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Short Communication

Alternate-Day Recombinant FSH Dosing Is Non-Inferior to Daily Dosing for Controlled Ovarian Stimulation in Women with Normal Ovarian Reserve Undergoing IVF/ICSI

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Abstract

Daily recombinant FSH (rFSH) administration remains the standard for controlled ovarian stimulation in IVF/ICSI, yet it increases treatment burden, cost, and discomfort for patients. Evidence supporting reduced frequency dosing, particularly among women with normal ovarian reserve, is limited. This pilot randomized controlled trial evaluated the feasibility of an alternate day rFSH protocol after an initial five day daily phase. Sixty women were randomized to either continued daily rFSH or alternate day dosing once a leading follicle reached ≥14 mm. Baseline characteristics and ovarian reserve markers were comparable across groups. The alternate day protocol significantly reduced total gonadotropin use and resulted in lower trigger day progesterone, while maintaining similar oocyte yield, MII oocyte rates, and embryological outcomes. Trends toward higher estradiol levels and more embryos were observed in the alternate day arm. These findings suggest that alternate day rFSH dosing is a feasible, patient friendly, and potentially cost saving strategy without compromising stimulation or laboratory outcomes. Larger studies are needed to validate its clinical utility.

Background and Objective

Recombinant follicle-stimulating hormone (rFSH) exhibits a prolonged half-life and sustained biological activity [1], raising the possibility that alternate-day administration could provide adequate follicular stimulation without compromising clinical outcomes. If proven non-inferior to daily dosing, this strategy may reduce injection burden, lower medication costs, and improve patient comfort while maintaining efficacy in terms of oocyte yield, fertilization, and pregnancy rates [2-4].

This pilot study aimed to compare daily versus alternate-day rFSH dosing in women with normal ovarian reserve undergoing IVF/ICSI, addressing a gap in current literature and exploring the feasibility of a more patient-friendly stimulation

protocol.

Material and Method

This was a single-center, prospective, pilot randomized controlled trial conducted over a six-month period at a tertiary fertility care center. The aim was to compare the efficacy of alternate-day versus daily recombinant FSH (rFSH) dosing protocols in women undergoing controlled ovarian stimulation (COS) for IVF/ICSI. A total of 60 women were enrolled and randomized equally (1:1) into two study arms: **Arm 1:** Conventional daily rFSH dosing and **Arm 2:** Alternate-day rFSH dosing from stimulation day 6 onward. Participants were randomized using a computer-generated sequence to one of two treatment arms. The starting dose of rFSH was individualized based on age, BMI, AFC, and AMH levels. All patients received daily rFSH for the first five days of stimulation. In **Arm 1 (Daily Dosing)**, rFSH was continued daily until the day of ovulation trigger. In **Arm 2 (Alternate-Day Dosing)**, patients continued rFSH daily until at least one leading follicle reached ≥14 mm in diameter, after which the same dose was administered on alternate days until the trigger. The remainder of the IVF protocol, including antagonist administration, trigger criteria, oocyte retrieval, fertilization (IVF or ICSI), embryo culture, and embryo transfer, followed the institution's standard clinical practice. Embryo transfers were performed on Day 5. The study was approved from institutional ethical committee.

Results

Among the 60 women included in this analysis, the median age was 31 years (IQR: 28.0–36.5; mean ± SD: 31.75 ± 4.78; range: 22–40), and the median BMI was 25.6 kg/m² (IQR: 23.32–28.92; mean ± SD: 25.68 ± 3.18; range: 18.5–29.9), reflecting a predominantly young population with BMI values spanning normal to overweight categories. Indicators of ovarian reserve were moderate, with a median AMH of 2.54 ng/mL (IQR: 1.94–3.36; mean ± SD: 2.71 ± 1.15; range: 0.72–5.86) and a median day 2 AFC of 13 (IQR: 10–16.75; mean ± SD: 13.51 ± 5.02; range: 4–34).

The median daily gonadotropin dose was 262.5 IU (IQR: 225–300; mean ± SD: 266.67 ± 59.60; range: 150–450), administered over a median of 10 days (IQR: 10–11; mean ± SD: 10.53 ± 1.26; range: 8–14), resulting in a median cumulative dose of 3000 IU (IQR: 2250–3375; mean ± SD: 2946.61 ± 843.02; range: 1350–4950). On the trigger day, estradiol (E2) levels exhibited substantial variability and right-skew (median: 2680.5 pg/mL; IQR: 1384.5–5077.5; mean ± SD: 3809.33 ± 3430.53; range: 403–13,800), while progesterone (P4) remained relatively low (median: 1.00 ng/mL; IQR: 0.70–1.42; mean ± SD: 1.19 ± 0.74; range: 0.30–4.20). Table 1 illustrates comparison among stimulation characteristics of alternative day with conventional protocols in most of the parameters are comparable except total dose of gonadotropin and days of trigger P4. Figure 1 shows compared with the conventional-dose protocol, the alternate-dose protocol [5] achieved significantly lower total gonadotropin exposure and lower trigger-day progesterone, while maintaining comparable oocyte yield, oocyte maturity (MII rate), and other outcomes. There were trends toward higher trigger-day estradiol and more embryos formed in the alternate-dose arm [6].

