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Letrozole vs. Clomiphene Citrate for Infertility in Polycystic Ovarian Syndrome

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Introduction

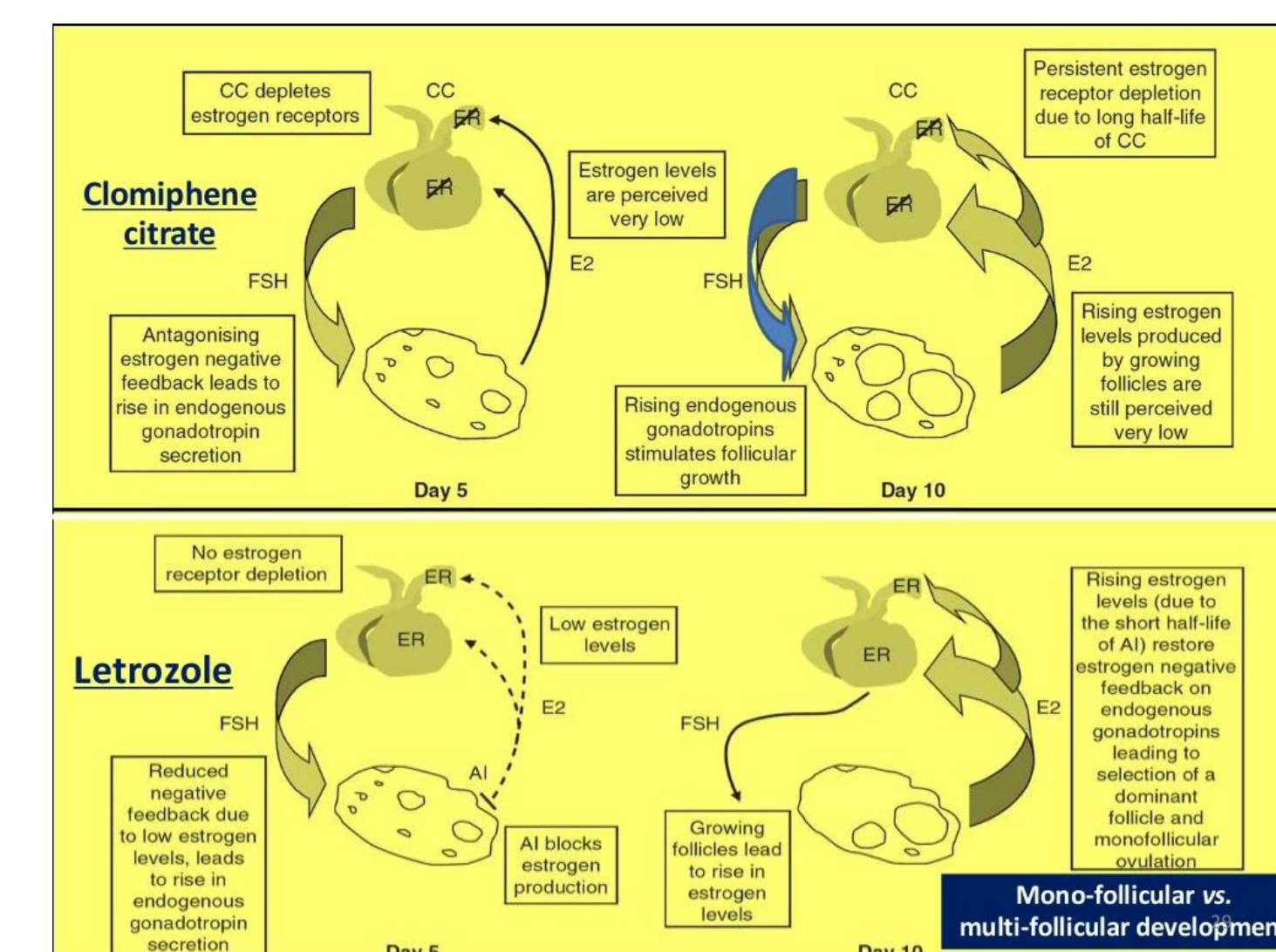
- Polycystic Ovarian Syndrome (PCOS) is the leading cause of anovulatory infertility and the most common endocrinopathy in women of reproductive age (Rosenfield & Ehrmann, 2016)
- Currently, the first-line treatment for infertility associated with PCOS is **clomiphene citrate**, which was introduced 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 a decreased adverse effect profile, a lower incidence of simultaneous 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. 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
- CONCLUSION:** The results provide information supporting letrozole as an adequate first-line alternative to clomiphene citrate for infertility in patients with PCOS.

