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# Letrozole vs. Clomiphene Citrate for Infertility in Polycystic Ovarian Syndrome

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INFERTILITY IN POLYCYSTIC OVARIAN SYNDROME

by

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A Scholarly Project

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## Abstract

Polycystic Ovarian Syndrome (PCOS) is the leading cause of anovulatory infertility and the most common endocrinopathy in women of reproductive age (Rosenfield & Ehrmann, 2016). It has been recognized that women with PCOS often struggle with infertility and require medication to stimulate ovulation to become pregnant. Currently, the first-line treatment for infertility associated with PCOS is clomiphene citrate, which was introduced in the 1960s (Morad & Farag, 2015). However, it has been proposed that an aromatase inhibitor, specifically letrozole, should become the first-line treatment for these patients due to a decreased adverse effect profile, a lower incidence of simultaneous multiple gestation pregnancies, and a decreased risk of congenital abnormalities. The purpose of this study is to determine if letrozole is an equal or better alternative to clomiphene citrate for infertility treatment in PCOS patients. An extensive literature review was performed, and letrozole was found to have higher ovulation rates, fewer twin pregnancies/more single births, higher pregnancy rates, and higher live birth rates compared to clomiphene citrate. There were conflicting results for endometrial thickness and single follicle stimulation. Neither letrozole or clomiphene citrate was superior to the other for ovarian hyperstimulation syndrome. There were no significant differences between letrozole and clomiphene citrate regarding congenital abnormalities and miscarriage rates. The results regarding ectopic pregnancies were comparable between both groups. In conclusion, the results provide information supporting letrozole as an adequate first-line alternative to clomiphene citrate for infertility in patients with PCOS.

### Infertility in Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome (PCOS) is the leading cause of anovulatory infertility and the most common endocrinopathy in women of reproductive age (Rosenfield & Ehrmann, 2016). It has been recognized that women with PCOS often struggle with infertility and require medication to stimulate ovulation to become pregnant. Currently, the first-line treatment for infertility associated with PCOS is clomiphene citrate, which was introduced in the 1960s (Morad & Farag, 2015). In addition, 25% of patients with infertility are clomiphene citrate resistant and unable to ovulate, and many are unable to conceive with clomiphene citrate and subsequently experience clomiphene citrate failure (Legro et al., 2014). Clomiphene citrate has also been associated with a limited efficacy including a 22% live birth rate and increased risk of multiple pregnancies (Legro et al., 2014).

It has been discussed that an aromatase inhibitor, specifically letrozole, should become the first-line treatment for these patients due to a decreased adverse effect profile, a lower incidence of simultaneous multiple gestation pregnancies, increased endometrial thickness better promoting pregnancy, and a decreased risk of cardiac congenital abnormalities.

#### **Statement of the Problem**

Clomiphene citrate has been the first-line treatment for infertility in patients with PCOS for quite some time. If an alternative to clomiphene citrate is available that is safer, more efficacious and bears less adverse effects, it should be implemented as the first-line treatment in daily medical practice.

## **Research Questions**

In the patient with polycystic ovarian syndrome, is letrozole compared to clomiphene citrate more effective for ovulation induction, endometrial thickness, single follicle stimulation/single gestation birth, pregnancy rate, and live birth rate?

In the patient with polycystic ovarian syndrome, is letrozole compared to clomiphene citrate safer for the mother and baby regarding ovarian hyperstimulation syndrome, congenital anomalies, ectopic pregnancies, and miscarriage rates?

If letrozole is found to be more effective and safe, this could have a tremendous impact on healthcare for PCOS patients struggling with infertility. Today, some women may feel defeated with current treatment options. The possibility that letrozole may improve outcomes for these women and their families is very promising.

## **Review of Literature**

Online database searches were performed for the literature review using PubMed, Cochrane Library, and ClinicalKey. The searches included terms related to infertility in patients with PCOS such as letrozole, clomiphene citrate, Femara, Clomid, infertility, PCOS, safety of letrozole, safety of clomiphene citrate, among many others. The information used to produce this scholarly project includes information from within the last five years, except for one article referenced from 2011 due to historical information regarding the medication. The population used for all studies in the literature review were adult women of childbearing age diagnosed with polycystic ovarian syndrome. All significant findings in the studies are defined as having a p-value <0.05. Studies that didn't specifically relate to PCOS patients were excluded.

The literature review is divided into four sections to guide the reader beginning with the pathophysiology of PCOS and its effects on infertility. The second section of the literature

review discusses the current treatment options for patients with PCOS struggling with infertility. The remaining two sections of the literature review focus on comparing the efficacy and safety of letrozole compared to clomiphene citrate.

