Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2025**; 52(11): 43781
https://doi.org/10.31083/CEOG43781

Original Research

Evaluation of the Follitropin Delta and Clomiphene Citrate Combination in Low Prognosis Women Undergoing *In Vitro* Fertilization: A Retrospective Study

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Academic Editor: Michael H. Dahan
Submitted: 13 June 2025 Revised: 20 August 2025 Accepted: 3 September 2025 Published: 26 November 2025

Abstract

Background: In assisted reproductive technology, particularly *in vitro* fertilization (IVF), optimizing ovarian stimulation protocols using individualized recombinant follicle-stimulating hormone (FSH) preparations, such as follitropin delta, has gained attention for its potential to improve treatment outcomes and reduce the risk of ovarian hyperstimulation syndrome (OHSS). This study aimed to evaluate the efficacy of combining follitropin delta and clomiphene citrate (CC) in women with a suboptimal response to ovarian stimulation using follitropin alpha during IVF. **Methods**: A retrospective study was conducted in women undergoing two consecutive IVF cycles at the Military Institute of Clinical Embryology and Histology, Vietnam. The first cycle utilized follitropin alpha, followed by a second cycle with follitropin delta plus CC. Embryological outcomes were assessed, including the number of stimulated follicles, the number of oocytes retrieved, and embryo quality at cleavage and blastocyst stages. A mixed-effects model with a negative binomial or Poisson distribution was applied to analyze repeated measurements within the same individual. **Results**: A total of 57 women were included in the final analysis. Following a suboptimal response to follitropin alpha, ovarian stimulation with follitropin delta plus CC resulted in a significant increase in the number of total day 3 embryos ($p = 0.018$), total day 5–6 embryos ($p = 0.017$), and good-quality blastocysts ($p = 0.028$). The number of stimulated follicles also showed a trend toward improvement ($p = 0.043$). No significant differences were observed in the number of oocytes retrieved or metaphase II (MII) oocytes. **Conclusions**: In women who previously demonstrated a suboptimal ovarian response, follitropin delta combined with CC was associated with improved embryological outcomes compared to conventional follitropins. These findings suggest that combining follitropin delta and CC may optimise ovarian response and embryo quality in this patient population. Further studies are warranted to confirm these results and assess the impact of this combination treatment on clinical pregnancy and live birth rates.

Keywords: *in vitro* fertilization; follitropin delta; ovarian stimulation; poor ovarian response; embryo quality

1. Introduction

In vitro fertilization (IVF) requires controlled ovarian stimulation to drive multiple follicle development and to optimize the number of retrieved oocytes. The regimen for controlled ovarian stimulation typically employs gonadotropins such as recombinant follicle-stimulating hormone (FSH), including follitropin alpha or follitropin beta, or human menopausal gonadotropin (hMG) [1–3]. Follitropin delta is a contemporary recombinant FSH analogue synthesized in a human cell line and can be administered at a dose calculated based on an algorithm that considers the anti-Müllerian hormone (AMH) level and body weight of each individual [4]. This is regarded as a step toward a more individualized ovarian stimulation in IVF. In recent years, numerous randomized controlled trials (RCTs) have assessed the clinical efficacy and safety of follitropin delta in IVF and have compared these findings with those for traditional gonadotropins [5–7]. The evidence from these investigations indicates that the individualized dosing strategy of follitropin delta can yield a comparable IVF success rate to conventional gonadotropin protocols [5–8]. Clinical outcomes from an IVF cycle, including clinical pregnancy, ongoing pregnancy, and live birth rates, are statistically comparable to those achieved with fixed-dose follitropin alpha/beta or urinary gonadotropin [5,6]. While some studies demonstrated that follitropin delta can yield a tendency for improved outcomes [5–7], a comprehensive meta-analysis revealed no significant difference in overall pregnancy outcomes [8]. Therefore, in terms of clinical IVF

