A proof-of-concept study evaluating the effect of personalized dosages of follitropin delta in intra-uterine insemination (IUI): Personalized IUI Treatment Study (PITS)

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INTRODUCTION

Although exogenous FSH has been used in IUI for decades, clear and effective criteria to select the proper starting dose of FSH have not been identified yet. In this regard, the personalization of the starting and maintenance dose of gonadotropins therefore represents the first and fundamental step.

Follitropin delta is a recombinant FSH, uniquely expressed in a human fetal retinal cell line. It is the first recombinant human FSH preparation where the dosage can be personalized using a validated algorithm derived from a woman's basal AMH and body weight for controlled ovarian stimulation in IVF.

The aim of this single cohort, prospective study was to evaluate the effect of follitropin delta on the ovarian response using a personalized dosing regimen in controlled ovarian stimulation for IUI.

We hypothesize that a personalized dosing algorithm of follitropin delta based on AMH and body weight would allow a better management of women's IUI cycle, resulting in a higher chance of pregnancy without increasing the rate of multiple pregnancies.

MATERIAL AND METHODS

Design: This was a single center, open-label, single-cohort prospective study assessing the efficacy and safety of a personalized dosage of follitropin delta for intrauterine insemination. Patients were enrolled at one center to receive up to 3 cycles of IUI. The study protocol was approved by local regulatory authorities, as well as independent ethics committee.

Participants: Between September 2019 and January 2021, a total of 110 patients signed a written consent to take part in this study. Women enrolled in the study were between 18 and 42 years of age, had at least one permeable Fallopian tube or one pregnancy in the last 3 years. Additional inclusion criteria were regular menstrual cycles from 26 to 39 days, presence of both ovaries, use of ejaculated sperm (fresh or frozen) from partner or donor, semen analysis considered adequate for IUI in accordance with the centre's standard practice. The main exclusion criteria were high risk for OHSS (AMH ≥ 35 pmol/L (4.9 ng/mL)), body weight > 100 Kg, history of severe malformation or uterine anomaly including fibroids ≥ 5 cm, uncontrolled thyroid or adrenal dysfunction, pituitary tumour or persistent ovarian cysts or enlargement not due to PCOS > 3 cm. Other exclusion criteria were the use of hormone treatment in the last 3 months prior to start of stimulation, the diagnosis of hydrosalpinx, malignancies, breast pathology incompatible with gonadotropin stimulation, hypersensitivity to follitropin delta or to any ingredient in the formulation and the addition of other infertility medication that can influence follicle stimulation and maturation such as growth hormone (GH). The patients were followed up to 3 cycles of IUI monitoring the established quantitative objectives.

Procedures: Targeted ovarian response was defined as 2 to 3 follicles ≥ 16 mm on the day of the trigger or one day before. If only 1 mature follicle had developed, the physicians proceeded with the IUI as per clinic's standard of care. If more than 3 mature follicles have developed, a cancelation or a conversion to IVF were considered.

The triggering medication was choriogonadotropin alfa (Ovidrel®; EMD Serono) and was administered when clinically indicated. Luteal phase support with 100 mg progesterone vaginal tablets (Endometrin®; Ferring Pharmaceuticals) twice daily was started on the day of the IUI for all women participating in the study until day 14 when the urine pregnancy test was performed.

Adapted algorithm for IUI:

Measured AMH pmol/L	Rounded AMH pmol/L	AMH ng/mL	Dosage factor IUI
< 14.5	< 15	< 2.1	0.05 mcg/kg
14.5-16.4	15-16	2.1-2.24	0.0475 mcg/kg
16.5-17.4	17	2,38	0.045 mcg/kg
17.5-18.4	18	2,52	0.0425 mcg/kg
18.5-20.4	19-20	2.66-2.8	0.04 mcg/kg
20.5-22.4	21-22	2.94-3.08	0.0375 mcg/kg
22.5-24.4	23-24	3.22-3.36	0.035 mcg/kg
24.5-27.4	25-27	3.5-3.78	0.0325 mcg/kg
27.5-32.4	28-32	3.92-4.48	0.03 mcg/kg
32.5-39.4	33-39	4.62-5.46	0.0275 mcg/kg
> 39.5	> 40	> 5.6	0.025 mcg/kg

Table 3

		Dose customisation 2nd cycle		
		< 35 years old	35-40 years old	> 40 years old
Num. follicles ≥16 mm Last TVU prior to IUI	1 follicle	Initial dose (ID) + 25%	ID + 25%	ID + 50%
	2 follicles	ID	ID	ID
	3 follicles	ID – 20%	ID	ID
	≥ 4 follicles*	ID – 33%	ID – 33%	ID – 33%