### **The Pathophysiology of Polycystic Ovarian Syndrome and Its Effects on Infertility**

**Normal physiology.** A condensed review of physiology related to natural ovulation will be discussed. First, the ovary's functional unit is known as a follicle. Within the follicle is an oocyte, or the immature egg, which is surrounded by granulosa cells and theca cells. In the non-PCOS woman, the hypothalamus is appropriately stimulated to release gonadotropin-releasing hormone (GnRH), which acts on the anterior pituitary gland in the brain to release follicle stimulating hormone (FSH) and luteinizing hormone (LH). LH works on the theca cells of the ovary to produce androgens, while FSH works on the granulosa cells of the ovary to convert these androgens into estradiol. Once converted, this large amount of estradiol stimulates the brain to release more LH, known as the LH surge, which stimulates the dominant follicle to grow and eventually release the egg into the fallopian tube for implantation in the uterus. This process is known as ovulation (Reed & Carr, 2015).

**Pathophysiology of PCOS.** According to Dumesic, Oberfield, Stener-Victorin, Marshall, and Laven (2016), PCOS is an endocrinopathy in which the cause isn't well understood. However, it is known that it consistently produces a plethora of metabolic complications including menstrual irregularities and increased levels of androgens. This occurs in response to abnormal circulation of sex steroids, insulin activity, and distinct ovarian characteristics. It is thought that obesity exacerbates these complications and they can vary in severity depending on ethnicity and race (Dumesic et al., 2016).



***Androgen excess.*** According to Rosenfield and Ehrmann (2016), there is strong evidence to support the hypothesis that the excess androgen production that occurs in PCOS is a result of a defect in the theca cells of the ovary. Specifically, studies have shown that the theca cells in PCOS patients have a higher number of cytochrome P450c17 enzymes and a higher number of proteins known as DENND1A that are used in steroidogenesis. The exact purpose of DENND1A in steroidogenesis is unknown, however there is discussion that it may facilitate up-regulation in signaling the LH receptors. Furthermore, there are increased numbers of LH receptors in the PCOS patient (Rosenfield & Ehrmann, 2016). Rosenfield and Ehrmann (2016) also discuss that dysregulation of the zona reticularis within the adrenal cortex may be another factor contributing to excess androgens in PCOS patients, as the normal steroidogenesis process of the zona reticularis is altered and results in increased androgen production (Rosenfield & Ehrmann, 2016).

It is believed that there is increased ovarian sensitivity to LH in the patient with PCOS, thus increasing LH secretion and causing an overabundance of LH. The excess insulin as previously discussed has been identified as a cause of this hypersensitivity, as excess insulin sensitizes the ovary to LH. However, LH excess is only present in half of PCOS patients. The increased LH compared to FSH results in more androgens, since fewer androgens are being converted to estradiol (Rosenfield & Ehrmann, 2016).

***Metabolic syndrome and insulin resistance.*** Close to half of patients with PCOS have insulin-resistant hyperinsulinism (Rosenfield & Ehrmann, 2016). Rosenfield and Ehrmann (2016) state that "insulin resistance in PCOS is characterized by reduced sensitivity and responsiveness to insulin-mediated glucose utilization primarily in skeletal muscle and adipose tissue, although the nature of these defect differs," (Rosenfield & Ehrmann, 2016). The over-release of insulin is thought to be due to a compensatory response to the insulin resistance, which

also promotes increased androgen levels. Type II diabetes mellitus may occur if pancreatic beta cells begin to fail due to the increased insulin secretion from insulin resistance (Rosenfield & Ehrmann, 2016).

***Etiologies.*** Rosenfield and Ehrmann (2016) discuss that both environmental and genetic factors trigger PCOS. Genetic factors that can contribute to PCOS include high levels of androgens, insulin resistance, and altered insulin secretion, while environmental effects may be due to impaired fetal growth, exposure to androgens in vitro, and obesity (Rosenfield & Ehrmann, 2016).

### **Current Treatment Options for Infertility in Patients with Polycystic Ovarian Syndrome**

**First-line treatments.** In obese women with PCOS, lifestyle changes are strongly recommended to achieve a weight loss of 5-10% which may successfully induce ovulation without the need for pharmacological therapy (Melo, Ferriani, & Navarro, 2015). Clomiphene citrate is currently the recommended first-line pharmacological treatment for ovulation induction in patients with PCOS. The usual dose and duration of clomiphene citrate is 50 mg per day for five days, but it may be increased by 50 mg up to a maximum of 150 mg for five days if there is no ovulation or development of follicles (Legro, 2016). In patients resistant to clomiphene citrate, metformin may be added as an adjunct medication which may improve pregnancy rates; the addition of metformin is still considered first-line treatment if the patient is resistant to clomiphene citrate alone (Melo et al., 2015).

Clomiphene citrate was first approved for ovulation induction in the 1960s. It belongs to the pharmacological category referred to as nonsteroidal selective estrogen receptor modulators (SERMs). It works by binding to the estrogen receptors as it has a very similar structure to

estrogen. This decreases the ability for true estrogen to bind to estrogen receptors, which produces an antiestrogenic effect. In response, the pituitary gland releases more FSH since it appears that the estrogen level is low, which in turn stimulates the ovaries to ovulate (Morad & Farag, 2015).

