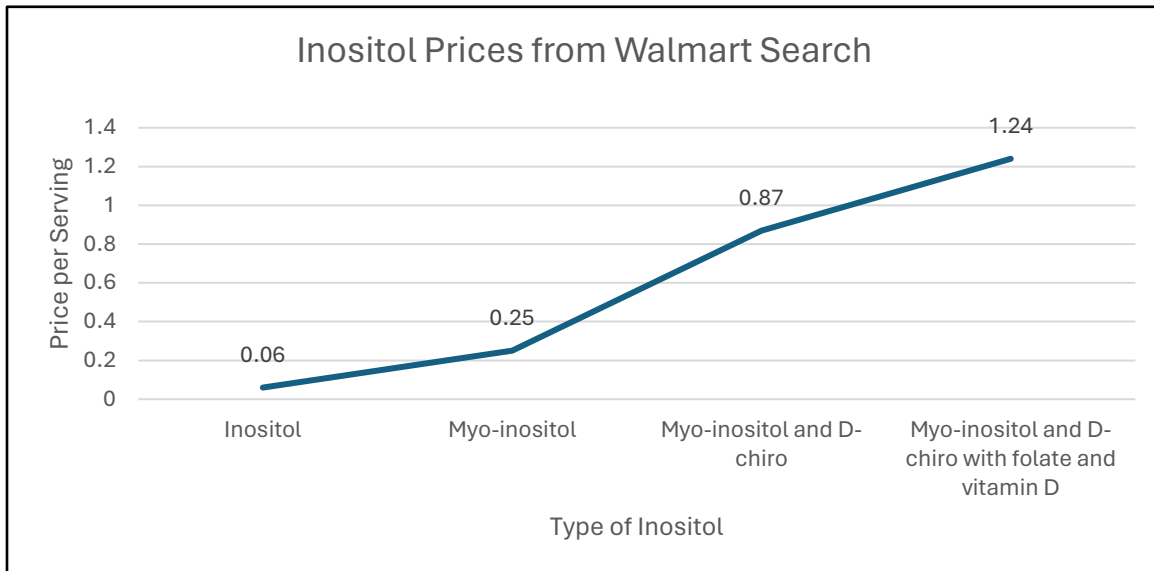
When considering the cost of a medication, there are multiple factors that can affect how much you pay. Often the cost for other prescription medicines is determined by brand, dosage, insurance, and pharmacy. Metformin is the generic name of the medication and while there are multiple brand names, one of the most used names in the United States is Glucophage. The FDA disclosed that the difference in price between a generic and a name brand medicine is generally because the clinical trials do not have to be repeated. The producer’s cost is significantly reduced due to this meaning that “although generic medicines have the same therapeutic effect as their branded counterparts, they are typically sold at substantial discounts, an estimated 80 to 85% less, compared with the price of the brand-name medicine” (Center for Drug Evaluation and Research, 2021). A preliminary search on the website GoodRX (n.d.), discovered that the generic Metformin has a significantly cheaper retail price than brand names Glucophage and Riomet as seen in Figure 3. The price of the generic metformin is an important factor to patients as they are choosing treatments and is likely to influence both physicians and patients’ decision to take metformin vs inositol.

Figure 3

(GoodRx, n.d.)

Inositol Cost

It is difficult to quantify the cost of inositol because it is a supplement. There are several sites that sell inositol and there are several different blends as well. An internet search on Walmart (n.d.) with the keywords “inositol powder” gave several results. Four main blends were identified: (1) inositol (2) myo-inositol (3) myo-inositol and D-chiro inositol and (4) myo-inositol and D-chiro-inositol with folate and vitamin D. Although there were differences between brands, there was a steady increase in price depending on which blend it was as seen in Figure 4. There was no brand that sold all 4 blends as their products; however, it is likely that the cost of inositol supplements in their powder form can cost from \$0.05 to \$1.24 per dose and upward. Because inositol is a supplement and not a regulated medication, it is nearly impossible to account for every brand and blend on the market. The variance does not allow for an accurate standardization of cost so this preliminary search can only create an estimate.

Figure 4

(Walmart, n.d.)

