THE USE OF LETROZOLE WITH LOW DOSE GONADOTROPINS COMBINED WITH FOLLICLE ASPIRATION IN PATIENTS UNDERGOING INTRAUTERINE INSEMINATION YIELDS HIGH PREGNANCY RATES WITH LOW RISK OF MULTIPLE-GESTATION

Authors: Olmsted K (1), Alu S (1), Schnorr J (1,2), Cook H (1,2), McLaughlin J (1,2), Peterson A (1,2), Gray J (2), Riestenberg C (1,2).
Affiliations: (1) Dept of OB/GYN, The Medical University of South Carolina, Charleston, SC, USA; and (2) Coastal Fertility Specialists, Mount Pleasant, SC, USA

Background
Ovarian stimulation (OS) combined with intrauterine insemination (IUI) is the recommended first-line treatment for patients with unexplained infertility.[1] Studies evaluating the efficacy and safety profile of various OS agents have yielded conflicting results, with the majority of studies showing increased pregnancy and live birth rates with the use of conventional-dose gonadotropins compared to oral agents at the cost of higher multiple-gestation rates. Current guidelines recommend the use of oral OS agents in combination with IUI as the treatment regimen that maximizes per-cycle fecundity while minimizing the risk of multiple-gestation, treatment cost and complexity and risk of cycle cancellation.[1] We aimed to investigate the pregnancy and multiple-gestation rates associated with a protocol of letrozole alone, low-dose follicle-stimulating hormone (FSH) alone, and both combined sequentially (letrozole 2.5 mg x 5 days starting on cycle day 3, FSH 37.5 daily starting on cycle day 7) with close ultrasound monitoring and use of ultrasound guided follicular aspiration for management of hyperstimulation.
Objective
To assess the pregnancy and multiple-gestation rate associated with the use of letrozole alone, low-dose FSH, and Letrozole/FSH in combination with follicular aspiration in patients undergoing IUI.
Materials and Methods
Retrospective review of patients undergoing IUI using the three regimens previously described from January 2022 to December 2023. Patients less than 45-years-old with infertility, at least one patent fallopian tube, normal mullerian anatomy and >10 million motile sperm on semen analysis were included. Patients were monitored with ultrasound, estradiol and LH levels. Patients with more than 3 follicles measuring > 14mm were offered follicular aspiration versus cycle cancellation prior to IUI that was performed 36-40 hours after hCG administration or the day following an LH surge. The primary outcome was ongoing pregnancy rate (OPR), defined as an ongoing viable intrauterine pregnancy at 8 weeks gestational age. Secondary outcomes included rate of multiple-gestation, follicle aspiration, and cycle cancellation.
Results
A total of 1,622 subjects were included in this study, of which 222 underwent OS with letrozole, 342 with low-dose FSH, and 1,057 with letrozole/FSH. There was a significant difference in average patient age (29.6 vs. 34.3 vs. 32.7), baseline AMH (6.3 vs. 3.4 vs. 4.3) and FSH levels (6.9 vs. 8.2 vs. 7.2) between letrozole vs. low-dose FSH vs. letrozole/FSH (Table 1). OPR was significantly higher in the letrozole/FSH group compared to letrozole only (14.1% vs. 8.1%, p = 0.03). There was no difference in OPR among other group comparisons. Multiple-gestation rates were not significantly different among the groups: letrozole vs. FSH vs. letrozole/FSH (0.45% vs. 0.88% vs. 1.32%, p = ns). Cycle cancellation and follicle aspiration rates were also not significantly different among the groups (Table 2).
Conclusion
The OS regimen of letrozole with low-dose gonadotropins in combination with ultrasound monitoring and follicle aspiration as needed for hyperstimulation yields significantly higher ongoing pregnancy rates in comparison to letrozole alone, with no difference in cycle

cancellation, multiple-gestation or follicle aspiration rates in those undergoing intrauterine insemination.

Table 1 Baseline Patient Characteristics

Characteristic	Letrozole (N = 222)	FSH (N = 342)	Letrozole/FSH (N = 1,057)	Letrozole vs. FSH	FSH vs. Letrozole/ FSH	Letrozole vs. Letrozole/FSH
	Average			*p-value*		
Age	29.56	34.29	32.77	< 0.001	< 0.001	<0.0001
Body mass index	27.93	27.94	28.12	0.49	0.32	0.33
Antimullerian hormone	6.30	3.36	4.28	< 0.001	0.001	< 0.001
Follicle stimulating hormone	6.93	8.21	7.23	< 0.001	< 0.001	0.04

Table 2 Ongoing Pregnancy, Multiple Gestation, Follicle Aspiration and Cycle Cancellation

Variable	Letrozole (N = 222)	FSH (N = 342)	Letrozole/FSH (N = 1,057)	Letrozole vs. FSH	FSH vs. Letrozole/FSH	Letrozole vs. Letrozole/FSH
	Number/total number (percent)			*p-value*		
Ongoing Pregnancy	18/222 (8.11)	37/342 (10.82)	149/1057 (14.10)	0.25	0.17	0.03
Multiple Gestation	1/222 (0.45)	3/342 (0.88)	14/1057 (1.32)	0.34	0.42	0.28
Follicle Aspiration	5/222 (2.25)	10/342 (2.9)	29/1057 (2.7)	0.87	0.86	0.72
Cycle Cancellation	19/222 (8.56)	26/342 (7.63)	69/1057 (6.53)	0.71	0.52	0.31

Support

Coastal Infertility Specialists

References:

1. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org; Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertil Steril. 2020 Feb;113(2):305-322. doi: 10.1016/j.fertnstert.2019.10.014. PMID: 32106976.