ORIGINAL RESEARCH ARTICLE

Efficacy and safety of simplified follitropin delta dosing in women undergoing intrauterine insemination in Indonesia

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Abstract

Available evidence indicate that Intrauterine Insemination (IUI) cycles with controlled ovarian stimulation (COS) yield better oocyte quality and higher pregnancy rates compared to those without COS in infertile women. As follitropin delta is an improved version of recombinant FSH, its ability to stimulate the development of multiple ovarian follicles is supposedly superior to follitropin alfa. The objective of this study was to evaluate the efficacy and safety of follitropin delta with a simplified dosage equivalent method in Indonesian women undergoing IUI. The design of this study was a retrospective observational study conducted from February 2022 to December 2023 involving 248 IUI cycles at Halim Fertility Center (HFC) IVF Center, Indonesia. Controlled Ovarian Stimulation was performed with follitropin delta with a simplified dosage equivalent method in IUI. From this study, we found that the clinical pregnancy rate (CPR) for IUI was 27.8%. The Ovarian Hyperstimulation Syndrome (OHSS) rates was 0.4%, with 2,9% multiple pregnancies in the follitropin delta with a simplified dosage equivalent method. This study showed no statistically significant differences in pregnancy rates based on age groups and BMI (p=0.288 vs p=0.934). WE conclude that follitropin delta may improve the outcome of intrauterine insemination in women undergoing IUI. *(Afr J Reprod Health 2025; 29 [3]: 58-67).*

Keywords: Intrauterine insemination; Follitropin delta; Simplified dosage; Clinical; Outcome

Résumé

Les preuves disponibles indiquent que les cycles d'insémination intra-utérine (IIU) avec stimulation ovarienne contrôlée (COS) donnent une meilleure qualité d'ovocytes et des taux de grossesse plus élevés que ceux sans COS chez les femmes infertiles. Comme la follitropine delta est une version améliorée de la FSH recombinante, sa capacité à stimuler le développement de plusieurs follicules ovariens est censée être supérieure à celle de la follitropine alfa. L'objectif de cette étude était d'évaluer l'efficacité et l'innocuité de la follitropine delta avec une méthode simplifiée d'équivalent posologique chez les femmes indonésiennes subissant une IIU. La conception de cette étude était une étude observationnelle rétrospective menée de février 2022 à décembre 2023 portant sur 248 cycles d'IIU au centre de FIV du Halim Fertility Center (HFC), en Indonésie. La stimulation ovarienne contrôlée a été réalisée avec de la follitropine delta avec une méthode simplifiée d'équivalent de dose en IIU. À partir de cette étude, nous avons constaté que le taux de grossesse clinique (CPR) pour l'IIU était de 27,8 %. Les taux de syndrome d'hyperstimulation ovarienne (SHO) étaient de 0,4 %, avec 2,9 % de grossesses multiples dans le delta de la follitropine avec une méthode simplifiée d'équivalent de dose. Cette étude n'a montré aucune différence statistiquement significative dans les taux de grossesse en fonction des groupes d'âge et de l'IMC (p = 0,288 vs p = 0,934). NOUS concluons que la follitropine delta peut améliorer les résultats de l'insémination intra-utérine chez les femmes subissant une IIU. *(Afr J Reprod Health 2025; 29 [3]:58-67).*

Mots-clés: Insémination intra-utérine; Follitropine delta; Posologie simplifiée; Clinique; Résultat

Introduction

As the global population continues to expand, infertility afflicts about 8-12% of couples at reproductive age worldwide, which has been recognised as a public health issue by the World Health Organisation (WHO).[1] The European Society for Human Reproduction and Embryology (ESHRE) reported that cases with male infertility (20-30%), female infertility (20-35%), both partners (25-40%), and unexplained infertility (10-20%) are the primary reasons patients seek medical care.[2] Consequently, an increasing number of couples are pursuing infertility treatments, specifically

intrauterine insemination (IUI) because of its accessibility, safety, and affordability with a typical success rate of 10-20%.[3]