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?



Literature Review

Efficacy

- Ghahiri et al: RCT, n=101. No significant difference regarding ovulation and pregnancy rates
- Sharief & Nafee: RCT, n=75. Letrozole: Lower number of mature follicles (p=0.0001). Letrozole: Higher endometrial thickness (p=0.0001). Letrozole: Higher ovulation rate (p=0.05). No significant difference in pregnancy rates
- Hussain et al: RCT, n=150. Letrozole: Higher ovulation rate (p=0.001). Letrozole: Higher single follicle ovulation (p=0.0270). Letrozole: Greater endometrial thickness (p=0.031). No significant difference regarding pregnancy rate
- Legro: RCT, n=750. Letrozole: Higher cumulative live birth rate (p=0.007). Letrozole: Higher ovulation rate (p<0.001). Letrozole: Greater single pregnancy rate (p=0.03)
- Liu et al: RCT, n=268. No significant difference regarding pregnancy and live birth rate. Letrozole treatment group: Higher ovulation rate (p<0.001)
- Amer et al: RCT, n=159. Letrozole: Higher pregnancy rate (p=0.022). Letrozole: Higher rate of ovulation and pregnancies per cycle (p=0.045, p=0.035, respectively). Clomiphene citrate: Greater endometrial thickness (p=0.002)
- Al-Shaikh: prospective clinical trial, n=85. Letrozole: Higher number of mature follicles (p<0.05). Clomiphene citrate: Higher endometrial thickness (p<0.05). No significant difference in pregnancy rates per cycle

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 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
- Ghahiri et al: n=101. Five miscarriages in both groups. No cases of ovarian hyperstimulation syndrome (OHSS)

Discussion

- Ovulation rate: Ghahiri et al. (2016) and Amer et al. (2017) found no significant difference, while Sharief & Nafee (2015), Hussain et al. (2013), Legro et al. (2014) and Liu et al. (2017) all found letrozole to have statistically significant higher ovulation rates
- Endometrial thickness: Sharief & Nafee (2015) and Hussain et al. (2013) found that letrozole had significantly higher endometrial thickness, while Al-Shaikh et al. (2017) found that clomiphene citrate had higher endometrial thickness
- Single follicle stimulation/single gestation birth: Sharief & Nafee (2015) found that letrozole had a higher rate of single follicles, while Al-Shaikh et al. (2017) reported letrozole to have a higher number of single follicles. Sharief & Nafee (2015) reported one twin pregnancy in the clomiphene citrate group/none in the letrozole group, and Legro (2014) reported a higher single pregnancy rate with letrozole
- Pregnancy rates: Legro et al. (2014) and Amer et al. (2017) found letrozole to have higher pregnancy rates with letrozole, other studies found no significant difference
- Live birth rates: Legro et al. (2014) found letrozole to have a significantly higher live birth rate, while Liu (2017) found no significant difference
- Ovarian Hyperstimulation Syndrome (OHSS): Ghahiri et al. (2016) and Hussain et al. (2013) reported no cases of OHSS, while other studies did not disclose this information
- Congenital abnormalities: No significant difference between the two drugs (Sharma et al, [2014], Legro et al. [2014, Amer et al. [2017], and Liu et al. [2017])
- Ectopic pregnancies: rates between the studies ranged from 2%-10.3% in the letrozole group and 0.0%-12.5% in the clomiphene group
- Miscarriage rates: No significant findings other than Tatsumi et al. (2017) reporting a much lower miscarriage rate with letrozole compared to normal pregnancy