Product Regulation

Prescription and over the counter medications are regulated through the Food and Drug Administration (FDA). In the 1950s, amendments to the Food, Drug and Cosmetic Act “mandated that any drugs that can cause a habit or be dangerous to a patient must be dispensed by a healthcare provider through a prescription and must be labeled appropriately stating that you cannot receive the drug without a prescription” (Chang et.al, 2016). This created the distinction between prescription medications and nonprescription.

Metformin is a prescription medication which means that it is regulated by the FDA, requires a doctor’s prescription, and is distributed through a pharmacy. Although it is not a controlled substance, it is still controlled in the sense that not everyone has access to it. A prescription requires an evaluation of physical condition as well as lab work and a health history. The FDA continues to make sure the medication is safe to be consumed, while the doctor ensures that the specific patient is safe to take it.

Inositol on the other hand, is marketed as a supplement. The FDA does regulate “finished dietary supplement products and dietary ingredients” (Center for Food Safety and Applied Nutrition, 2024). According to the Dietary Supplement Health and Education Act of 1994, the role of the FDA (2024) is to enforce these rules:

- Manufacturers and distributors of dietary supplements and dietary ingredients are prohibited from marketing products that are adulterated or misbranded. That means that these firms are responsible for evaluating the safety and labeling of their products before marketing to ensure that they meet all the requirements of the Federal Food, Drug, and Cosmetic Act as amended by DSHEA and FDA regulations.
- FDA has the authority to take action against any adulterated or misbranded dietary supplement product after it reaches the market (FDA, 2024).

Inositol has been recognized as a nutrient supplement and the ingredient is “used in food with no limitations other than current good manufacturing practice” (*CFR - Code of Federal Regulations Title 21*, 2023). Other parameters of inositol manufacturing include not exceeding levels that are defined by the FDA and the safety of inositol in infant formula. According to the Code of Federal Regulations (2023), inositol “may also be used in infant formula in accordance with section 412(g) of the ACT, or with regulations promulgated under section 412 (a) (2) of the Act.” As a popular supplement, inositol comes in many forms and from many places. International brands that go through major companies, such as Amazon, still must follow the same regulations the FDA lays down in the United States. Taking that into consideration, nutritional supplements are not as strictly regulated as prescription medications are. There are many brands and blends on the market, and it is not limited to only a few manufacturers. This can lead to manufacturing errors that may not be caught by regulatory organizations.

Physicians can give prescriptions for medications, but they can also recommend supplements based on clinical evidence and patient assessments. One of the factors they may look at is how regulated the product they are prescribing or recommending is. Metformin is strictly regulated through the FDA and is only available at pharmacies. Inositol has regulations but it has many channels of obtainment. It could be made locally within the United States, but it could also be sold from international brands. Additionally, there are different types of inositol blends that can be marketed which may have different effects on their consumers. From this aspect, metformin may be a more popular treatment option recommended by physicians compared to inositol.

Belief of Treatment

Western culture relies heavily on prescription medications. Pharmaceuticals are frontline treatments for ailments and are a “recognized entry point towards misuse, opioid use disorder, and ultimately overdose” (Battaglia et al., 2023). The idea is that these engineered treatments provide a normally quick response to whichever symptom is being treated. Metformin as a glycemic prescription medication takes “approximately 3 hours to take effect after administration, and its half-life is about 20 hours” (Corcoran & Jacobs, 2023). As a short-term medication, there is an effect on insulin resistant PCOS. As a long-term medication, it is unclear whether there are advantageous effects of the medication in terms of hyperandrogenism and other symptoms associated with the condition. Additionally, the use of metformin during pregnancy is still being researched and debated on safety and efficacy. With the western mindset, it may be more advantageous to prescribe metformin before other treatments, simply due to the short-term effects that have been clinically proven.

In comparison to Western medicine, Eastern medicine practitioners “use various psychological and/or physical approaches as well as herbal products to address health problems” (U.S. Department of Health and Human Service [USDHHS], 2023). The use of herbal or additional supplementation is traditionally called a complementary or alternative medicine (CAM) in comparison to conventional medicine (CM). According to a Tangkiatkumjai et al. (2020), there are several reasons to seek out CAM rather than CM such as the “perceived benefits (84% of publications), and safety of CAM (37%), and dissatisfaction with CM (37%).” There remains a prevalence of CAM usage in countries other than the United States, particularly in Asian countries. One study attributed the preference to being “influenced by members of their social network, [has] low costs of CAM, easier access to CAM and tradition than Western populations” (Tangkiatkumjai et al., 2020). Dietary supplementation in the United States has a moderately high usage, however prescription medication was found to be used more frequently and with an increased consumption rate across the country.