A retrospective meta-analysis has proven that IUI cycles with controlled ovarian stimulation (COS) yield better oocyte quality and higher pregnancy rates compared to those without COS in infertile women.[4] Moreover, studies involving mild male infertility and unexplained infertility cases have shown that outcomes of IUI with COS are not inferior to in vitro fertilization (IVF).[5,6] Oocyte recovery yield in patients undergoing COS depends on the degree of exposure to exogenous gonadotropins to improve ovarian response and treatment outcomes, including safety and efficacy. Follitropin alfa is the most frequently prescribed drug used for COS, but the use of its promising newer counterpart, follitropin delta, has been increasing. Follitropin delta is a novel recombinant FSH with a modified molecular structure developed using a human cell line (PER.C6VR) from follitropin alfa.[7]

Follitropin delta is specifically engineered to have a longer half-life in the body compared to traditional forms of FSH because it is a more stable and pure form of the hormone. Follitropin alfa typically requires more frequent dosing, while follitropin delta has an extended duration of action, allowing for less frequent dosing and a more patient-friendly dosing regimen.[8] As follitropin delta is an improved version of recombinant FSH, its ability to stimulate the development of multiple ovarian follicles is supposedly superior to follitropin alfa. Nevertheless, additional research is required to confirm this hypothesis. In Indonesia, follitropin delta was first introduced in August 2021 and most IVF centres use it for IVF/ICSI. Clinical trials involving various sample groups have demonstrated that personalized dosing of follitropin delta is required according to each woman's serum anti-Müllerian hormone (AMH) concentration and body weight to minimize ovarian response and risk of ovarian hyperstimulation syndrome (OHSS) without compromising pregnancy outcomes.[9–13]

However, AMH measurement remains difficult in Indonesia. Only large cities like Jakarta and Surabaya have access to clinical laboratories that perform AMH measurement, hence samples from other locations must be sent to these institutions. Another challenge is the possibility of sample quality to deteriorate during transportation, leading to erroneous measurement results. Furthermore, AMH measurement is an additional expense for IVF patients and clinicians typically use antral follicle count (AFC) to predict ovarian response rather than AMH. A straightforward and efficient method to determine the starting dosage of follitropin delta for IUI is therefore required, particularly for IVF centres or doctors who do not conduct routine AMH measurements due to the above mentioned restrictions. The dose equivalence of follitropin delta was introduced by JC Arce in 2020, with 10 mcg of follitropin delta being equivalent to 150 IU follitropin alfa.[14]

This method of dose equivalence was considered more effective and suitable for determining the initial dose of follitropin delta for IVF centres or doctors that are restricted in conducting AMH measurements. Additionally, many doctors in Indonesia have already established their IUI protocol using IU and are more familiar with it. So hypothetically, the dose equivalence of follitropin delta can also be implemented to determine the initial dose for IUI. Currently there is no clinical evidence of follitropin delta with dose equivalence for IUI, especially in the Indonesian population. Based on our understanding, this is the first study to evaluate the efficacy and safety of follitropin delta usage with a simplified dosage equivalent method for ovarian stimulation prior to intrauterine insemination. The purpose of this study is to assess the efficacy and safety of follitropin delta with a simplified dosage equivalent method in Indonesian women undergoing IUI.

Methods

Study design and participants

A retrospective observational study was conducted from February 2022 to December 2023 involving 248 IUI cycles at Halim Fertility Center, Indonesia. The retrospective observational design was used to analyze existing patient data, allowing for the evaluation of treatment outcomes in a real-world setting. This approach provides valuable insights into the effectiveness and safety of the treatment while avoiding the challenges of a prospective trial. COS was performed in IUI patients who received follitropin delta with a simplified dosage equivalent method.

Infertile couples are eligible if they have fulfilled at least one of the following inclusion criteria: female

age of less than 40, unexplained infertility, bilaterally patent tubes, mild male factor with total motile sperm count (TMSC) of 10-20x10^6/ml, FSH level less than 10 mIU/ml and anovulation. Exclusion criteria were endometriosis cyst, adenomyosis, congenital uterine anomalies, total sperm motile count of less than 5x10^6, spontaneous ovulation and poor ovarian response.

In this study, we performed controlled ovarian stimulation with follitropin delta from February 2022 to December 2023. In the schematic study that from 288 patients in follitropin delta group, we found 19 patients with lost to follow up due to the patient's distant residence presents significant challenges in accessibility, making it difficult to reach and 21 patients did not undergo IUI (cancellation) (due to conditions such as ovulation challenges or patient illness) in this study. All patients with lost to follow up and cancellation were excluded in this study (Figure 1).