Letrozole is currently being debated as either an equal or better alternative to clomiphene citrate due to the reasons discussed earlier in this project. Its most significant historical use in the healthcare field has been for FDA-approved treatment of postmenopausal breast cancer, however utilizing it for infertility is currently an off-label use. The usual dose and duration of letrozole is 2.5 mg per day for five days, however if no ovulation or development of follicles occur it may be increased by 2.5 mg up to a maximum dose of 7.5 mg for five days (Legro, 2016). Legro (2016) states that "based on current meta-analyses ...women with PCOS are about 50% more likely to have a live birth with letrozole compared to clomiphene," (Legro, 2016).

Letrozole works on a different pathway and is categorized as a nonsteroidal aromatase inhibitor, meaning that it inhibits the enzyme that converts testosterone and androstenedione into various forms of estrogen. Inhibiting this conversion also results in less estrogen binding to the estrogen receptors in the brain, thus stimulating FSH to be released from the brain and inducing ovulation (Morad & Farag, 2015).

**Second and third-line treatments.** Second-line treatment options include injectable gonadotropins that aim to induce ovulation, however this method has a higher rate of multiple gestation pregnancies and is much costlier than clomiphene citrate and/or clomiphene citrate and metformin combined; another second-line treatment option includes laparoscopic ovarian drilling (LOD) in patients resistant to clomiphene citrate. Of course, since this option requires surgery, it is much costlier as well as has increased risks and should only be performed if surgery is

necessary for another obstetrical or gynecological reason. Both methods may result in ovarian hyperstimulation syndrome (OHSS), as patients with PCOS are more sensitive to this occurring (Melo et al., 2015). Lastly, the third-line treatment option for infertility in PCOS patients includes in vitro fertilization (IVF). This method is very costly and is typically only used when other options have failed (Melo et al., 2015).

### **Efficacy of Letrozole versus Clomiphene Citrate to Induce Ovulation and Pregnancy Outcomes**

A randomized control trial by Ghahiri, Magharehabed, and Mamourian (2016) aimed to compare the efficacy and safety of letrozole and clomiphene citrate on ovulation and pregnancy. The study included 101 women with a mean age of 25 years with primary or secondary infertility due to PCOS. It was found that 58% of patients treated with letrozole became pregnant and 47% of patients treated with clomiphene citrate became pregnant, however this was not statistically significant ( $p=0.23$ ). Thirty patients treated with clomiphene citrate and 36 patients treated with letrozole had regular menstrual cycles either during or after treatment, however this also was not statistically significant ( $p=0.21$ ). The ovulation rate was similar between both groups with the clomiphene citrate group having a 58.8% ovulation rate and the letrozole group having a 72% ovulation rate, however again this was not statistically significant. All patients completed this study, but one from each group did not present after treatment so the authors were unable to follow those pregnancy outcomes. The study concluded that letrozole is not superior to clomiphene citrate, but that they are equally effective (Ghahiri et al., 2016).

A randomized control trial was conducted by Sharief and Nafee (2015) that compared letrozole and clomiphene citrate in 75 patients between the ages of 18 and 36 with PCOS. All patients had been infertile for at least two years and had hirsutism, normal prolactin and FSH

levels, and normal thyroid function. All partners were tested for normal semen analysis. The authors found that the letrozole group had a statistically significant lower number of mature follicles, with the letrozole group having  $1.3 \pm 0.31$  mature follicles and the clomiphene citrate group having  $2.4 \pm 1.1$  mature follicles ( $p=0.0001$ ). The study also found that the letrozole group had a significantly higher endometrial thickness, with the letrozole group having an endometrial thickness in the sagittal plane of  $84 \pm 1.8$  mm and the clomiphene citrate group having an endometrial thickness in the sagittal plane of  $52 \pm 1.2$  mm ( $p=0.0001$ ). The letrozole group also had a significantly higher ovulation rate with the letrozole group having an 82.9% ovulation rate and the clomiphene citrate group having a 62.5% ovulation rate ( $p=0.05$ ). However, the pregnancy rates were not significantly different with the letrozole group having a pregnancy rate of 28.6% and the clomiphene citrate group having a pregnancy rate of 17.5% ( $p=0.254$ ). The authors concluded that letrozole may be preferred in select groups of patients, but that more studies are needed (Sharief & Nafee, 2015). It is important to consider that the study had a small sample size in comparison to other studies included in this project.