practice, safety outcomes, e.g., ovarian hyperstimulation syndrome (OHSS), must be investigated in addition to the effectiveness before any new ovarian stimulation protocols are adopted. Recent RCTs consistently demonstrate a significantly reduced incidence of OHSS or excessive ovarian response following follitropin delta use compared to regular gonadotropins [5,6,8,9]. The finding regarding the improvement in safety outcomes associated with follitropin delta observed in the initial cycle may be extrapolated to subsequent treatment cycles [9]. This can be a therapeutically important benefit, as OHSS may result in hospitalization and the cessation of the cycle. Because the dose of follitropin delta is calculated based on serum AMH and body weight, it is necessary to validate the clinical effectiveness of follitropin delta across diverse groups of women based on these biomarkers. Alternatively, clomiphene citrate (CC) and letrozole have both been used with gonadotropins in poor responders and have been shown to reduce the amount of gonadotropin used without reducing the pregnancy rate [10].

Prior studies have directly compared follitropin delta with traditional gonadotropins as two separate arms and measured the outcomes in both groups. This parallel study design may introduce confounders due to inter-patient variability, including variations in age, ovarian reserve, and underlying fertility diagnoses. The clinical interpretation of this design illustrates how clinicians should select the type of gonadotropin in the first cycle, taking into account baseline characteristics. However, we argue that a pre–post design, wherein women are administered conventional follitropin (e.g., alpha or beta) in the first IVF cycle, followed by follitropin delta in the subsequent cycle, provides a substantial benefit by utilizing each participant as the control. This within-subject comparison may help mitigate the impact of differences in baseline characteristics and the potential for post-randomization bias [11], facilitating decision-making in the context of ovarian stimulation after a failed IVF cycle. Therefore, this study aimed to assess embryological outcomes using a pre-post design to evaluate whether the combination of follitropin delta and CC offers advantages over follitropin alpha in women with a low prognosis.

2. Materials and Methods

2.1 Study Design

This retrospective study recruited 57 women undergoing two IVF cycles at the Military Institute of Clinical Embryology and Histology in Vietnam, from January 2024 to December 2024. The initial IVF cycle was initiated with follitropin alpha, followed by follitropin delta plus CC in the subsequent cycle. All participants had provided written informed consent for their clinical data to be used for research purposes, in accordance with the ethical principles delineated in the Declaration of Helsinki [12].

2.2 Study Population

This study involved a retrospective review of medical records and laboratory databases from the Military Institute of Clinical Embryology and Histology. Eligible participants included women aged 18 to 40 years diagnosed with poor ovarian response (POR) according to the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) criteria [13], characterized by maternal age, ovarian reserve indicators (antral follicle count (AFC) <5 and/or AMH <1.2 ng/mL), and prior ovarian response to stimulation (≤ 9 oocytes retrieved). All women were included, regardless of whether their cycle was canceled before oocyte retrieval. The exclusion criteria included: IVF cycles performed for indications other than infertility; cycles utilizing *in vitro* maturation; cycles using spermatozoa from different male partners across the two treatment cycles.

2.3 Methods

2.3.1 Controlled Ovarian Stimulation

In this retrospective analysis, ovarian stimulation protocols were initiated on the second day of the menstrual cycle, with either gonadotropin-releasing hormone antagonist (GnRHanta) protocols (Cetrotide [Merck Serono, Darmstadt, Germany] or Orgalutran [MSD, Haarlem, Netherlands]) or progesterone-primed ovarian stimulation (PPOS) protocols (Utrogestan [Besins Healthcare, Paris, France]).

Follitropin alpha (Gonal-F [Merck Serono, Darmstadt, Germany]) was utilized to stimulate multifollicular growth in the first IVF cycle. The initial gonadotropin dosage was tailored, varying from 150 to 300 international units (IU), depending on ovarian reserve, maternal age, and prior ovarian stimulation history. Recombinant FSH was provided alongside menotropin at a dosage of 75 IU per day (IVF-M [LG Chem, Seoul, South Korea]). Serial transvaginal ultrasonography was utilized to assess ovarian response, facilitating necessary dosage adjustments. In the following IVF cycle, follitropin delta (Rekovelle [Ferring Pharmaceuticals, Copenhagen, Denmark]) was delivered at a constant daily dosage of 18 µg. Additionally, CC (Clomid [Sanofi, Paris, France]) was prescribed at a dose of 100 mg/day for five days, starting on the second day of the cycle. No luteinizing hormone (LH) supplementation was administered during the second cycle.