DFI	(n)	Mean ± SD	Median (IQR)	95 % CI (Mean)	P
Female Age					
Conventional Dose	30	32.86 ± 5.13	34.50 (27.75, 38.00)	(30.94, 34.78)	0.076*
Alternate Dose	30	30.63 ± 4.18	30.50 (28.00, 33.00)	(29.06, 32.19)	
Female BMI					
Conventional Dose	30	25.77 ± 3.01	25.75 (22.57, 28.62)	(24.65, 26.90)	0.864*
Alternate Dose	30	25.58 ± 3.38	25.25 (23.37, 29.32)	(24.31, 26.84)	
AMH					
Conventional Dose	30	2.07 ± 1.22	2.52 (2.05, 3.13)	(2.24, 3.16)	0.819*
Alternate Dose	30	2.72 ± 1.09	2.61 (1.79, 3.52)	(2.31, 3.13)	
Day-2 AFC					
Conventional Dose	30	13.26 ± 5.48	12.00 (10.00, 16.00)	(11.21, 15.31)	0.436*
Alternate Dose	30	13.76 ± 4.58	14.00 (10.00, 17.25)	(12.05, 15.47)	
Daily Dose of Gonadotropin					
Conventional Dose	30	262.50 ± 67.51	225.00 (225.00, 300.00)	(237.28, 287.71)	0.301*
Alternate Dose	30	270.83 ± 51.31	300.00 (225.00, 300.00)	(251.67, 289.99)	
Total Days of Ovarian Stimulation					

Conventional Dose	30	10.70 ± 1.29	11.00 (10.00, 11.25)	(10.21, 11.18)	0.294*
Alternate Dose	30	10.36 ± 1.24	10.00 (10.00, 11.00)	(9.90, 10.83)	
Total Dose of Gonadotropin					
Conventional Dose	30	3170.00 ± 892.41	3300.00 (2418.00,3843.00)	(2836.76, 3503.23)	0.036*
Alternate Dose	30	2715.51 ± 733.85	2700.00 (2212.50, 3187.50)	(2436.37, 2994.66)	
Trigger Day E2					
Conventional Dose	30	3019.63 ± 2563.77	2200.00 (1038.00, 4313.00)	(2062.03, 3976.69)	0.098*
Alternate Dose	30	4599.30 ± 4009.84	2859.50 (1796.25, 6394.00)	(3101.99, 6096.60)	
Trigger Day P4					
Conventional Dose	30	1.39 ± 0.82	1.15 (0.80, 1.87)	(1.08, 1.70)	0.036*
Alternate Dose	30	0.98 ± 0.59	0.95 (0.50, 1.38)	(0.76, 1.20)	
Number of Oocyte Expected					
Conventional Dose	30	10.13 ± 4.38	10.50 (6.00, 14.00)	(8.49, 11.77)	0.213*
Alternate Dose	30	12.03 ± 5.22	12.50 (8.00, 15.25)	(10.08, 13.98)	
Number of Oocyte Retrieved					
Conventional Dose	30	9.20 ± 5.41	8.00 (4.00, 14.25)	(7.18, 11.21)	0.189*
Alternate Dose	30	10.53 ± 4.03	11.00 (6.75, 14.00)	(9.02, 12.03)	
MII					
Conventional Dose	30	6.10 ± 3.76	5.00 (3.00, 9.00)	(4.69, 7.50)	0.190*
Alternate Dose	30	7.00 ± 3.09	7.00 (4.00, 9.00)	(5.84, 8.15)	
MII Rate					
Conventional Dose	30	66.90 ± 15.77	67.00 (55.25, 75.00)	(61.00, 72.79)	0.923*
Alternate Dose	30	66.46 ± 13.47	68.00 (56.75, 73.50)	(61.43, 71.49)	
No of Embryo Formed					
Conventional Dose	30	1.73 ± 1.52	1.50 (1.00, 2.25)	(1.16, 2.30)	0.052*
Alternate Dose	30	2.30 ± 1.31	2.00(2.00, 3.00)	(1.80, 2.79)	

SD: Standard Deviation, IQR: Interquartile Range, CI: Confidence Interval, P: P Value, P<0.05: Statistical Significance, *: Mann Whitney U test.

Table 1: Comparison of Conventional vs Alternate Day Dose

Conclusion

Alternate-day rFSH dosing after an initial daily phase appears non-inferior to conventional daily administration for controlled ovarian stimulation in women with normal ovarian reserve. It appears to be a feasible and potentially cost-saving alternative to daily dosing in IVF/ICSI cycles. It may reduce patient burden without compromising treatment outcomes, but further evidence is needed to support broader clinical adoption.

Declaration

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Disclosure: There is no conflict of interest among the authors.

Attestation Statement:

- The subjects in this trial have not concomitantly been involved in other randomized trials.
- Data regarding any of the subjects in the study has not been previously published unless specified.
- Data will be made available to the editors of the journal for review or query upon request

Data Sharing Statement: The data will be made available on request.

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