* Previous cycle would have been canceled as per cancelation criteria

Table 4

		Dose customisation 3rd cycle		
		< 35 years old	35-40 years old	> 40 years old
Num. follicles ≥16 mm Last TVU prior to	1 follicle	2nd dose + 25%	2nd dose + 50%	2nd dose + 50%
	2 follicles	2nd dose	2nd dose	2nd dose
	3 follicles	2nd dose	2nd dose	2nd dose
	≥ 4 follicles*	2nd dose – 33%	2nd dose – 33%	2nd dose – 20%

* Previous cycle would have been canceled as per cancelation criteria

Table 5

Follow-up: US Results	
If more than 3 follicles ≥ 11 mm	Decrease RKV dose by 20%
If at Day 15 of stimulation there are no follicles > 11 mm	Consider cycle cancelation
In all other cases	Continue same dose of RKV

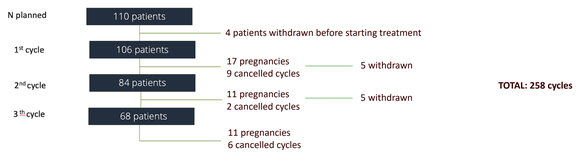
Statistical methods: We hypothesize that the personalized dosage of follitropin delta will have a pregnancy rate of 16% per cycle versus 12% obtained with IUI showed by the literature. By enrolling 100 patients (around 300 cycles), we will have 75-80% power to detect a signal (p<0.10 to p<0.05).

This study employed a single-cohort, prospective, open-label design. Continuous variables were assessed for normality of distribution and reported as means and standard deviations. Difference between continuous variables were assessed by T-test or ANOVA and multivariate regression analysis for normally distributed variables or by Wilcoxon signed-rank test for non-normally distributed variables. Correlation between continuous variables were assessed by Pearson's correlation test. Effect size was assessed by Cohen's d test. Categorical variables are expressed as a percentage and were compared by Chi-square test or multivariate regression analysis. Results for pregnancy outcome were assessed by intention to treat.

The effect of age on treatment efficacy was assessed by the differences in the pregnancy outcomes between patients classified in the following age groups: < 35 years, 35-40 years and > 40 years. We used ANOVA to assess the differences between the different age cohorts for continuous variables and multivariate logistic regression for categorical variables. Statistical tests were performed using SPSS version 26 and R for Cohen's d test.

RESULTS

FLOW CHART



Pregnancy outcomes

Characteristic	1st cycle (n=106)	2nd cycle (n=84)	3rd cycle (n=68)	OVERALL	P value
PREGNANCY OUTCOMES					
Positive pregnancy test	22 (20.2%)	12 (14.3%)	13 (19.1%)	18.2% (47/258)	0.11
Biochemical pregnancy	5 (4.7%)	0 (0%)	2 (2.9%)	2.7% (7/258)	0.21
Clinical pregnancy	16 (16.0%)	12 (14.3%)	11 (16.2%)	15.1% (39/258)	0.36
Ongoing pregnancy	15 (14.15%)	12 (14.28%)	9 (13.23%)	13.95% (36/258)	0.08
Live birth	15 (14.15%)	11 (13.09%)	9 (13.23%)	13.56% (35/258)	0.29
Early miscarriage rate (Before 12 weeks)	2 (1.8%)	0 (0%)	2 (2.9%)	1.6% (4/258)	0.40

Results per intention to treat.
Note: Values are mean +/- standard deviation or numbers and percentages unless otherwise indicated.
NA= not available NS= not statistically significant.

Safety endpoints

Characteristic	1st cycle (n=106)	2nd cycle (n=84)	3rd cycle (n=68)	OVERALL	P value
SAFETY MEASURES					
Proportion of patients with cancelled cycles	9 (8.5%)	2 (2.4%)	6 (8.9%)	6.6% 17/258)	0.29
Multiple pregnancy rate per cycle	2 (1.9%)	1 (1.2%)	3 (4.4%)	2.3% (6/258)	0.21
Multiple pregnancy rate per clinical pregnancy	2 (12.5%)	1 (8.3%)	3 (27.3%)	15% (6/40)	0.12