Final oocyte maturation was initiated with the presence of a minimum of two follicles with diameters above 17 mm, via subcutaneous administration of 0.25 mg recombinant human chorionic gonadotropin (Ovitrelle [Merck Serono, Darmstadt, Germany]). Cycle cancellation due to follicular arrest during ovarian stimulation was defined by the absence of follicles over 12 mm in diameter on day 8 of gonadotropin administration.

2.3.2 Oocyte Retrieval and Embryo Culture

Oocyte retrieval was performed at 36 hours after the oocyte maturation trigger, utilizing intravenous anesthesia and transvaginal ultrasound-guided follicular aspiration. The aspirated follicular fluid was promptly transported to the laboratory for the retrieval of oocytes. All identified oocytes were fertilized using intracytoplasmic sperm injection (ICSI). Embryos were cultured till the cleavage or blastocyst stage.

2.3.3 Outcomes

The outcomes of this study included the daily dose of gonadotropin, total dose of gonadotropin, duration of stimulation, estradiol level at the trigger day, number of oocytes retrieved, fertilization rate (determining two pronuclei divided by the number of oocytes retrieved), the number and quality of embryos at cleavage according to the Istanbul consensus [14], and the blastocyst stages based on Gardner's criteria [15,16]. "Good-quality" blastocysts were defined following the classification described by Munné S *et al*. [17], which considers blastocysts with an expansion stage $\geq$3, inner cell mass, and trophectoderm grades AA, AB, and BA as good quality.

2.4 Statistical Analysis

Descriptive statistics were performed for baseline characteristics and outcomes, including the mean and standard deviation, or median and interquartile ranges, as appropriate, for continuous variables. Categorical variables were characterized using numerical values and proportions.

Due to the discrete nature of the embryology outcomes in our investigation and the possibility of overdispersion, employing linear models may yield erroneous standard errors and skewed parameter estimates, thereby exacerbating type I error rates [18–20]. Identifying the optimal distribution for count variables is required to ensure that model assumptions accurately represent the underlying data structure, thereby facilitating more valid inferences. Applying an incorrect distribution can jeopardize the accurate interpretation of impact sizes and significance levels, thereby compromising the validity of the study [19]. Furthermore, we evaluated these outcomes as raw counts instead of percentages (e.g., fertilization rate) due to the nature of this pre-post study, which assesses each outcome at two time points within the same individual. Model fit was confirmed through both visual inspection of worm plots and a quantitative analysis of residual z-scores. This validation process confirmed an excellent fit for all models, with no evidence of significant systematic deviation or the presence of extreme statistical outliers (defined as $|\text{z-score}| > 3$) [21]. The final count distribution for each outcome was determined empirically by comparing candidate models (Poisson, negative binomial, zero-inflated Poisson [ZIP], and zero-inflated negative binomial) via the Akaike information criterion (AIC). The ZIP model yielded the lowest AIC across all seven outcomes, indicating a substantial excess of zero counts in the data, and was, therefore, selected for all final analyses.