Intrauterine insemination (IUI) protocol

IUI patients were stimulated with follitropin delta (Rekovelle, Ferring, Germany) using dose equivalence method of 5 µg starting on day 2 or 3 of the cycle. Then, follicle development was monitored starting from day 8 by ultrasound where the follicle diameter and endometrium growth were measured. The administered dose of follitropin delta was personally adjusted based on each follicular response. If the follicle diameter is more than or equal to 12 mm, the dose remained at 5µg. If the follicle diameter has not reached 12 mm, the dose was increased to 10µg. If there is an increase of at least 2 mm of each follicle after each day of ultrasound monitoring, the dose remained the same. If there is no increase in 2 mm, the dose was increased. Ovulation was triggered with dual trigger GnRH-a (Lucrin 1 mg; AbbVie, New South Wales, Australia) and hCG (Ovidrel 250 µg, Merck KgaA) at the same time when the leading follicle reached a diameter ≥ 17 mm. The IUI procedure was performed 36 hours after ovulation triggering and only once procedure was done.[15] Figure 2

Semen preparation and insemination

Fresh semen samples were collected after a period of 3-5 days of sexual abstinence at HFC for IUI procedure. Swim-up protocol was applied to all samples and insemination was conducted 36h after inducing dual trigger.[15]

Luteal phase support

For 14 days, oral micronized progesterone 300 mg was prescribed for luteal phase support. A subsequent urinary pregnancy test was examined to determine the biochemical pregnancy rate. Clinical pregnancy was diagnosed by ultrasonographic visualisation of one or more gestational sacs or definitive clinical signs of pregnancy, such as presence of fetal cardiac activity 2 weeks after a positive urinary pregnancy test.

Statistical analysis

The method of this study involved a descriptive study with cross sectional design. The sample of this study were women undergoing IUI cycle with follitropin delta treatment from February 2022 to December 2023. All collected data or variable was analysed using descriptive statistics. The continuous variables were calculated to find the mean and standard deviation to provide a summary of the central tendency and spread of continuous variables. Categorical variables were divided and presented as number and percentage to be summarised into groups. Analysis was conducted using the Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL, USA).

Ethical approval

This study was approved by the Health Research Ethical Committee of Stella Maris Women's and Children's Hospital, Medan, Indonesia with the number 011-1/Dir/RSIA.SM/I/2023.

Results

The sample data in this study consists of a total of 248 IUI cycles from January 2022 to December 2023 that were administered with follitropin delta. Table 1 presents the demographic mean (± standard deviation (SD)) baseline characteristic data of participants by age (yr), BMI (kg/m^2), duration of infertility (yr), antral follicle count (AFC), FSH (mIU/ml), LH (mIU/ml), AMH (mIU/ml) and total sperm motile count (TMSC).

