American Society for Reproductive Medicine 2015 Annual Meeting
October 17 to 21, 2015 ● Baltimore, Maryland

Title:

WHAT IS THE IDEAL STARTING DOSE FOR PATIENTS UTILIZING LETROZOLE FOR OVULATION INDUCTION (OI)? ANALYSIS OF 4251 CYCLES

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Objective:
Letrozole (LET), an aromatase inhibitor, is an effective ovulation induction agent for OI and controlled ovarian stimulation (COS). Total dosage administration is generally limited to 5 days at 2.5 to 7.5 mg daily, albeit no studies have determined an optimal starting amount. We sought to compare the efficacy in achieving a pregnancy within different LET starting doses.

Design:
Retrospective cohort analysis

Materials and Methods:
All patients who underwent COS with LET with or without intrauterine insemination (IUI) from January 2001 to December 2015 were included. Patients were administered a fixed dose of LET for 5 days beginning on cycle day 3 and segregated based on starting dosage (A: 2.5 mg; B: 5 mg; C: 7.5 mg). Main outcome measures included biochemical, clinical and multiple pregnancy rates (PR). Secondary outcomes involved age, day 3 follicle stimulating hormone (FSH), basal antral follicle count (BAFC), BMI, endometrial thickness at surge and number of follicles >14mm in diameter. Categorical variables were assessed by chi-square or Fisher's exact test for small frequencies, with significance at a p-value of <0.05. For comparison of all three groups together, significant differences were compared by ANOVA.

Results:

A total of 4251 cycles were identified (A: n=68; B: n=2604; C: n=1579). We observed an increased number of follicles >14mm ($p<0.05$) with increasing dosage (7.5 mg>5mg>2.5mg). Because the small number of cases in Group A, statistical comparison was only carried out between Group B and Group C. Both the biochemical (15.5% vs. 11.6%) and the clinical (12.8% vs. 9.9%) PRs were statistically significant increase in Group B when compared to Group C. The multiple PR and the miscarriage rate were similar between groups.

Conclusions:

Letrozole has been shown to be an efficient and effective agent in inducing both ovulation and superovulation. There has been debate as to the optimal starting dose of letrozole. The 5mg-daily yields higher clinical PRs ($p<0.05$) than 7.5mg. In addition, this group had a lower prevalence of multiple PR and miscarriage rates (p=NS). To strengthen these findings, a randomized trial in cohorts of patients of diverse diagnoses that investigates a range of LET start and total dosages would enhance individualized clinical application.

Support:

None.

Table:

	2.5 mg	5 mg	7.5 mg	ANOVA	Chi-Square (5 mg vs. 7.5 mg)
Cycles	68	2604	1579	4251	4183
Age	32.0±5.8	34.3±4.7	35.9±5.8	NS	p<0.05
D3 FSH	7.0±2.2	7.2±3.4	7.9±4.9	p<0.05	p<0.05
D3 E2	41.9±16.4	46.5±19.5	47.6±20.3	NS	NS
BMI	21.7±2.9	23.8±4.9	24.5±5.0	p<0.05	p<0.05
Peak E2 at surge	190.7±117.5	266.0±224.1	284.0±269.4	NS	NS
Fols>14mm at surge	1.7±0.7	1.9±1.0	2.2±1.1	p<0.05	p<0.05
Endo Thickness at surge	8.6±2.1	8.5±1.8	8.4±1.7	NS	NS
Biochemical PR	13.2% (9/68)	15.5% (397/2559) (45 pend)	11.6% (179/1537) (42 pend)		p<0.005
Clinical PR	13.2% (9/68)	12.8% (326/2540) (19 pend)	9.9% (152/1535) (2 pend)		p<0.005
Multiple PR	11.1% (1/9)	8.9% (29/326)	12.5% (19/152)		NS
Miscarriage rate	0% (0/9)	25.2% (100/397)	30.2% (54/179)		NS