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Title:

ELEVATED BODY MASS INDEX DOES NOT IMPACT THE EFFICACY OF AROMATASE INHIBITORS (AI) FOR OVULATION INDUCTION

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Objective: Clomiphene citrate (CC) and letrozole are oral ovulation induction agents with distinct mechanisms of action. We hypothesized that letrozole's blockade of aromatase activity, which is peripherally abundant in adipose tissue, may reduce efficacy in high BMI patients undergoing treatment for anovulation and unexplained infertility. The study sought to compare the efficacy between SERMs and AIs according to BMI.

Design: Retrospective cohort study

Materials and Methods: The study included all patients undergoing ovulation induction with CC or letrozole followed by intrauterine insemination from January 2002 to March 2017. Patients with thin mid-cycle endometrium (<7mm) or requiring >5 days of medication to achieve a mature follicle(s) were excluded. Patients were stratified into BMI categories according to WHO criteria

(Table 1). Clinical outcomes included implantation, clinical pregnancy, multiple pregnancy and early pregnancy loss (EPL). Data was analyzed by Student's t-test, chi square, linear and binary logistic regression.

Results: A total of 5990 patients underwent ovulation induction with CC (n=3640) and letrozole (n=2350). Baseline demographics, cycle characteristics and clinical outcomes are shown in Table 1. Across all BMI categories, the CC group achieved significantly more mature follicles at time of hCG trigger. For every 1 kg/m^2 increase in BMI, there was a significant decrease in the number of mature follicles achieved (CC: β= -0.019, p<0.0001 vs. letrozole: β = -0.013, p<0.0001). Irrespective of the medication used, when controlling for age and ovarian reserve markers, BMI did not significantly modify the odds of implantation (OR 1.03 [95% CI 0.98-1.08], p=0.2), ongoing pregnancy (OR 1.03 [95% CI 0.99-1.08], p=0.2), multiple gestation (OR 0.87 [95% CI 0.6-1.3], p=0.5) or EPL (OR 1.02 [95% CI 0.93-1.1], p=0.7).

Conclusion: Despite the fact that the extraglandular conversion of C19 steroids to estrogen takes place primarily in adipose tissue, letrozole maintains efficacy similar to CC in patients with elevated BMI. Letrozole provides several advantages over CC in that it has less side effects and estrogen antagonism within the endometrium. High BMI patients can be reassured that letrozole is a viable treatment option, as increased adiposity does not appear to antagonize the aromatase blockade to a degree that impacts clinical outcome.

Support: None

Table 1:

Demographics, cycle characteristics and clinical outcome according to oral ovulation induction agent and WHO BMI category

BMI	<18.5			18.5-24.99			25-29.99			≥30		
	Clomid	Letrozole	P value	Clomid	Letrozole	P value	Clomid	Letrozole	P value	Clomid	Letrozole	P value
Number of patients	123	100	--	2342	1567	--	739	463	--	436	220	--

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Age	34.1 ± 4.4	34.0 ± 3.9	NS	35.5 ± 4.2	35.2 ± 4.2	NS	36.2 ± 4.2	35.8 ± 4.2	NS	36.0 ± 4.6	35.9 ± 4.1	NS
AMH	3.2 ± 2.3	4.2 ± 5.5	NS	3.0 ± 3.0	3.6 ± 4.1	0.0031	3.2 ± 3.1	3.5 ± 6.5	NS	2.6 ± 3.0	3.3 ± 4.1	NS
Day 3 FSH	7.7 ± 2.5	7.4 ± 2.7	NS	7.7 ± 2.9	7.5 ± 2.8	0.0325	7.5 ± 3.0	7.3 ± 2.9	NS	7.0 ± 2.6	7.2 ± 2.9	NS
Mature follicles	2.0 ± 0.9	1.7 ± 0.8	0.0129	1.9 ± 0.9	1.6 ± 0.8	<0.0001	1.7 ± 0.8	1.5 ± 0.7	<0.0001	1.7 ± 0.8	1.5 ± 0.7	0.0014
Endometrial thickness at ovulation trigger	8.3 ± 1.2	8.5 ± 1.4	NS	8.6 ± 2.3	8.7 ± 1.5	NS	8.8 ± 1.6	8.9 ± 1.6	NS	8.9 ± 4.7	8.9 ± 1.8	NS
Pregnancy rate	13.8% (17/123)	6.0% (6/100)	NS	11.6% (272/2342)	11.7% (183/1567)	NS	12.9% (95/739)	11.0% (51/463)	NS	11.2% (49/436)	14.1% (31/220)	NS
Implantation rate	12.2% (15/123)	6.0% (6/100)	NS	9.4% (220/2342)	10.1% (158/1567)	NS	10.3% (76/739)	8.9% (41/463)	NS	8.7% (38/436)	12.7% (28/220)	NS
Ongoing pregnancy rate	11.4% (14/123)	6.0% (6/100)	NS	8.3% (195/2342)	8.7% (137/1567)	NS	9.1% (67/739)	8.2% (38/463)	NS	7.3% (32/436)	11.4% (25/220)	NS
Multiple pregnancy rate	1.6% (2/123)	0.0% (0/100)	NS	1.1% (25/2342)	0.7% (11/1567)	NS	12.2% (9/739)	0.0% (0/463)	0.017	0.5% (2/436)	0.5% (1/220)	NS
Early pregnancy loss	2.4% (3/123)	0.0% (0/100)	NS	3.3% (78/2342)	2.9% (46/1567)	NS	3.8% (28/739)	2.8% (13/463)	NS	3.9% (17/436)	2.7% (6/220)	NS

Table 2:

The impact of BMI on the odds of clinical outcome according to oral ovulation induction agent. Results expressed as adjusted odds ratios.

	Clomiphene citrate	Letrozole
Implantation	OR 1.01 [95% CI 0.97-1.1], p=0.7	OR 1.03 [95% CI 0.98-1.08], p=0.2
Ongoing clinical pregnancy	OR 1.003 [95% CI 0.96-1.05], p=0.9	OR 1.03 [95% CI 0.99-1.08], p=0.2
Multiple gestation	OR 0.92 [95% CI 0.79-1.07], p=0.3	OR 0.87 [95% CI 0.6-1.3], p=0.5
Early pregnancy loss	OR 1.04 [95% CI 0.94-1.1], p=0.5	OR 1.02 [95% CI 0.93-1.1], p=0.7