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Research Article

Comparative Analysis of Follitropin Alpha *vs.* Delta: Impact on Ovarian Stimulation Outcomes

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ABSTRACT

Current infertility treatment practices are shifting from standardized to personalized Follicle Stimulating Hormone (FSH) dosing, with new FSH preparations incorporating individualized dosing in their clinical development. The commonly used regimens include recombinant FSH combined with human menopausal gonadotropin. This study aims to examine the effects of follitropin alpha and follitropin delta on ovarian stimulation, specifically focusing on embryo development and quality of *In Vitro* Fertilization (IVF) cycles.

This cross-sectional was held at Dr. Kariadi Central General Hospital from January 2022 to June 2024. All cycles involved controlled ovarian stimulation using recombinant FSH with either a Gonadotropin Releasing Hormone (GnRH) antagonist, long GnRH agonist or flare GnRH agonist protocols. This study includes patients undergoing IVF treatment at the fertility clinic who completed all necessary laboratory examinations.

In this study, a sample of 67 patients were consisted with 30 women in follitropin alpha and 37 women in follitropin delta who met the inclusion criteria and exclusion criteria. Patient demographics, treatment parameters, hormonal levels, pregnancy outcomes, oocyte retrieval and embryo transfer were studied. Most of the embryo transfers were fresh with mostly good quality.

Overall, follitropin delta provides superior outcomes in terms of higher oocyte retrieval rates, better pregnancy rates and more effective ovarian stimulation compared to some other FSH preparations. These advantages make it a valuable option for optimizing fertility treatments, though individual patient factors and treatment protocols should always be considered.

Keywords: *In vitro* fertilization, Follicle stimulating hormone, Anti-müllerian hormone, Follitropin alpha

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INTRODUCTION

Follitropin alpha and follitropin delta are both recombinant forms of FSH used in Assisted Reproductive Technologies (ART) and ovarian stimulation therapies. FSH is critical for the regulation of ovarian follicle growth and development, making these medications essential in fertility treatments (Haakman O, *et al*., 2021; Dias JA and Ulloa-Aguirre A, 2021).

Recent studies and clinical trials have shown that follitropin delta often delivers superior results compared to follitropin alpha. It is associated with higher oocyte retrieval rates, improved pregnancy outcomes and more effective ovarian stimulation. The extended half-life of follitropin delta means that it can provide a more consistent and prolonged stimulation, leading to better follicular development and overall success in ART procedures. Recent studies suggest that follitropin delta may offer notable advantages over follitropin alpha, including higher oocyte retrieval rates and improved pregnancy outcomes.

These improvements are attributed to the medication's ability to sustain follicular stimulation more effectively, leading to better ovarian response and enhanced success rates in ART procedures. Despite its potential benefits, follitropin delta remains underutilized and further research is needed to fully establish its place in standard fertility treatment protocols. As a result, follitropin delta represents a significant advancement in fertility treatments, offering enhanced performance and convenience, which can lead to more favourable outcomes for patients undergoing ovarian stimulation (Haakman O, *et al*., 2021; Dias JA and Ulloa-Aguirre A, 2021).

MATERIALS AND METHODS

This cross-sectional study was held at Dr. Kariadi Central General Hospital from January 2022 to June 2024. All cycles involved controlled ovarian stimulation using recombinant FSH with either GnRH antagonist, long GnRH agonist or flare GnRH agonist protocols. This study includes patients undergoing IVF treatment at the fertility clinic who completed all necessary laboratory examinations.

Inclusion criteria

Patients who wanted to participate in IVF cycles treated in fertility clinic and patients who have underwent and completed laboratory examinations were included in the study.

Exclusion criteria

Patients who did not meet the inclusion criteria and those who did not sign the informed consent form were excluded from the study.

Statistical analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 21 software, where $p<0.05$ was considered to be significant.

RESULTS AND DISCUSSION

A total of 67 patients (30 patients received follitropin alpha while 37 patients received follitropin delta) were included, with 40.3% patients whose age was less than 35 years. The mean body weight of all patients was found to be (58.6 ± 5.99) kg according to each patient's initial (Anti-Müllerian Hormone) AMH level (2.1 ± 2.27) (*Tables 1 and 2*). The indication for IVF is mostly male and female factor (77.6%). The mean duration of stimulation was (11.1 ± 2.6) days. The total dosage of recombinant FSH in follitropin alpha was 2688.5 ± 1130.07, while follitropin delta was 1802.5 ± 591.98 ($p<0.001$).