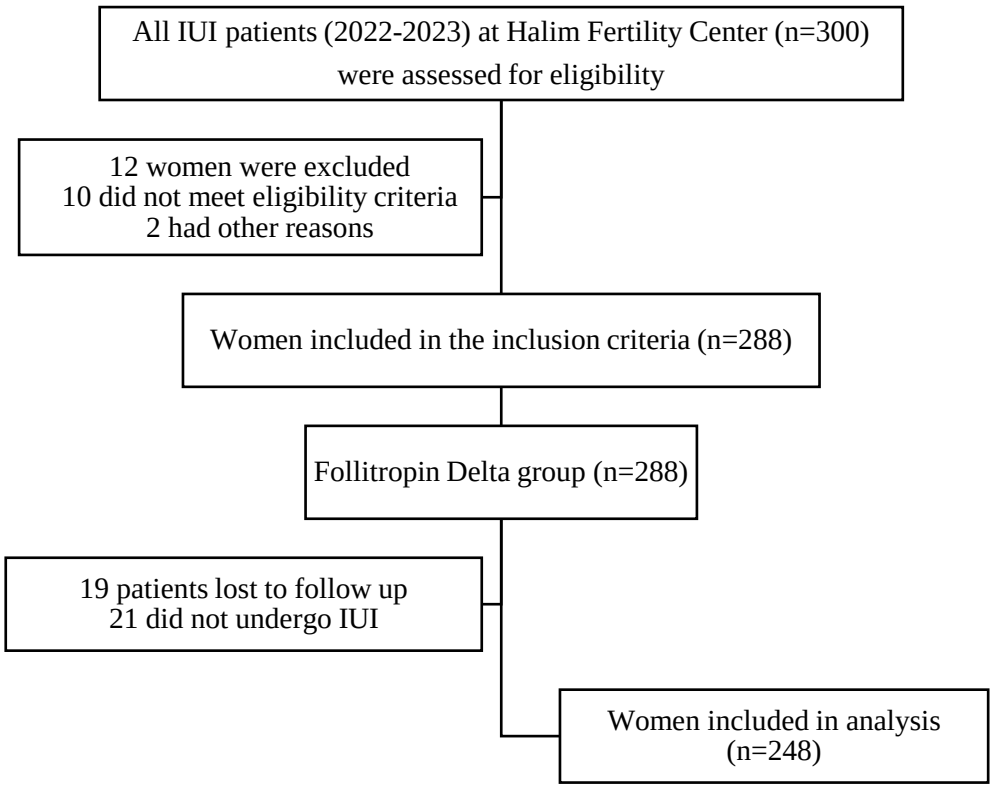

Figure 1: Schematic study of follitropin elta in OI/IUI patients at HFC

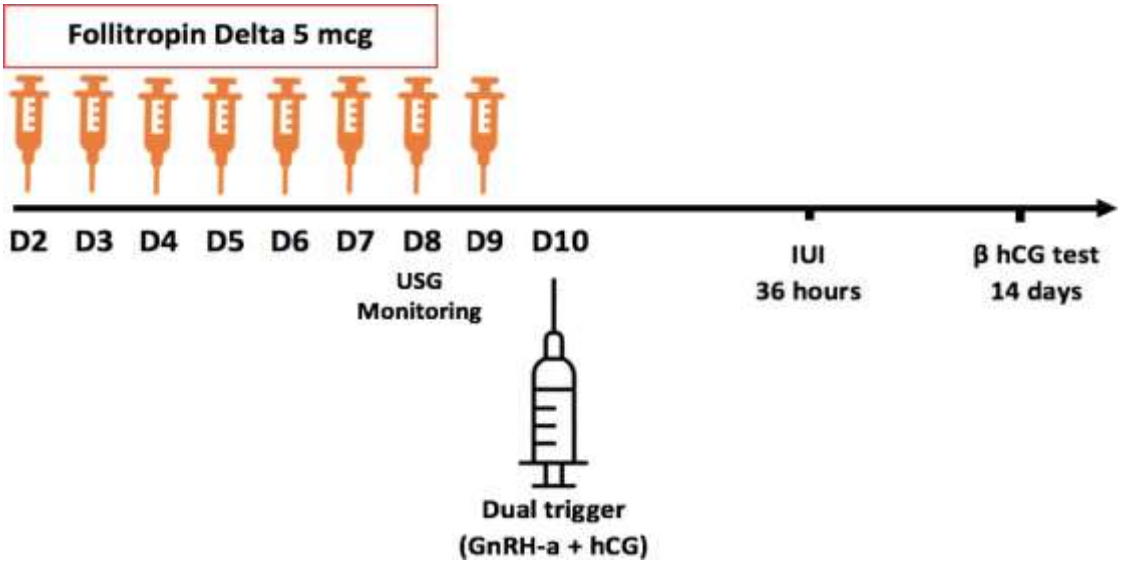

Figure 2: Controlled ovarian stimulation with follitropin delta in IUI protocol

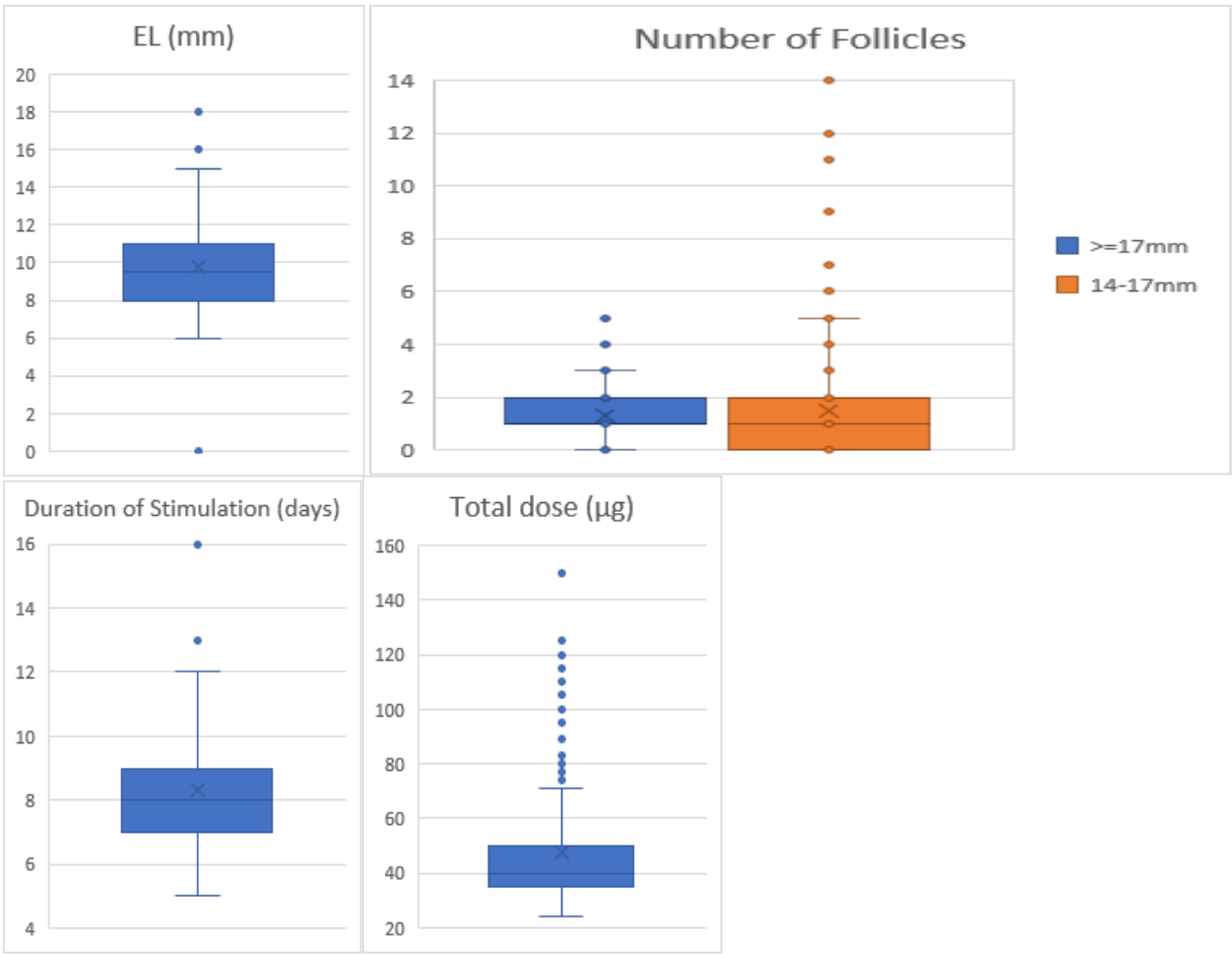

Figure 3: Box plot of the stimulation cycle parameters in the participants

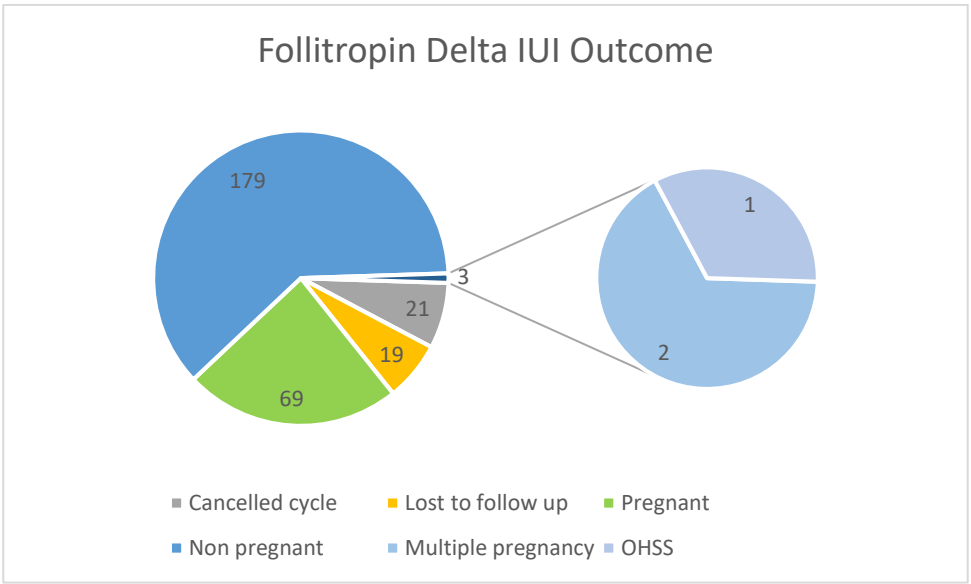

Figure 4: Pie chart of IUI outcomes

Table 1: The participants' demographic baseline characteristics

Variables	Follitropin Delta group (n=248)
Female age (yr)	32.56±3.75
<30 (%)	54 (21.77)
30-34 (%)	118 (47.58)
35-37 (%)	48 (19.35)
38-40 (%)	22 (11.29)
BMI (kg/m^2)	25.00±4.48
Underweight (%)	8 (3.23)
Normal (%)	134 (54.03)
Overweight (%)	80 (32.26)
Obese (%)	26 (10.48)
Duration of infertility (yr)	4.99±2.94
Infertility type	
Primary infertility (%)	191 (77.0)
Secondary infertility (%)	57 (23.0)
Etiology of Infertility	
Mild male factor (%)	59 (23.8)
Female factor (%)	58 (23.4)
Combined factor (%)	115 (46.4)
Unexplained (%)	16 (6.4)
AFC	13.07±6.36
FSH (mIU/mL)	5.66±1.90
LH (mIU/mL)	4.81±5.02
AMH (ng/mL)	3.73±2.19
TMSC (nx10^6/mL)	9.19±5.09

