

Impact of Follitropin Delta vs. Alfa on Premature Progesterone Elevation in Poor Responders

A retrospective case-control study by from IRCCS San Raffaele Scientific Institute examined whether 12 mcg of Follitropin Delta reduces premature progesterone elevation (PPE) in poor responder patients, potentially allowing fresh embryo transfers.

Papa Giuseppe Alessandro 1, Giorgia Grisafi 1, Emanuela Angelini 1, Luca Pagliardini 1,2, Daria Marzanati 2, Lisett Solano 2, Michela Molgora 1, Valeria Stella Vanni 1, Enrico Papaleo 1,2.

1 Department of Obstetrics and Gynecology, IRCCS San Raffaele Scientific Institute, Milan, Italy

2 Reproductive Sciences Laboratory, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background

Ovarian response to gonadotropin stimulation significantly influences IVF success, particularly in poor responders who face a reduced prognosis due to diminished ovarian reserve. Individualized dosing strategies, such as Follitropin delta, which integrates AMH levels and body weight, have improved predictability and precision compared to standard FSH dosing. Poor responders are prone to premature progesterone elevation (PPE), reducing endometrial receptivity and implantation rates, often necessitating "rescue" embryo freezing. However, the "freeze-all" strategy may not benefit this population and could reduce live birth rates. Tailoring stimulation protocols is critical, particularly to optimize embryo availability and fresh transfer success in this challenging group.

Study design, study duration

Retrospective, monocentric, case-control study conducted at the Fertility Center of IRCCS San Raffaele Hospital, Milan, between January 2019 and July 2023. It included 387 low ovarian reserve patients undergoing their first IVF/ICSI cycle. Patients were divided into two groups based on ovarian stimulation protocols: Follitropin delta (cases) and Follitropin alfa (controls), with matching criteria for age, AMH, antral follicle count, and additional stimulation with LH. A 1:2 case-control matching was applied.

Methods

The study included expected poor responder patients meeting Bologna Criteria (AMH ≤ 1.1 ng/mL, antral follicle count < 7 , age ≤ 41 years). Participants underwent ovarian stimulation with Follitropin delta (fixed dose 12 mcg/day due to low AMH levels) or Follitropin alfa (starting dose ≥ 225 IU). Patients with progesterone ≥ 1.1 on trigger day underwent "rescue" freeze-all. All models were adjusted for potential confounders, including age, AMH, AFC, BMI, and year of treatment.

Results

The incidence of progesterone ≥ 1.1 ng/mL at trigger was lower in Follitropin delta group (5% vs. 17%; OR=0.27, 95% CI 0.12–0.64, $p=0.003$), with reduced mean progesterone levels (0.47 $\pm$ 0.30 vs. 0.70 $\pm$ 0.50 ng/mL; [adjusted difference (AD)= -0.25, 95% CI: from -0.355 to -0.145, $p<0.0001$]). Estradiol levels at trigger were significantly lower with Follitropin delta (1039 $\pm$ 651 vs. 1237 $\pm$ 685 pg/mL, $p=0.013$), as well as total follicles (5.7 $\pm$ 3.3 vs. 6.7 $\pm$ 3.4; $p=0.003$) and follicles >16 mm (2.6 $\pm$ 1.7 vs. 3.3 $\pm$ 2.2; $p=0.001$). No difference was observed in stimulation length. Despite the significantly reduced number of oocytes retrieved (3.4 $\pm$ 2.7 vs. 3.8 $\pm$ 2.5; AD=0.85, 95% CI: 0.73–0.98, $p=0.025$) and MII oocytes (2.5 $\pm$ 2.3 vs. 3.0 $\pm$ 2.1; AD=0.82, 95% CI: 0.70–0.96 $p=0.016$) in the Follitropin delta group, the number of available D3 embryos (2.4 $\pm$ 1.9 vs. 2.5 $\pm$ 2.0; $p=0.303$) and embryo quality scores (2.1 $\pm$ 0.6 vs. 2.1 $\pm$ 0.7; $p=0.579$) were similar between the two groups. In terms of cumulative ongoing pregnancy rates, logistic regression analysis did not show a statistically significant result for patients receiving Follitropin delta compared to other gonadotropins (OR=1.29, 95%CI 0.77–2.16, $p=0.334$).



The incidence of
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trigger

reduced mean
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levels

Estradiol levels at
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and) and MII
oocytes

Follitropin delta
(fixed dose 12
mcg/day due to
low AMH levels)

5%
OR=0.27, 95% CI
0.12–0.64,
 $p=0.003$

0.47 $\pm$ 0.30 ng/mL;
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 $p<0.0001$

1039 $\pm$ 651 pg/mL,
 $p=0.013$

3.4 $\pm$ 2.7 AD=0.85,
95% $p=0.025$
2.5 $\pm$ 2.3 AD=0.82,
95% $p=0.016$

Follitropin alfa
(starting dose $\geq$
225 IU)

17%

0.70 $\pm$ 0.50 ng/mL

1237 $\pm$ 685 pg/mL

3.8 $\pm$ 2.5
3.0 $\pm$ 2.1

Limitations, Reason for cautions

This is a retrospective monocentric study with a small sample size, which may affect result reliability. Additionally, only first cycles with 12 mcg of Follitropin delta, according to prescribing information for these patients, were included. Larger, prospective, randomized studies are needed to validate these results and their clinical implications.

Conclusions

Follitropin delta fixed dose of daily 12 mcg reduces progesterone levels in poor responder patients, favoring fresh embryo transfer strategy. Despite the lower follicles and mature oocytes, the number of D3 and top quality embryos, as well as the cumulative ongoing pregnancy rates, are comparable between the two groups.