Another randomized control trial conducted by Hussain et al. (2013) compared letrozole and clomiphene citrate for ovulation rates, pregnancy rates, endometrial thickness, and whether the drug induced only a single follicle to ovulate to prevent multiple gestation pregnancies. The study consisted of 150 participants aged between 18 and 40 with PCOS. The participants' partners all required normal semen analysis. The letrozole group had a 78.7% ovulation rate compared to a 53.3% ovulation rate in the clomiphene citrate group ( $p=0.001$ , 95% CI [1.16, 1.88]). The letrozole group had a 25.3% pregnancy rate compared to a 16% in the clomiphene citrate group ( $p=0.221$ , 95% CI [0.83, 3.03]). The letrozole group had 44.6% single follicle ovulations compared to 26.7% in the clomiphene citrate group ( $p=0.0270$ , 95% CI [0.75, 1.99]).

The letrozole group had a 9.2 mm endometrial thickness with a standard deviation of 2.3 mm compared to the clomiphene citrate group having an endometrial thickness of 8.4 mm with a standard deviation of 2.2 mm ( $p=0.031$ , 95% CI [0.1, 3.2]). The only statistically significant difference in this study included the ovulation rate ( $p=0.001$ ) and endometrial thickness ( $p=0.031$ ), which both favored the letrozole group (Hussain et al., 2013). After controlling for variables such as type of infertility, age, duration of infertility, BMI, and baseline FSH and LH levels, it was determined that patients who received letrozole were greater than three times more likely to ovulate than patients who were treated with clomiphene citrate ( $p=0.003$ , 95% CI [1.45, 6.30]). It was also found that BMI played a role in determining successful ovulation, with an inverse relationship between BMI and chances of a successful ovulation, however patients with various BMI's were distributed similarly in both groups ( $p=0.004$ , 95% CI [0.85, 0.97]) (Hussain et al., 2013). The study concluded that patients treated with letrozole had statistically significant higher ovulation rates and increased endometrial thickness compared to clomiphene citrate (Hussain et al., 2013). Lastly, the study found that letrozole was better at stimulating only one follicle, unlike clomiphene citrate which had higher rates of multiple follicle stimulation resulting in multiple simultaneous gestations (Hussain et al., 2013). Overall, the authors felt that letrozole was better than clomiphene citrate for ovulation induction. Limitations of this study include that 10% of the participants were over 35 years of age, which is a more difficult population to successfully conceive (Hussain et al., 2013).

A double-blind, randomized trial conducted by Legro et al. (2014) consisted of 750 women between the ages of 18 and 40 and aimed to determine if letrozole produced better pregnancy outcomes than clomiphene citrate. The primary outcome measured in the study was live birth, while secondary outcomes included congenital abnormalities, pregnancy loss,

ovulation, and multiple simultaneous gestation pregnancies. The study determined that the letrozole group had a significantly higher cumulative live birth rate than letrozole, with the letrozole group having a cumulative live birth rate of 27.5% compared to 19.1% for the clomiphene citrate group ( $p=0.007$ , 95% CI [1.10, 1.87]). However, there was not a significant difference in the live birth rate "according to treatment cycle," (Legro et al., 2014). The letrozole group showed a significantly higher ovulation rate than clomiphene citrate at every visit following the initial visit, with the letrozole group having an 88.5% ovulation rate and the clomiphene citrate group having an ovulation rate of 76.6% ( $p < 0.001$ , 95% CI [1.08, 1.24]). There was also a significantly greater rate of single pregnancy with the letrozole group compared to the clomiphene citrate group, with the letrozole group having a single pregnancy rate of 34.1% and the clomiphene citrate group having a single pregnancy rate of 26% ( $p=0.03$ , 95% CI [1.03, 1.58]). The study found that the clomiphene citrate group experienced improvement in patients' androgen levels and hirsutism. Letrozole had a greater decrease in anti-Mullerian hormones compared to clomiphene citrate but had less of an increase in endometrial thickness when compared to clomiphene citrate. However, the authors feel that the results on ovulation and live birth rates reflect that improvement in hyperandrogenism might not be needed for successful ovulation and live birth. Letrozole also had a significantly lower estradiol level than clomiphene citrate when measured. The dropout rate and/or those that were excluded include 22.6% in the clomiphene citrate group and 19.5% in the letrozole group. The reasons for these withdrawals were statistically insignificant between the two groups, however the authors acknowledged that this was a high dropout rate and that could be attributed to participants feeling discouraged and leaving to find alternative treatments before the study could be finished (Legro et al., 2014). Overall, the authors felt that letrozole was better than clomiphene citrate for ovulation induction

in patients with PCOS but that more studies are needed regarding its safety on teratogenic effects (Legro et al., 2014). A limitation of this study includes a large percentage of the participants being classified as obese, however the authors feel that this is an accurate reflection of many patients with PCOS in the U.S. The authors also mention that there were no lifestyle interventions required prior to the start of the study which is recommended practice. Lastly, the authors feel that more studies are necessary to determine the safety of letrozole (Legro et al., 2014).