Note: Mean±Standard Deviation. BMI = body mass index; FSH= follicle-stimulating hormone; LH = Luteinizing hormone; AMH = antimullerian hormone; AFC = antral follicle count; TMSC = total motile sperm count

The participants had a mean age of 32.56 ± 3.75 years, mean BMI of 25.00 ± 4.48 kg/m^2, mean AFC of 13.07 ± 6.36, FSH concentration of 5.66 ± 1.90 mIU/ml, LH concentration of 4.81 ± 5.02, mean AMH concentration of 3.73 ± 2.19 ng/ml, and TMSC of 9.19 ± 5.09x10^6/ml. (Table 1) Primary infertility occured in 77% of the participants and lasted for approximately 4.99 ± 2.94 years. Infertility caused by combined male and female factor is present in almost 50% of patients, and almost 25% of patients are caused by mild male factor or female factor only, making up 6.4% of unexplained infertility cases.

Table 2 lists the ovarian stimulation cycle parameters in the participants. The mean duration of administration of follitropin delta from day 2 or 3 until triggering day is 7.94 ± 1.64 days with a total dose of 48.09 ± 20.67 μg of follitropin delta on average. It was found that 32.26% of patients were given an additional adjusted dosage of follitropin delta. The average number of follicles that are larger than 17 mm was 1.25 ± 0.87 in patients, while the number of follicles with size 14-16 mm is 1.47 ± 2.14. The mean endometrial thickness of patients is 9.47 ± 2.16 mm.(Table 2)

Table 2: The ovarian stimulation cycle parameters in the participants

Parameter	Follitropin Delta (n=248)
Endometrial thickness (mm)	9.47±2.16
Number of follicle 14-16 mm	1.47±2.14
Number of follicles ≥17 mm	1.25±0.87
Total dose (μg)	48.09±20.67
Duration of stimulation (days)	7.94 ±1.64
Number of patients with additional adjustment dose (n, %)	80/248 (32.26%)

Note: Mean±Standard Deviation

Table 3: Outcome of intrauterine insemination procedure

Parameter	Follitropin Delta (n=248)
Clinical pregnancy rate (n, %)	69/248 (27.8%)
Multiple pregnancy rate (n, %)	2/69 (2.9%)
OHSS rate (n, %)	1/248 (0.4%)
Cancellation rate (n, %)	21/288 (7.3%)
Lost to Follow Up (n, %)	19/288 (6.6%)

Table 4: Outcome of intrauterine insemination procedure based on female age

Variable	Clinical Pregnancy rate Follitropin Delta (n=248)	*p-value*
Female age (yr)		
<30 (%) (n=54)	16 (29.63)	
30-34 (%) (n=118)	38 (32.20)	0.288
35-37 (%) (n=48)	10 (20.83)	
38-40 (%) (n=28)	5 (17.86)	