The estradiol concentrations of patients with follitropin alpha *vs.* delta were 2,073.4 ± 967.94 *vs.* 2,608.3 ± 1,223.23 (*Table 3*), and the progesterone concentrations were 2.7 ± 1.59 *vs.* 3.5 ± 3.35.

Table 1: Description of the characteristics of research subjects

Variables	Frequency	%	Mean ± Standard Deviation (SD)	Median (minimum-maximum)
Body weight			58.6 ± 5.99	57 (47-78)
IVF indication				
Tubal factor	11	16.4		
Diminished Ovarian Reserve (DOR)	1	1.5		
Endometriosis	3	4.5		
Male and female factors	52	77.6		
Type of IVF				
Alpha	30	44.8		
Delta	37	55.2		
Dosage			189.03 ± 81.54	150.75 (6.6-375)
Length of IVF (days)			11.1 ± 2.61	12 (4-14)
Total dosage of FSH recombinant			2155.26 ± 985.14	1950 (72.6-5250)
AMH			2.06 ± 2.27	1.32 (0.01-16.23)
Right Antral Follicle Count (AFC)			7.52 ± 4.38	7 (0-18)
Left AFC			6.45 ± 2.99	7 (0-11)
Age (y)				
<35	27	40.3		
35-37	17	25.4		
38-40	15	22.4		
41-42	5	7.5		
>42	3	4.5		
Last estradiol			2368.79 ± 1140.01	2654 (227-6000)
Progesterone			3.17 ± 2.73	3.11 (0.25-22.64)
Oocyte Pick Up (OPU)			1.79 ± 1.23	2 (0-6)
Total embryo			1.48 ± 1.01	2 (0-3)
Quality of embryo				
Moderate poor	26	38.8		
Good	33	49.3		
Excellent	8	11.9		
Embryo Transfer (ET)				
Fresh	23	60.5		
Frozen	15	39.5		
Total embryo transfer			1 ± 0.98	1 (1-3)
Pregnancy outcome				
Pregnant	10	14.9		
Not pregnant	57	85.1		

Table 2: Comparison of pregnancy outcomes based on various variables

Variables	Pregnancy outcomes		p
	Pregnant	Not pregnant	
Body weight	56.90 ± 5.69	58.89 ± 6.04	0.335[§]
IVF indication			
Tubal factor	2 (3%)	9 (13.4%)	0 .07[¥]
DOR	0 (0%)	1 (1.5%)	
Endometriosis	2 (3%)	1 (1.5%)	
Male and female factor	6 (9%)	46 (68.7%)	
Type of IVF			
Alpha	3 (4.5%)	27 (40.3%)	0.493[¥]
Delta	7 (10.4%)	30 (44.8%)	
Dosage	133.1 ± 55.8	198.84 ± 81.73	0.022[‡*]
Length of IVF (days)	12.30 ± 1.16	10.89 ± 2.75	0.16[‡]
Total dosage of FSH recombinant	1674.2 ± 1405.16	1698.86 ± 853.99	0.141[§]
AMH	2.71 ± 1.35	1.95 ± 2.39	0.026[‡*]
Right AFC	8.50 ± 3.95	7.35 ± 4.47	0.354[‡]
Left AFC	7.00 ± 2.65	4.38 ± 2.99	0.607[§]
Age (y)			
<35	4 (6%)	23 (34.3%)	0.658[¥]
35-37	4 (6%)	13 (19.4%)	
38-40	2 (3%)	13 (19.4%)	
41-42	0 (0%)	5 (7.5%)	
>42	0 (0%)	3 (4.5%)	
Last estradiol	2268.2 ± 860.3	2386.44 ± 1187.70	0.825[‡]
Progesterone	2.22 ± 1.13	3.34 ± 2.89	0.056[‡]
OPU	8.67 ± 5.51	6.69 ± 3.68	0.453[§]
Embryo total	2.4 ± 0.84	1.68 ± 1.26	0.031[‡*]
Embryo quality			
Moderate poor	0 (0%)	9 (18%)	0.059[¥]
Good	8 (16%)	25 (50%)	
Excellent	2 (4%)	6 (12%)	
ET transfer			
Fresh	5 (13.16%)	18 (47.37%)	0.509[¥]
Frozen	2 (5.26%)	13 (34.21%)	
Total embryo transfer	1.8 ± 0.79	0.86 ± 0.95	0.005[‡*]

