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Letrozole co-treatment in ovarian stimulation with r-FSH delays embryo morphokinetics and worsen clinical outcomes

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OBJECTIVE

Letrozole has been considered a potential strategy to improve IVF outcomes, as inhibition of cytochrome P450 aromatase enzyme activity would increase the levels of androgens by blocking their aromatization to estrogen. Letrozole may also improve ovarian response to FSH and be a potential tool for mild ovarian stimulation strategies. Although a positive effect of letrozole in lowering the total does of FSH, key IVF outcomes have not consistently been found to be significantly improved by the supplementation with letrozole. The goal for the present study was to investigate if there is any effect of using letrozole during controlled ovarian stimulation (COS) on morphokinetic events in a time-lapse imaging (TLI) system..

MATERIALS AND METHODS

- Retrospective cohort
- March 2019 – December 2020
- Private university-affiliated IVF center

Design and setting

Patients

- n= 2592 ICSI cycles
- 358 injected oocytes
- Culture in a TLI system incubator until D5 of embryo development

: 320 patients (2414 embryos) stimulated with rFSH only

VS.

38 patients (178 embryos) treated with rFSH plus letrozole

Evaluated parameters

- **Timing to:**
- Pronuclei appearance (tPNa) and pronuclei fading (tPNf);
- Two (t2), three (t3), four (t4), five (t5), six (t6), seven (t7), and eight cells (t8), and to blastulation (tB);
- Durations of the second (t3-t2) and third (t5-t3) cell cycles (cc2 and cc3, respectively);
- Timing to complete synchronous divisions s1 (t2-tPNf), s2 (t4-t3), and s3 (t8-t5)

- **ICSI outcomes**
- Pregnancy rate;
- Implantation rate;
- Miscarriage rate

RESULTS

Co-treatment with letrozole compared to FSH-only significantly resulted in longer tPNa, tPNf, t2, t3, t4, t5, t6, t7, and tM. Significant differences were also observed in clinical pregnancy rates and implantation rates, favouring COS with FSH-only.

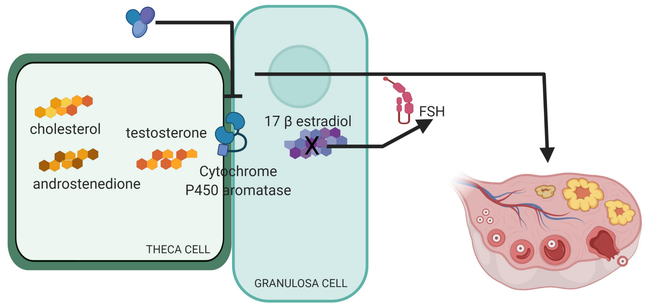
Table 1. Generalized mixed model results for the association between oocyte AMH and embryo morphokinetics.

Evaluated parameters	FSH ONLY	FSH + LETROZOLE	p-value
tPNa	8.79h ± 0.49	6.43h ± 0.09	<0.001
tPNf	27.06h ± 0.73	24.13h ± 0.13	<0.001
t2	29.6h ± 0.74	26.84h ± 0.13	<0.001
t3	40.18h ± 0.84	37.10h ± 0.15	<0.001
t4	41.92h ± 0.86 vs.	39.14h ± 0.16	<0.001
t5	52.91h ± 1.19	49.07h ± 0.22	0.002
t6	56.19h ± 1.16	51.85h ± 0.21	<0.001
t7	59.22h ± 1.25	54.71h ± 0.23	<0.001
Tm	99.27h ± 2.67	89.69h ± 0.39	<0.001
Pregnancy rate	12.50%	34.15%	0.027)
Implantationrate	12.50%	21.95%	<0.001

CONCLUSION

Co-treatment with letrozole and FSH delays embryo morphokinetics and worsen clinical outcomes when compared with the conventional FSH-only protocol.

IMPACT STATEMENT



The inhibition of the cytochrome P450 aromatase enzyme and estradiol production by the granulosa cells may have detrimental effect on the growing follicle disrupting vital mechanisms for oocyte function and subsequent embryo development.