Liu et al. (2017) conducted a randomized control trial to compare ovulation induction between clomiphene citrate alone, clomiphene citrate combined with metformin, letrozole alone, or letrozole combined with metformin in 268 patients with PCOS. The study also aimed to determine if letrozole could replace the first-line treatment of clomiphene citrate. Ovulation, pregnancy, and live birth rates were recorded. The pregnancy rate and live birth rate both favored the letrozole group, with a pregnancy rate of 52.1% in the letrozole group and 39.7% in the clomiphene citrate group, and a live birth rate of 35.3% in the letrozole group and 26.4% in the clomiphene citrate group, however neither of these findings were statistically significant ( $p > 0.5$ ). Ovulation rates were studied, however the article combined the letrozole group alone and letrozole + metformin therapy together and named it the letrozole treatment group, and did the same with the clomiphene citrate group by taking the clomiphene citrate group alone and clomiphene citrate + metformin therapy together and naming it the clomiphene citrate treatment group, so this may be skewed as it includes metformin in both of the treatment groups. With this being said, the ovulation rate was significantly higher in the letrozole treatment group with an ovulation rate of 73.3% compared to an ovulation rate of 52.7% in the clomiphene treatment group ( $p < 0.001$ ). There were no congenital abnormalities noted in any of the 63 newborns. The



study concluded that clomiphene citrate should remain the first-line treatment for infertility in patients with PCOS. The authors feel that their results differed in comparison to other studies, however they attribute this to the Chinese population included in the study (Liu et al., 2017).

A double-blind, randomized controlled trial conducted by Amer, Smith, Mahran, Fox, and Fakis (2017) aimed to determine if letrozole produced better pregnancy rates than clomiphene citrate in women with PCOS. The study consisted of 159 participants who were between the ages of 18 and 39 with a BMI of 35 kg/m<sup>2</sup> or less. The authors found that there were significantly higher pregnancy rates with the letrozole group than the clomiphene citrate group, with the letrozole group having a pregnancy rate of 61.2% and the clomiphene citrate group having a pregnancy rate of 43% (p=0.022, 95% CI [1.1, 2.0]). Other statistically significant findings of the study included a higher rate of pregnancies in the letrozole group for those with a BMI of less than 30 kg/m<sup>2</sup>. The letrozole group also had a higher rate of ovulation and pregnancies per cycle than the clomiphene citrate group, with the letrozole group having a 19% pregnancy rate per cycle and a 75% ovulation rate per cycle, whereas the clomiphene citrate group had an ovulation rate per cycle of 67% and pregnancy rate per cycle of 12% (p=0.045, 95% CI [0.9, 1.2] for ovulation rate per cycle; p=0.036, 95% CI [1.03, 2.3] for pregnancy rate per cycle). The endometrial thickness was significantly higher in the clomiphene citrate group with a median endometrial thickness of 9.0 mm compared to 8.4 mm in the letrozole group (p=0.002). The authors mentioned that women with a BMI greater than 35 kg/m<sup>2</sup> were excluded but justified this by discussing that this is standard practice in European studies since these patient populations are at increased risks for complications and provide more challenges (Amer et al., 2017).

Al-Shaikh, Al-Mukhtar, Al-Subaidu, Al-Rubaie, and Al-Khuzae (2017) conducted a prospective clinical trial in Iraq consisting of 85 women diagnosed with PCOS struggling to conceive. There were 45 women in the clomiphene citrate group and 40 women in the letrozole group. The trial measured follicular amount and size, endometrial thickness, and pregnancy rates. The trial did not measure miscarriage rates due to losing contact with the patients, however they were informed of a few miscarriages. The trial found no significant difference between follicular size, however there was a significant difference between the number of mature follicles which was higher in the letrozole group. The mean number of mature follicles that were 17 mm in size or greater was  $1.42 \pm 0.66$  in the letrozole group and  $1.15 \pm 0.44$  in the clomiphene citrate group ( $p < 0.05$ ) (Al-Shaikh et al., 2017). The trial also reported significant differences in the endometrial thickness between both groups, with the clomiphene citrate group having a higher mean. The mean endometrial thickness in the clomiphene citrate group was  $9.62 \text{ mm} \pm 2.66 \text{ mm}$ , whereas the letrozole group had a mean endometrial thickness of  $8.02 \text{ mm} \pm 1.24 \text{ mm}$  ( $p < 0.05$ ). The trial reported no significant difference in pregnancy rates per cycle between the two groups with clomiphene citrate having a 12.12% pregnancy rate per cycle and letrozole having a 9.09% pregnancy rate per cycle ( $p > 0.05$ ) (Al-Shaikh et al., 2017).