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.
- 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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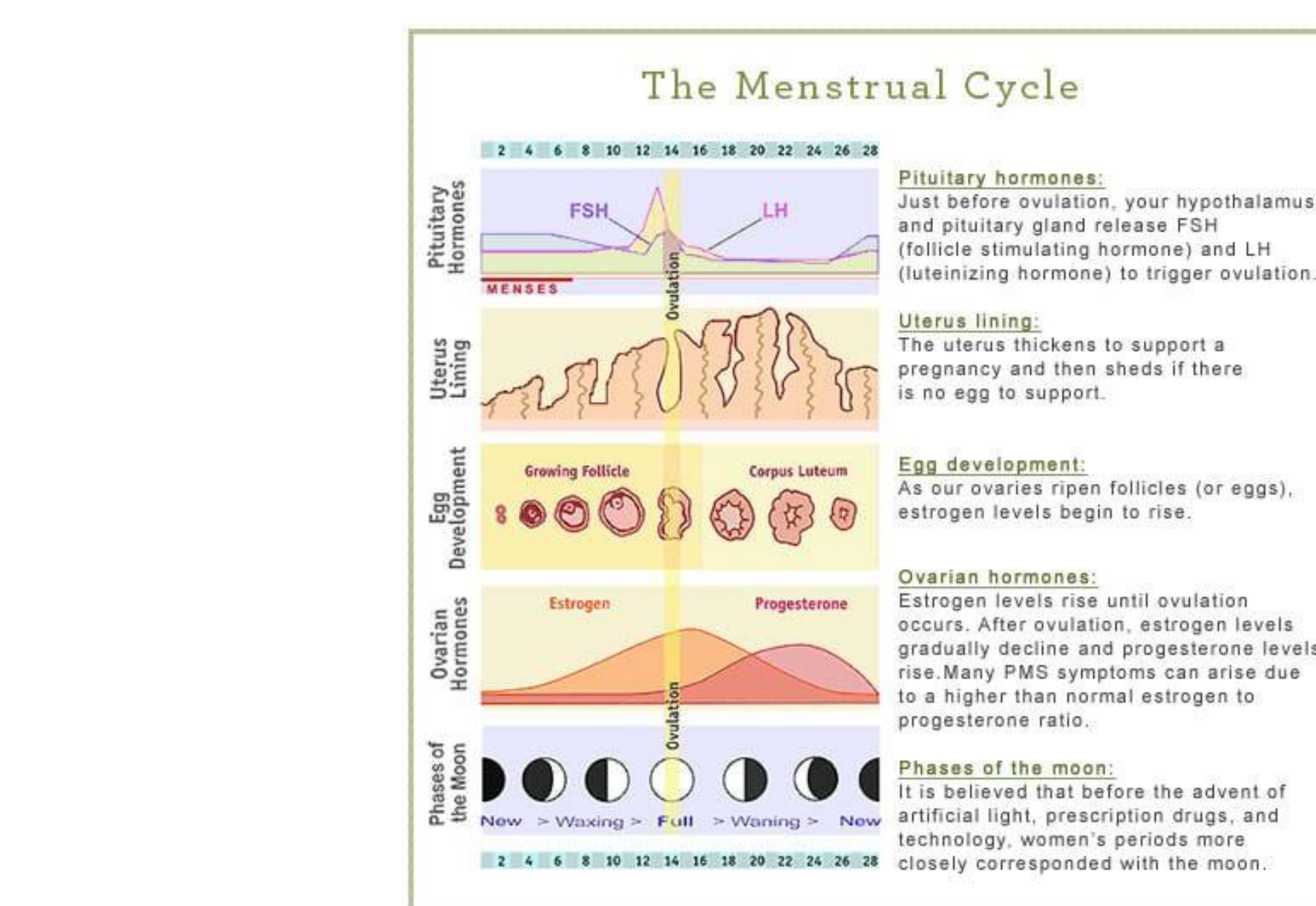
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Statement of the Problem

- 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

