Letrozole vs. Clomiphene Citrate for Infertility in Polycystic Ovarian Syndrome

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Introduction

• Polycystic Ovarian Syndrome (PCOS) is the leading cause of anovulatory infertility and the most common endocrinopathy in women of reproductive age (Rosenthal & Elmaleh, 2016).
• 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 an on-going adverse effect profile, a lower incidence of multiple gestation pregnancies, and a decreased risk of congenital abnormalities.

Abstract

• PURPOSE: To determine if letrozole is an equal or better alternative to clomiphene citrate for infertility treatment in PCOS patients
• LITERATURE REVIEW: 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.

Literature Review

Efficacy

• Ghiassi et al: RCT, n=101. No significant difference regarding ovulation and pregnancy rates compared to clomiphene citrate
• Sharief & Nafee: RCT, n=750. Letrozole: Lower number of mature follicles (p=0.0001). Letrozole: Greater endometrial thickness (p=0.05). No significant difference in pregnancy rates
• Hussain et al: RCT, n=150. Letrozole: Higher ovulation rate (p=0.001). Letrozole: Greater endometrial thickness (p=0.031). No significant difference regarding pregnancy rate
• Legro et al: RCT, n=750. Letrozole: Higher cumulative live birth rate (p=0.0001). Letrozole: Higher single pregnancy rate (p=0.01). Letrozole: Greater single pregnancy rate (p=0.03)
• Liu et al: RCT, n=63. No congenital abnormalities in either group
• Akhtar et al: RCT, n=750. Letrozole: Greater endometrial thickness (p=0.001). Letrozole: Higher ovulation rate (p=0.001). Letrozole: Higher single follicle ovulation (p=0.0270). Letrozole: Higher rate of ovulation and pregnancies compared to clomiphene (p=0.022).

Safety

• Sharma et al: n=201. No significant difference in rate of congenital or chromosomal abnormalities compared to natural conception.
• Legro et al: n=750. No significant difference in rate of congenital defects, pregnancy loss, or miscarriage rate. Letrozole: Lower neonatal death rate and fetal death rate (p=0.05)
• Liu et al: n=63. No congenital abnormalities in either group
• Ghiassi et al: n=101. Five miscarriages in both groups. No cases of ovarian hyperstimulation syndrome (OHSS)

Applicability to Clinical Practice

• 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.

Discussion

• Ovulation rate: Ghiassi et al. (2016) and Amer et al. (2017) found no significant difference, while Sharief & Nafee (2015) found letrozole to have significantly higher ovulation rates compared to clomiphene citrate. Sharief & Nafee (2015) reported a significantly higher ovulation rate with letrozole compared to clomiphene citrate.

Statement of the Problem

• 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).
• If an alternative to clomiphene citrate is available that is safer and more effective, it should be implemented as the first-line treatment in daily medical practice.

Research Question

• 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?

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