#### **Safety of Mother and Baby – Letrozole Versus Clomiphene Citrate**

There has been discussion regarding congenital abnormalities with letrozole use for ovulation induction compared to clomiphene citrate. A study conducted by Novartis Pharmaceuticals in Canada was presented to the American Society for Reproductive Medicine in 2005 that provided information that there was a substantial number of birth defects in babies born to mothers that had taken letrozole for ovulation induction. The company sent a global notice to all physicians informing them that letrozole was contraindicated in all premenopausal

or pregnant women due to the increased risk of birth defects. However, Casper and Mitwally (2011) stated that "...this study had several methodologic problems and was never accepted for peer-reviewed publication," (Casper & Mitwally, 2011).

Casper & Mitwally (2011) go on to discuss that shortly after this happened, another study was performed with 911 babies that were conceived after either clomiphene citrate or letrozole treatment. In this study, it was found that only 2.4% of babies whose mothers were treated with letrozole and 4.8% of babies whose mothers were treated with clomiphene citrate had congenital malformations or chromosomal abnormalities. However, this was deemed statistically insignificant due to the small sample size of the study. The authors also mentioned that the Centers for Disease Control later conducted a study called the National Birth Defects Prevention Study which confirmed that there is a higher risk of congenital cardiac abnormalities with clomiphene citrate compared to letrozole (Casper & Mitwally, 2011).

A study conducted by Sharma et al. (2014) disclosed that there were 5 out of 201 babies (2.5%) with congenital or chromosomal abnormalities whose mothers were treated with letrozole for ovulation induction, compared to 10 out of 251 babies (3.9%) whose mothers were treated with clomiphene citrate ( $p < 0.648$ , 95% CI [0.207, 1.829] for overall congenital malformations,  $p < 0.907$ , 95% CI [0.249, 2.407] for structural malformations,  $p < 0.226$ , 95% CI [0.018, 5.191] for chromosomal anomalies). The control group included 5 out of 171 babies with congenital or chromosomal abnormalities (Sharma et al., 2014). However, it was concluded that there wasn't a significant difference in the rate of congenital or chromosomal abnormalities when natural conception was used or if the mothers were treated with letrozole or clomiphene citrate. Sharma et al. (2014) disclosed in the study that 47 children were born outside of their institute and thus the information regarding anomalies was provided by the parents. Sharma et al. (2014) also

discuss that the study is retrospective with a relatively small study group, which may be another limitation in their study (Sharma et al., 2014).

A retrospective cohort study was performed by Tatsumi et al. (2017) to compare congenital anomalies and adverse pregnancy or neonatal outcomes in patients with natural conception versus ovulation induction with the use of letrozole. The study included 3,136 women with natural cycles and 792 women who used letrozole to achieve pregnancy. Miscarriage rates, ectopic pregnancy rates, stillbirth rates, and live birth rates were measured for pregnancy outcomes. Although this study does not compare letrozole and clomiphene citrate, the findings regarding letrozole are still relevant to the research studied in this project. The letrozole group was found to have a 12.2% miscarriage rate compared to a 26.4% miscarriage rate for natural cycle pregnancy ( $p < 0.001$ , 95% CI [0.30, 0.47]). The ectopic pregnancy rate in the letrozole group was 0.13% and 0.7% in the natural cycle pregnancy group ( $p = 0.078$ , 95% CI [0.02-1.23]). The stillbirth rate was 0.37% and 0.38% in the letrozole and natural groups, respectively ( $p = 0.920$ , 95% CI [0.30, 3.83]). The live birth rate was 87.1% and 72.2% in the letrozole and natural groups, respectively; it is unknown what the p-value or confidence interval is for this outcome as they are not disclosed in the article. Major congenital anomalies including cardiovascular, musculoskeletal, and chromosomal anomalies existed in 1.9% and 1.5% in the letrozole and natural groups, respectively, however this was disclosed as not significant ( $p = 0.869$ ). The authors of the study concluded that letrozole does not increase the risk of major congenital anomalies compared to natural cycle pregnancy. The authors also included that the use of letrozole may in fact decrease the chances of miscarriage in fresh-embryo cycles. Tatsumi et al. (2017) mentioned in the study that only increased risk for large congenital anomalies

associated with letrozole were able to be ruled out and that the follow-up period for this study was shorter compared to other studies (Tatsumi et al., 2017).

In the study conducted by Legro et al. (2014), more congenital defects were noted in the letrozole group with four in the letrozole group having a congenital defect compared to one in the clomiphene citrate group, however this was not significant ( $p=0.65$ , 95% CI [0.75, 1.60]) (Legro et al., 2014). The authors didn't find any significant difference in pregnancy loss or multiple gestation pregnancies between either group. The miscarriage rate was comparable between both groups with the letrozole group having a miscarriage rate of 31.8% and the clomiphene citrate group having a miscarriage rate of 29.1%, but this was not statistically significant ( $p=0.65$ ). Statistically significant findings included a 3% neonatal death rate and 1.5% fetal death rate with clomiphene citrate compared to 1% neonatal death rate and 1% fetal death rate with letrozole. The exact p-value for these significant findings was not included in the article but was disclosed as significant with a p-value  $<0.05$  (Legro et al., 2014).