Inositol is a supplement which has fairly new use for the treatment of PCOS which may affect the belief in its efficacy. For those using dietary supplements, a study found that the “use is higher in the older population, and among females, non-Hispanic whites, and people with a higher level of education” (Aznar-Lou et al., 2019). Although PCOS is a lifelong condition, it is found mostly in females of reproductive age which was not outlined in the study. Additionally, the aspect of pregnancy is a factor in which some females of reproductive age feel wary about over the counter supplementation. Inositol is still a new supplement that warrants more research on the efficacy, and more importantly, the safety for the potential consumers of the product. It may be more easily accepted as a viable treatment by patients that prefer CAMs or are more likely to use other dietary supplements.

Ethical Considerations

Preadolescents/Adolescents

Most symptoms of PCOS are discovered with the onset of puberty, which occurs during the late preadolescent or adolescent years. A study found that the “prevalence of PCOS in adolescents was 11.04% [and the] mean age of the participants was 16.99 years” (Naz et al., 2019). To determine if inositol is a viable treatment for the syndrome rather than metformin, research must be conducted. However, the most accurate results would require the inclusion of preadolescents and adolescents diagnosed with PCOS to determine the best treatment. This would include the research of metformin and inositol in subjects of these age groups, which brings to light some ethical considerations.

In the United States, one is legally considered an adult when they turn 18 years old. When it comes to research consent, there may be some variations. It is largely accepted that parental or guardian consent must be obtained for minors, however it is important to include that participating minors must show assent too. Assent is the expression of approval which is not taken as legal and written consent. To determine the participants capability of assent, “the IRB will take into account the age, maturity, and psychological state of the potential child participants” (*IRB Guidelines*, n.d.). Additionally, the need for one versus two parents to sign consent is determined by the type of research being conducted and the risks associated. With high risks, two parents were required unless one was “deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child” (*IRB Guidelines*, n.d.). It is generally accepted for minors in research to be considered ethical with assent when capable and parental consent. However, a study showed that:

young children could understand complex concepts like research risks and benefits, [but] there remained a significant minority of children under around the age of 10 who had difficulties understanding research concepts [and that it was not until] comprehension increased with grade level, with 15 – 16 year olds [that they had] a similar understanding of research as adults. (Crane & Bromme, 2017)

Research continues to debate the ethicality of including preadolescent and adolescent minors in studies and obtaining their consent.

Ethical considerations for pregnant females in research have long been debated due to risks the research may impose on the mother and the fetus. When obtaining participants for research, the subjects are normally divided into (1) the mother (2) the fetus or (3) both. In the case of PCOS, the mother is normally the subject, however the research of medication or supplementation effects during pregnancy could cause harm or risk to the fetus. When considering how ethical the research may be, it is important to determine who the subject is.

When the mother is the subject, the focus is to treat their health needs. Robertson (1999), states that treating symptoms of pregnancy such as nausea or a cold is considered a health need but “if the drug used to treat those conditions is teratogenic, it would be unethical to take it even though it is directed at treating her ‘health.’” This is the biggest concern in the debate of the ethicality of pregnant females in clinical research. The inclusion of these subjects must always bear in mind that there could be fatal harm or adverse effects to either the fetus or the mother.

Although metformin in recent years has been considered a generally safe medication, the American Diabetes Association (ADA) states that metformin has “evidence of safety and efficacy from randomised trials whilst noting that long term safety data for offspring is lacking” (Hyer et al., 2018). This brings the concern of possible risk to fetus. Similarly, inositol has been

deemed generally safe for consumption during pregnancy by the FDA but there are calls for more research to “establish long-term maternal and foetal safety, involving a larger number of patients from different ethnicities and with different risk factors” (Formoso et al., 2019).