Cumulative pregnancy outcomes up to 3 cycles

	Cumulative rate up to 3 cycles
Positive pregnancy test	44.34%
Clinical pregnancy	37.73%
Ongoing pregnancy	33.96%
Live birth	33.02%

Ovarian response outcomes

Characteristic	1st cycle (n=106)	2nd cycle (n=84)	3rd cycle (n=68)	P value
OVARIAN REPONSE				
Number of cycles with 2-3 follicles	36 (34%)	31 (37%)	32 (47%)	0.044
Number of mature follicles obtained per cycle				
0	4 (3.8%)	2 (2.4%)	3 (4.4%)	
1	64 (60.4%)	51 (60.7%)	32 (47.1%)	
2	30 (28.3%)	26 (31%)	20 (29.4%)	
3	6 (5.7%)	5 (6%)	12 (17.6%)	- -
4	2 (1.9%)	0 (0%)	1 (1.5%)	
> 4	0 (0%)	0 (0%)	0 (0%)	
Duration of stimulation (days)	8.59 ± 3.06	7.98 ± 2.64	7.82 ± 2.5	0.06
Endometrial thickness (mm)	9.26 ± 2.29	9.51 ± 2.05	10.1 ± 2.7	0.036
Initial dose of follitropin delta	3.25 ± 0.74	3.99 ± 1.06	5.20 ± 1.89	< 0.0001
Dose adjustment during cycle (decrease by 20%)	6 (5.6%)	12 (14,3%)	12 (17,6%)	
Total dose per cycle	27.75 ± 12.7	31.37 ± 12.57	40.06 ± 19.10	< 0.0001

Note: Values are mean +/- standard deviation or numbers and percentages unless otherwise indicated.
NA= not available NS= not statistically significant.

DISCUSSION

This is the first study to evaluate the use of follitropin delta for ovarian stimulation prior to intrauterine insemination.

Three other RCTs have compared clomiphene citrate (CC)/IUI with gonadotropin/IUI. The first RCT (29) randomized 93 couples. Ongoing pregnancy rate per cycle was 9.6% with CC/IUI and 15.6% with gonadotropin/IUI, with multiple pregnancy rate of 13.3% in the gonadotropin/IUI group. The second trial (30) randomized 68 couples, and after four cycles of IUI the cumulative live birth rate was 28.2% in CC/IUI group and 26.9% in gonadotropin/IUI group, although there was a higher cancellation rate primarily for over-response in the gonadotropin/IUI group (8.7%). The third RCT was AMIGOS trial, in which the authors compared gonadotropin (follitropin alfa) with estrogen antagonist and aromatase inhibitor in up to 4 IUI cycles. The cumulative clinical pregnancy rate was 35.5%, 28.3% and 22.4%, and the cumulative live birth rate was 32.2%, 23.3% and 18.7%, respectively, for these 3 categories of agents. The multiple pregnancy rate in the AMIGOS trial was 31.8%, 9.4% and 13.4%, respectively, including 24 twins and 10 triplets in the gonadotropin/IUI group. In PITS study we have obtained higher cumulative clinical pregnancy rate (37.7%) and cumulative live birth rate (33%) comparing with these three RCTs with only three cycles of IUI instead of four. The multiple pregnancy rate in PITS study (15% with no triplets) was half of that observed in AMIGOS trial (31.8%) with lower cancelation rate than that observed in Dankert's RCT. This allows us to conclude that the proposed dosing regimen is safe.

This low multiple pregnancy rate observed in our study might be explained by:

Our strict criteria to avoid more than three mature follicles leading to high percentage of patients achieving the targeted 2 or 3 mature follicles in each cycle (34%, 37% and 46%, respectively)

The use of a novel, human derived recombinant FSH (follitropin delta), which has been shown to produce a balanced safe and efficacious stimulation including in patients with polycystic ovaries (PCO).

In our study we observed that personalised approach using personalized dosing of follitropin delta results in a higher clinical pregnancy rate with a multiple pregnancy rate at the same level as with oral agents and approximately half the rate reported with gonadotropins, leading to the dosing regimen proposed in this study to be considered for use in clinical practice. However, given the study's small sample size, absence of a control group and therefore potentially limited generalisability to practices outside of North America, the results of this trial should be further validated by a larger, multi-centre study.

CONCLUSION

This study is the first to use follitropin delta for ovarian stimulation for intrauterine insemination. It supports the hypothesis of a potential benefit of the use of a personalized dosing regimen of follitropin delta for IUI in terms of pregnancy outcomes. However, a larger, randomized study will be required to confirm our initial findings.

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