Legro (2016) discusses that the half-life of letrozole is much shorter than clomiphene citrate, with a two-day half-life. This may provide reasoning for its discussed effects as it is removed from the body more rapidly than clomiphene citrate. He also explains that the congenital birth defect rate of letrozole are comparable to clomiphene citrate with a birth defect rate less than 5% in two studies (Legro, 2016).

The study conducted by Liu et al. (2017) reported no congenital abnormalities in the 63 newborns in any of the groups (Liu et al., 2017).

The study conducted by Ghahiri et al. (2016) reported five miscarriages in both the letrozole and clomiphene citrate group. In addition, no cases of ovarian hyperstimulation syndrome occurred (Ghahiri et al., 2016).

## Discussion

With the efficacy and safety of letrozole compared to clomiphene citrate presented through various studies in the literature review, the research will now be evaluated and discussed in a holistic approach addressing each of the research questions presented in the introduction.

Significant findings of the studies included an overall higher ovulation rate, single follicle ovulation and single pregnancy rate compared to twin pregnancy rate with letrozole, and either no significant difference in pregnancy rate or a higher pregnancy rate with letrozole.

Significant findings of the studies regarding the safety of the mother and baby include no significant difference in congenital abnormalities between the two groups or no congenital defects at all; differing results on ectopic pregnancy rates; and either no significant difference in miscarriage rates or significant findings favoring letrozole for much lower miscarriage rates.

**In the patient with polycystic ovarian syndrome, is letrozole compared to clomiphene citrate more effective for ovulation induction, endometrial thickness, single follicle stimulation/single gestation birth, pregnancy rate, and live birth rate?**

**Ovulation rates.** Ghahiri et al. (2016) and Amer et al. (2017) found that there was no statistically significant difference in ovulation rates between letrozole and clomiphene citrate, while Sharief and Nafee (2015), Hussain et al. (2013), Legro et al. (2014), and Liu et al. (2017) all found that letrozole had statistically significant higher ovulation rates. Amer et al. (2017) revealed that there may be limitations in his study due to the exclusion of women with PCOS that had a BMI greater than 35 kg/m<sup>2</sup> (Amer et al., 2017).

**Endometrial thickness.** Sharief and Nafee (2015) and Hussain et al. (2013) found that letrozole had significantly higher endometrial thickness than clomiphene citrate group while Al-Shaikh et al. (2017) found that clomiphene citrate had a significantly higher endometrial

thickness than letrozole. Amer et al. (2017) found that there was not a statistically significant difference in endometrial thickness between either group, however as mentioned previously, Amer's (2017) study may have limitations due to the exclusion of women with PCOS that had a BMI greater than 35 kg/m<sup>2</sup> (Amer et al., 2017).

**Single follicle stimulation/single gestation birth.** Sharief and Nafee (2015) found that letrozole had a significantly lower number of mature follicles and Hussain et al. (2013) found that letrozole had a higher rate of single follicles than clomiphene, however Hussain et al.'s (2013) findings were not significant. Al-Shaikh et al. (2017) however did report a significant difference in the number of mature follicles greater than 17 mm, with letrozole having a higher number compared to clomiphene citrate. Al-Shaikh et al. (2017) did however mention in their study that the letrozole dose was higher in this study (5 mg) which may have enhanced the effects of the drug (Al-Shaikh et al., 2017).

Ghahiri et al. (2016) reported no twin pregnancies in either group, however Sharief and Nafee (2015) reported one twin pregnancy in the clomiphene citrate group and none in the letrozole group. Amer et al. (2017) reported no twin pregnancies in the letrozole group but disclosed a 12.5% twin birth rate in the clomiphene citrate group, however this was not significant (Amer et al., 2017). Legro (2014) reported a significantly higher single pregnancy rate with letrozole group compared to clomiphene citrate group (Legro, 2014).

**Pregnancy rates.** Ghahiri et al. (2016), Sharief and Nafee (2015), Hussain et al. (2013) Liu et al. (2017), and Al-Shaikh et al. (2017) all found that the pregnancy rates were not statistically different between letrozole and clomiphene. However, Legro et al. (2014) and Amer et al. (2017) found that there were statistically significant higher pregnancy rates with letrozole compared to clomiphene citrate.

**Live birth rates.** Legro et al. (2014) found letrozole to have a significantly higher live birth rate than clomiphene citrate while Liu (2017) did not find any significant difference in live birth rate. While Tatsumi (2017) didn't compare letrozole and clomiphene citrate, letrozole was found to have a higher live birth rate than natural pregnancies (Tatsumi, 2017).