Table 3 presents the outcomes of the IUI procedures. The clinical pregnancy rate (CPR) of IUI patients using follitropin delta is 27.8%. There was only 1 OHSS case (0.4%) and 2 multiple pregnancy cases (2.9%) that were reported. There were 21 patients (7.29%) who cancelled for IUI, while 19 patients (6.6%) have lost to follow up.(Table 3)

Table 4 evaluates the clinical pregnancy rate of intrauterine insemination (IUI) procedures using Follitropin Delta in different age groups among 248 women. The clinical pregnancy rate decreases as age increases. Women under the age of

Table 5: outcome of intrauterine insemination procedure based on BMI

Variable	Clinical pregnancy rate follitropin delta (n=248)	*p-value*
BMI (kg/m²)		
Underweight (%) (n=8)	3 (37.50)	
Normal (%) (n=129)	35 (27.13)	0.934
Overweight (%) (87)	24 (27.59)	
Obese (%) (n=24)	7(29.17)	

30 had a clinical pregnancy rate of 29.63%, with 16 out of 54 women achieving pregnancy. In the 30–34 age group, the rate was slightly higher at 32.20%, with 38 out of 118 women achieving pregnancy. However, for women aged 35–37 years, the rate dropped to 20.83% (10 out of 48 women), and for those aged 38–40 years, it declined further to 17.86% (5 out of 28 women). The p-value of 0.288 suggests that the differences in pregnancy rates among the age groups are not statistically significant.

Table 5 evaluates the clinical pregnancy rates of IUI procedures using Follitropin Delta across different BMI categories in 248 women. Among underweight women (BMI <18.5 kg/m²), the clinical pregnancy rate was the highest at 37.50%, with 3 out of 8 women achieving pregnancy. Normal-weight women (BMI 18.5–24.9 kg/m²) had a pregnancy rate of 27.13%, with 35 out of 129 women achieving pregnancy. In the overweight group (BMI 25–29.9 kg/m²), the rate was similar at 27.59% (24 out of 87 women), and obese women (BMI ≥30 kg/m²) had a slightly higher rate of 29.17% (7 out of 24 women). The p-value of 0.934 indicates no statistically significant differences in pregnancy rates based on BMI

Discussion

Follitropin alfa and beta have been thoroughly researched and has demonstrated to be effective in stimulating follicular development in women undergoing IVF and IUI, making it the main gonadotropin used for both IUI and IVF with the highest success rate compared to other gonadotropins, such as urinary FSH and human menopausal gonadotropin (hMG). Follitropin delta, derived from fetal retinal human cell line, demonstrates increased structural and functional similarity to endogenous human FSH compared to follitropin alfa and beta, which are expressed in Chinese hamster ovary (CHO) cells.[7] Follitropin delta exhibits a superior safety profile attributed to its distinctive glycosylation pattern, resulting in reduced clearance and enhanced ovarian response compared to other recombinant FSH formulations, despite having a similar absolute bioavailability.

Follitropin delta dosage is personalised according to the patient's body weight and serum anti-Müllerian hormone (AMH) levels.[16] This customised dosage schedule has been used in a number of multi-center studies, such as the ESTHER-1/2, GRAPE, MARCS and STORK trial.[9–13] Ever since Arce's discovery of the dose equivalence method, it is now typically used in low to middle income countries, such as Indonesia, as it is more accessible. Follitropin delta dosage in this study was not determined by a woman's body weight or AMH levels. On the contrary, a simplified dosage equivalent regimen of 10 μg of follitropin delta, which is equivalent to a daily dose of 150 IU of follitropin alfa was used.[14] It has not been customary to utilise follitropin delta for ovarian stimulation in IUI; instead, it is usually used for ovarian stimulation in IVF. The ESTHER-1/2 trials, which were conducted in Europe, Canada, and Brazil, have demonstrated that the continued pregnancy rates remained non-inferior and safety was improved in follitropin delta compared to follitropin alfa when lower dosage of follitropin delta was required.[9,10] Results from the Asian GRAPE trial, which included women from Taiwan, South Korea, China, and Vietnam, were comparable to the ESTHER-1/2 trials.[11]

