

# **A COMPARISON OF SIDE EFFECTS ASSOCIATED WITH LETROZOLE “STAIR-STEP” VERSUS TRADITIONAL PROTOCOL IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME**

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## **Background:**

Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility in reproductive age women. It is established that Letrozole improves fertility outcomes for patients with PCOS compared to clomiphene citrate for ovulation induction<sup>1</sup>. We have previously shown that a letrozole stair-step protocol decreases time to initial ovulation without compromising pregnancy rates<sup>2</sup>. Several studies have demonstrated increased side effects (SE) when using a clomiphene stair-step protocol, however data is lacking regarding SE with a Letrozole stair-step protocol<sup>1, 3, 4</sup>.

## **Objective:**

The purpose of this study is to evaluate the frequency and nature of side effects (SEs) reported using a letrozole stair-step protocol versus a traditional protocol in patients with anovulation due to PCOS desiring fertility.

## **Materials and Methods:**

This is a prospective cohort analysis of patients with anovulatory infertility and PCOS undergoing ovulation induction with letrozole in the Pregnancy in Polycystic Ovary Syndrome II (PPCOSII) trial who did not ovulate on their first dose of medication. The traditional protocol group underwent a progestin-induced withdrawal bleed before proceeding to an increased dose, while the stair-step protocol group proceeded to a higher letrozole dose without first inducing menses. The choice of stair-step versus traditional protocol was based on provider preference. Patient characteristics and reported SEs were compared by treatment group using unpaired t-tests, chi-squared tests and Fischer's exact tests. Wilcoxon rank sum test compared distribution of SEs.

## **Results:**

104 patients met inclusion criteria: 35 on the traditional protocol and 69 on the stair-step protocol. Patient characteristics were similar in each group. The proportion of patients reporting  $\geq 1$  SE was greater in the stair-step group (81.2% vs 65.7%,  $p=0.08$ ); however, this difference did not reach statistical significance. The most commonly reported number of SEs in the stair-step group (21.7%) was 2 compared with 0 in the traditional group (34.3%). However, the distribution of the total number of SEs did not differ between treatment groups ( $p=0.16$ ). “Hot flashes” were the only SE reported significantly more frequently under the stair-step protocol. Notably, increased reporting of headaches was also observed with less precision ( $p=0.06$ ). The most common SEs in rank order included: pain, headache, nausea, hot flashes and mood changes.

## **Conclusions:**

The Letrozole stair-step protocol has been shown to decrease time to ovulation with similar pregnancy outcomes compared to the traditional protocol. Our findings show that use of a letrozole stair-step protocol does not meaningfully increase overall frequency of side effects when compared to the traditional protocol, although hot flashes and headaches may be more

common. Given these findings, the Letrozole stair-step protocol can be offered as an alternative to the traditional protocol to patients with anovulation due to PCOS as a way to safely decrease time to ovulation.

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**References**

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2. Reynolds, AC., Burks, H., Gavrizi, S., Boecking, K. (2020). "Letrozole 'Stair-Step' Protocol Versus Traditional Protocol In Patients with Polycystic Ovary Syndrome." *Fertility and Sterility* 114(3):Supp e9.
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**Table 1. Distribution of Patient Characteristics and Reported SEs by Traditional and Stairstep Protocol**

Patient Characteristics	Traditional (n=35) Mean (SD)	Stairstep (n=69) Mean (SD)	p-value
Age (years)	29.5 (4.2)	28.3 (3.9)	0.15 <sup>a</sup>
BMI (kg/m)	36.6 (9.9)	33.6 (8.5)	0.12 <sup>a</sup>
Duration of infertility (months)	39.2 (37.4)	46.5 (44.9)	0.51 <sup>a</sup>
<b>Individual SEs</b>	<b>n (%)</b>	<b>n (%)</b>	
Pain	16 (45.7)	34 (49.3)	0.73 <sup>b</sup>
Headache	11 (31.4)	35 (50.7)	0.06 <sup>b</sup>
Nausea	6 (17.1)	15 (21.7)	0.58 <sup>b</sup>
Hot Flashes	2 (5.7)	15 (21.7)	0.04 <sup>b</sup>
Mood Changes	4 (11.4)	13 (18.8)	0.33 <sup>b</sup>
<b>Any Reported SEs</b>			
Yes	23 (65.7)	56 (81.2)	0.08 <sup>b</sup>
No	12 (34.3)	13 (18.8)	

- a. t-test for independent means
- b. Chi-square test