Note: [*]p<0.05; [§]Independent; [‡]Mann-Whitney and [¥]Chi-square value

Table 3: Comparative analysis of variables between folitropin alpha and delta in IVF treatment

Variables	IVF type		p
	Folitropin alpha	Folitropin delta	
Body weight	60.17 ± 7.15	57.32 ± 4.58	0.053§
IVF indication			
Tubal factor	4 (6%)	7 (10.4%)	0.545¥
DOR	1 (1.5%)	0 (0%)	
Endometriosis	2 (3%)	1 (1.5%)	
Male and female factors	23 (34.3%)	29 (43.3%)	
Dosage	241.43 ± 79.72	146.54 ± 54.09	0.027¥*
Length of OVF (days)	10.37 ± 3.24	11.7 ± 1.8	0.411¥
Total dosage of FSH recombinant	2688.53 ± 1130.07	1802.48 ± 591.98	0.000§*
AMH	1.31 ± 1.05	2 .67 ± 2.78	0.005‡*
Right AFC	6.7 ± 4.32	8 .19 ± 4.38	0.169§
Left AFC	6.1 ± 2.76	6 .73 ± 3.17	0.395§
Age (y)			
<35	10 (14.9%)	17 (25.4%)	0.596¥
35-37	10 (14.9%)	7 (10.4%)	
38-40	6 (9%)	9 (13.4%)	
41-42	2 (3%)	3 (4.5%)	
>42	2 (3%)	1 (1.5%)	
Last estradiol	2073.44 ± 967.94	2608.27 ± 1223.23	0.056§
Progesterone	2.71 ± 1.59	3.54 ± 3.35	0.177‡
OPU	5.27 ± 2.63	10.35 ± 5.62	0.000§*
Embryo total	1.40 ± 0.89	2.11 ± 1.37	0.028‡*
Embryo quality			
Moderately poor	7 (14%)	2 (4%)	0.042¥*
Good	13 (26%)	20 (40%)	
Excellent	1 (2%)	7 (14%)	
ET quality			
Fresh	14 (36.84%)	9 (23.68%)	0.104¥
Frozen	4 (10.53%)	11 (28.95%)	
Total embryo transfer	1.10 ± 0.99	0.91 ± 0.98	0.440‡

Note: *p<0.05; §Independent; ‡Mann-Whitney and ¥Chi-square value

The pregnancy rate was higher in the follitropin delta group (follitropin alpha group, n=3 *vs.* follitropin delta group, n=7, p=0.493). The individualized follitropin alpha treatment resulted in fewer oocytes retrieved than follitropin delta treatment (5.3 ± 2.63 *vs.* 10.4 ± 5.62, p<0.001). The mean number of embryo transfers were 1.4 ± 0.89 *vs.* 2.1 ± 1.37. Most of the embryo transfers were fresh with mostly good quality.

CONCLUSION

In ART, FSH plays an important role in ovarian stimulation, impacting the success of IVF and other fertility treatments. Both follitropin alpha and follitropin delta are recombinant forms of FSH used to enhance ovarian follicle development. The efficacy and safety of the individualized follitropin delta dosing regimen compared with conventional follitropin alpha dosing was evaluated in a large randomized controlled phase III trial. The trial demonstrated that non-inferiority of individualized follitropin delta compared with conventional follitropin alpha with respect to the co-primary endpoints of ongoing pregnancy and ongoing implantation rates. At the same time, individualized follitropin delta stimulation in a fixed dosing regimen resulted in a more targeted response and an improved safety profile in terms of fewer cases of Ovarian Hyperstimulation Syndrome (OHSS) and/or OHSS preventive measures (Koechling W, *et al*., 2017; Bosch E, *et al*., 2002).