**In the patient with polycystic ovarian syndrome, is letrozole compared to clomiphene citrate safer for the mother and baby regarding ovarian hyperstimulation syndrome, congenital anomalies, ectopic pregnancies, and miscarriage rates?**

**Ovarian hyperstimulation syndrome (OHSS).** Ghahiri et al. (2016) and Hussain et al. (2013) both reported no cases of ovarian hyperstimulation syndrome in either group (Ghahiri et al., 2016). Other studies did not disclose whether any cases of ovarian hyperstimulation syndrome occurred. In this regard, neither letrozole or clomiphene citrate is superior to the other for a decreased incidence of OHSS.

**Congenital abnormalities.** Sharma et al. (2014) found no significant difference between letrozole and clomiphene citrate and birth defects compared to natural conception, however Legro et al. (2014) reported a higher rate of congenital abnormalities in the letrozole group compared to the clomiphene citrate group, although this was not significant. Both Amer et al. (2017) and Liu et al. (2017) reported no congenital abnormalities between either group. Tatsumi et al. (2017) found that there was not a significant difference in congenital abnormalities between the letrozole group and natural pregnancies.

**Ectopic pregnancies.** In the clomiphene citrate groups, Ghahiri et al. (2016) reported an ectopic pregnancy rate of 8.3% while Legro et al. (2014) reported a higher rate of 12.5%. In addition, Amer et al. (2017) had no reports of ectopic pregnancies in the clomiphene citrate group (Amer et al., 2017).



In the letrozole groups, Ghahiri et al. (2016) reported the highest ectopic pregnancy rate of 10.3% and Legro et al. (2014) reported an ectopic pregnancy rate of 2.6%. Amer et al. (2017) reported the lowest ectopic pregnancy rate of 2% (Amer et al., 2017).

The ectopic pregnancy rates in the clomiphene citrate group ranged from 0.0%-12.5% while the ectopic pregnancy rate in the letrozole group ranged from 2% to 10.3%. When comparing letrozole and clomiphene citrate between the three studies, the study with the highest percentage of ectopic pregnancies was in the clomiphene citrate group, however another study reported no ectopic pregnancies with the clomiphene citrate group.

**Miscarriage rates.** Legro et al. (2014) reported the highest miscarriage rate in the clomiphene citrate group of 29.1% while Amer et al. (2017) reported the lowest miscarriage rate in the clomiphene citrate group of 17.6%. Ghahiri et al. (2016) reported a miscarriage rate of 25%. None of these values were significant with p values all greater than 0.05. However, Tatsumi et al. (2017) reported that the miscarriage rates were significant in his study with letrozole having a much lower miscarriage rate compared to natural cycle pregnancies. As mentioned previously, Al-Shaikh et al. (2017) was not able to determine a formal miscarriage rate but was informed of two miscarriages in the clomiphene citrate group and one in the letrozole group (Al-Shaikh et al., 2017).

In conclusion, letrozole was found to have higher ovulation rates, fewer twin pregnancies/more single births, higher pregnancy rates, and higher live birth rates compared to clomiphene citrate. There were conflicting results for endometrial thickness and single follicle stimulation. Neither letrozole or clomiphene citrate was superior to the other for ovarian hyperstimulation syndrome. There were no significant differences between letrozole and

clomiphene citrate regarding congenital abnormalities and miscarriage rates. The results regarding ectopic pregnancies were comparable between both groups.

### **Applicability to Clinical Practice**

Throughout the research presented and discussed in this project, letrozole was found to have an overall positive impact on infertility and either better or debatably better outcomes regarding its efficacy. Letrozole was found to have higher ovulation rates, fewer twin pregnancies/more single births, higher pregnancy rates, and higher live birth rates compared to clomiphene citrate. However, the other parameters and safety of letrozole compared to clomiphene citrate were either comparable or not statistically significant.

The applicability of this research to clinical practice is quite remarkable. For many years the first-line treatment of infertility in patients with PCOS has been clomiphene citrate; however, with the recent data from the studies discussed in this project, it is apparent that letrozole could be at the very least an equal alternative, with more research pointing towards an improvement in efficacy with letrozole compared to clomiphene citrate.

Infertility due to PCOS is a very common complaint and a struggle that is frequently brought to the provider's attention. Many women have tried to become pregnant with other fertility treatments to no avail or are beginning their infertility treatment journey. It is promising that with this research and ongoing research, letrozole will become a first-line pharmacological treatment for infertility in PCOS patients. Providers will be able to inform their patients of all treatment options available including letrozole and the positive impact it can have on infertility.

With a lower rate of multiple gestation pregnancies and a higher rate of ovulation, pregnancy, and live birth rates, women with infertility will be able to have more hope in their dreams of becoming a mother with the most effective medication available to them. This could

change the provider's way of practice if the provider is able to offer the patient an alternative medication that is superior to the traditional option, and ultimately providing the best outcome possible for each patient.

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