Conclusion

As women’s health continues to garner more attention for the diagnosis and treatment of reproductive disorders, it is important to determine all options of treatment for conditions such as PCOS. This syndrome affects many systems in the body and symptoms vary from person to person. Due to a historical lack of female participants in research, it is an important call to action for more research into PCOS and its treatments. Both metformin and inositol supplements for the treatment of the disorder are newer in the medical field meaning that further research could be done to determine the efficacy.

By researching the viability of inositol versus metformin for the treatment of PCOS, it is determined that there are several unknown factors. These include the safety of metformin as a prescription medication and the safety of inositol as a dietary supplement. As with most medications, patients most often want to determine if the benefits outweigh the risks; therefore, adverse effects of medications are deemed important to both the physician and the patient. When determining if one treatment had more adverse effects than the other, studies seem to present gastrointestinal side effects for both. However, these effects can vary depending on the dosage and other precipitating factors or comorbidities. Metformin had more reported serious effects including renal dysfunction and lactic acidosis while inositol, comparatively did not have these reported adverse effects. Safety of the treatment is a large component of whether physicians will recommend it to patients.

Along with safety, physicians should also consider the popularity of the treatment. When determining whether patients will be medication compliant, cost is a factor to be determined. Metformin is considered to be a cost-effective prescription medication with only a few caveats. A search found that there were elements to metformin that may change the cost. The first element being generic versus brand name, most generic medications are cheaper than brands because the cost of research is eliminated. At the time of the search there was a \$48+ difference between generic metformin and the brand Glucophage. Additionally, another element to the cost was the type of brand. The two brand names found were Glucophage and Riomet. Riomet has been reported to reduce gastrointestinal effects, however the difference between the two brands is about \$470+. Riomet's retail price at the time of the search was \$541.00. In comparison, inositol supplements were harder to put a price to due to multiple sellers and less strict regulations compared to metformin. The supplement was available in different forms and the price increased depending on what was in the specific blend. In general, the price of inositol varied from \$0.05 to \$1.24 per dose.

Another factor to the popularity of the treatments was how regulated the options were. It was found that the FDA regulates both metformin and inositol but to different degrees. Metformin, being a medication, is regulated strictly through the FDA and is only available with a prescription and from a pharmacy. Comparatively, inositol is a dietary supplement and is considered to be generally safe for consumption with the limitations that it must be manufactured under good practice. Inositol manufacturers can be outside of the United States or domestically and may have different blends for consumption. Therefore, physicians may feel more comfortable recommending metformin over inositol because regulations are stricter.

A large component of popularity is determined by how confident the patient believes in the efficacy of the treatment. The efficacy of CAMs and supplements is still a major topic of research in the United States today, and because inositol is a dietary supplement, there could be varying beliefs in its viability to treat PCOS symptoms. It was determined that those in the United States usually focus on medications to treat symptoms whereas those in Asian countries have a higher belief in CAM use. Factors affecting CAM use in Asian countries are determined by easier access, lower costs, and social influence. Additionally, a study found that those that are older, are female, are non-Hispanic whites, and are of higher education are more likely to take supplementations. Therefore, recommendations for inositol should consider the individual patient's beliefs and values.

Ethical considerations in women's health were a barrier to accurate and extensive studies for PCOS in the past. Some ethical concepts to consider for research are the consent of preadolescent and adolescent minors as well as the harm of the fetus or mother during clinical trials. It was found that it is considered generally acceptable to allow for participation of minor participants with both participant assent and parental consent. However, there are still debates when it comes to comprehension of the minors and whether they can accurately assent to clinical trials. When pregnant women are involved, the biggest debate is the risk that the trial may incur on the fetus development, wellbeing, or the mother's health. For both metformin and inositol, more research is required for the long-term effects they may have on the fetus after trials. The ethical considerations of this research do not have a clear solution.

Since there are many unknown areas to this topic, it is clear that more research is required to determine if inositol would be a comparable treatment as metformin for PCOS. This research will not only further women's health research, but it will allow patients more freedom in

treatment options. Expanding the medical field's knowledge to more treatments can influence those within healthcare such as prescribing providers, educators, and patients looking for relief. Taking these findings, considering more research into dietary supplementations for treatment of other conditions may take place.

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