The MARCS and STORK trials also revealed similar results as the previously mentioned trials, except follitropin delta was compared to other gonadotropins, which were hMG and follitropin beta.[12,13] In addition, a study by Haakman *et al.*,[17] claims that stimulation with follitropin delta and follitropin alfa or beta showed similar embryo development and pregnancy rates. However, it is important to note that these clinical trials compared conventional follitropin alfa dosing to individualised dosing regimen of follitropin delta, not the dose equivalence method in IVF patients. Two separate retrospective analysis of more than 1000 cycles conducted on 2010 and 2017 using follitropin alfa for IUI yielded a CPR of 16.2% and 13.3% respectively.[18,19] These studies fall within the usual success rate range of 10-20%. In contrast, a

more recent retrospective analysis of IUI conducted from 1997 to 2017 involving 2901 couples revealed a lower CPR of 9.38%.[4] According to the PITS study (2022) and a more updated PITS study (2023) by Minano *et al.,* the CPR was found to be 15.1% and 16.7% respectively where personalised dosage of follitropin delta is used for IUI treatment.[20,21] Using these analyses as a benchmark and the typical IUI success rate, the CPR of follitropin delta in Indonesian population is much higher, reaching 27.8%. This may be attributable to the use of the dose equivalence method. The aforementioned clinical trials also highlights that follitropin delta was associated with better safety outcomes, less side effects and overreactions were observed, and more women responded within the intended range. Minano *et al.,* (2022-2023) discovered that follitropin delta only induced 6 multiple pregnancy cases (14-15%) of the 40 and 43 clinical pregnancies respectively.[20,21] Qiao *et al.,*[11] discovered that individualised follitropin delta dramatically decreased the incidence of early OHSS, which was 9.6% with follitropin alfa and 5.0% with follitropin delta. Yang *et al.,*[22] discovered that the follitropin delta group had a lower incidence of early OHSS (6.1% vs. 11.0%) than the follitropin alfa group. This study supports the claim that follitropin delta has higher safety outcomes as there was only 1 case of OHSS out of 248 patients, who was diagnosed with PCO with an AFC of 20 at 29 years of age. It should also be considered that most PCO patients also cancelled for IUI due to risk of OHSS to be converted to IVF. However, it is worth mentioning that cancelled IUI cycles are also caused by a spontaneous ovulation during stimulation with follitropin delta before triggering with r-hCG or a poor ovarian response during gonadotropin stimulation where there is no follicular growth in the process.[22]

Moreover, two multiple pregnancies were reported with one twin pregnancy and one triplet pregnancy. Interestingly, both patients did not overreact with follitropin delta as there was only 1 follicle that was larger than 17 mm with AFC of 20 and 25. It is likely that dose equivalence method is safer compared to personalised dosing regimen for follitropin delta, but further studies are required to confirm this. The study's merits are its sizeable population, which made it possible to assess the in-depth perception of a sizable number of patients, and its application of the center's standard protocols and procedures, which replicates actual clinical practice. The limitation of the study was the absence of a comparative arm, potential biases from the retrospective design, and incomplete analysis of missing data. Although this may have added bias, it also mirrors a real-world clinical setting where patients present with a range of infertility etiologies. To the best of our knowledge, this study may be the first to assess the efficacy and safety of follitropin delta in its simplified dosage equivalent regimen in Indonesia women undergoing IUI

Study strengths and limitations

The strength of the study is to the best of our knowledge, this is the first study to assess the efficacy and safety of follitropin delta with simplified dosage equivalent regimen for ovarian stimulation in patient undergoing IUI in Indonesia and also in the world. The limitation of the study was the absence of a comparative arm, potential biases from the retrospective design, and incomplete analysis of missing data.

Conclusion

Our study showed that the new concept of follitropin delta with a simplified dosage equivalent method may improve the outcome of intrauterine insemination in Indonesian women undergoing IUI. These findings suggest a practical approach that we did not need to perform AMH Level testing because we use a simplified dose and this may improve accessibility and efficiency in fertility treatments, especially in resource-limited settings.

Future study should focus on comparing this method with traditional dosing regimens and exploring its impact on patient-centered outcomes such as satisfaction, emotional well-being, and quality of life. Additionally, prospective, controlled trials are needed to further validate these results and strengthen the evidence based.

Conflict of interests

The authors declare no conflict of interest regarding the publication of this article.

Authors' contributions

Conception and design of the study: BH, HPL
As Data collection: CAW

Data analysis and interpretation: HPL, CAW
Statistical analysis: HPL, CAW
Manuscript preparation: BH, HPL, CAW.

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