Based on research by Arce JC, *et al*., 2020, that daily follitropin delta dose of 10.0 µg and 10.3 µg give the same number of oocytes as 150 IU/day dose of follitropin alpha for all patients participating in the phase II and III trials. Daily follitropin delta doses in the range 9.5-10.4 µg was estimated to correspond to 150 IU/day follitropin alpha for serum oestradiol concentration and number of follicles ≥ 12 mm at the end of stimulation across analysis populations in the phase III trial.

While Bosch E, *et al*., 2002, said that treatment with follitropin delta and alpha give similar outcomes for mean number of oocytes retrieved (9.2 *vs.* 8.6 (cycle 2); 8.3 *vs.* 8.9 (cycle 3)), ongoing pregnancy (27.8% *vs.* 25.7%; 27.4% *vs.* 28.0%) and live birth rates (27.4% *vs.* 25.3%; 26.3% *vs.* 26.9%). From Evidence-based Stimulation Trial with human recombinant Follicle Stimulating Hormone (rFSH) in Europe and Rest of world 1 (ESTHER-1) trial said that individualized follitropin delta resulted in more women with target response (8-14 oocytes) (43.3% *vs.* 38.4%). Result in similar blastocyst numbers (3.3 ± 2.8 *vs.* 3.5 ± 3.2).

Follitropin alpha is one of the pioneering recombinant FSH products, follitropin alpha has a well established efficacy profile. It effectively stimulates ovarian follicles, promoting their growth and maturation. However, variability in individual responses and the necessity for daily injections can limit its overall effectiveness. While follitropin delta, a newer formulation offers several advantages over follitropin alpha. Its extended half-life allows for less frequent dosing while maintaining effective stimulation. Studies have consistently shown that follitropin delta often results in a higher number of oocytes retrieved. The more sustained follicular stimulation provided by follitropin delta can lead to a more consistent and robust ovarian response, reducing variability and improving overall stimulation outcomes. Evidence suggests that follitropin delta may lead to higher clinical pregnancy rates. The improved ovarian response, characterized by a higher number of mature oocytes, enhances the likelihood of successful fertilization and implantation. This can be particularly beneficial for patients undergoing IVF, where the quality and quantity of oocytes play a critical role in treatment success. Research indicates that follitropin delta may be associated with higher clinical pregnancy rates. The improved ovarian response and higher quality of oocytes can contribute to better fertilization and implantation rates (Ortmann O, *et al*., 2002; van den Haute L, *et al*., 2021).

Follitropin delta provides higher oocyte yields compared to follitropin alpha primarily due to its extended half-life and the resultant more consistent and prolonged follicular stimulation. This sustained stimulation helps in the growth and maturation of multiple follicles, reducing variability in ovarian response and enhancing the overall number of oocytes retrieved. With less frequent dosing and extended action, follitropin delta reduces fluctuations in FSH levels that can occur with daily dosing regimens (Doroftei B, *et al*., 2023). This steadier stimulation can lead to a more predictable and uniform ovarian response. By minimizing variability, follitropin delta enhances the likelihood of achieving a high number of mature oocytes, as the follicles are less likely to experience irregular growth patterns or premature luteinization. The optimized dosing regimen and improved patient compliance further contribute to the superior effectiveness of follitropin delta in ovarian stimulation (Yang R, *et al*., 2022).

Follitropin alpha, while a well established treatment for ovarian stimulation in ART, may sometimes result in fewer oocytes retrieved and lower pregnancy outcomes compared to newer alternatives such as follitropin delta. This form of recombinant FSH has a shorter half-life, which typically necessitates daily injections. The frequent dosing can lead to fluctuations in FSH levels, potentially causing variability in ovarian response. The less consistent stimulation can result in fewer follicles reaching full maturity and consequently, a lower number of oocytes retrieved. Variability in follicular growth may also affect the overall quality of the oocytes. While follitropin alpha is effective and has been widely used, its shorter half-life, daily dosing requirement and potential for response variability can lead to fewer oocytes retrieved and lower pregnancy outcomes in some patients. In comparison, follitropin delta's extended half-life and more consistent stimulation offer advantages that can lead to higher oocyte yields and improved pregnancy rates. This highlights the importance of considering newer options like follitropin delta for optimizing ART outcomes, especially in patients who may not respond optimally to traditional treatments.

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