In addition to determining the optimal distribution for each outcome, we also developed multivariable mixed-effects models to account for repeated observations within the same cohort. Due to the pre-post design, in which each woman is assessed during two IVF cycles, a mixed-effects framework was more appropriate than a fixed-effects model. This method designates random intercepts for individuals, thereby addressing within-subject correlation and encapsulating variation resulting from repeated measurements on the same participant across time. The models used female age, type of infertility, duration of infertility, serum AMH level, female body mass index (BMI), and the time interval between consecutive cycles as covariates. We incorporated a covariate denoting the cycle as a fixed effect to compare outcomes between the two IVF cycles. The coefficient for this variable measured the changes in the log link function between the first and second cycles, while controlling for all other factors. By combining this fixed effect with a random intercept for each woman, the models effectively account for individual-level variability while isolating the overall impact of cycle number on the outcomes. The link functions of the models with the three possible distributions indicate that a positive coefficient for the cycle indicator variable (ovarian stimulation transitions from follitropin alpha to follitropin delta) signifies a positive correlation with embryology outcomes. The mixed-effects count models in our study were fitted with a log link, meaning each regression coefficient (β) represents the natural logarithm of an incidence–rate ratio (IRR). To facilitate clinical interpretation, we converted the β coefficients into IRRs through the exponentiate function ($\text{IRR} = e^{\beta}$).

All statistical analyses were conducted using R programming, with a significance threshold established at $p < 0.05$. The package gamlss (Generalized Additive Models for Location, Scale, and Shape) was used to construct the model [22].

3. Results

3.1 Participants Characteristics

A total of 57 women participated in ovarian stimulation over two consecutive IVF cycles utilizing follitropin alpha and follitropin delta plus CC, respectively, between January and December 2024. Table 1 delineates the baseline characteristics of the studied population. The population had a mean female age of 36.5 $\pm$ 4.4 years and a mean BMI of 22.2 $\pm$ 2.2 kg/m^2. The majority of the studied population experienced secondary infertility (86.0%), with a median infertility duration of 4.0 years. The mean serum AMH level was 1.4 $\pm$ 1.0 ng/mL, and the median AFC was 8, IQR [2–19].

Table 1. Baseline characteristics of the included women.

Baseline characteristics	Value
Female age (years)	36.5 (4.4)
Female BMI (kg/m^2)	22.2 (2.2)
Type of infertility	
Primary	8 (14.0%)
Secondary	49 (86.0%)
Duration of infertility (years)	4.0 [0, 10.0]
AMH (ng/mL)	1.4 (1.0)
AFC	8 [2–19]
Time interval between two cycles (days)	28 [24–56]

Values are presented as the mean (standard deviation), median [min.–max.], or n (%), as appropriate.
BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count.

3.2 Characteristics of Ovarian Stimulation and Embryological Outcomes

The ovarian stimulation characteristics of the studied population are delineated in Table 2 (Ref. [19]). During the initial cycle, ovarian stimulation commenced with an average daily recombinant FSH dosage of 300 [300–300] IU, whereas the mean total recombinant FSH and menotropin dosages were 3000 [2475–3000] IU and 750 [450–750] IU, respectively. During the second cycle, the women received a mean total follitropin delta dose of 180 [180–198] µg. The paired analysis indicated that the duration of ovarian stimulation in the first cycle was shorter than in the second cycle (p = 0.004). The serum estradiol levels on the trigger day were similar in the two cycles (1775.0 [1216.0–2890.0] and 2058.0 [1478.5–2758.0], respectively; p = 0.357).

3.3 Results From Multivariable Mixed-Effect Models

As shown in Table 3, direct pairwise unadjusted comparisons revealed that the second treatment protocol yielded a significantly greater number of stimulated follicles (p = 0.042) and total day 3 embryos (p = 0.028). No significant differences were observed for other outcomes, including the number of oocytes retrieved and the number of good-quality embryos on days 5–6. To examine the adjusted associations between IVF cycles and embryology outcomes, mixed-effects multivariable models with negative binomial or Poisson distributions were constructed based on the distributions that best fit each outcome. The results from these models are shown in Table 4.

The analyses showed trends of increases in the number of stimulated follicles (p = 0.043), number of day 3 embryos (p = 0.018), number of day 5–6 embryos (p = 0.017), and number of good quality day 5–6 embryos (p = 0.028) between in the cycle with follitropin delta compared with the cycle stimulated by follitropin alpha. There was no difference in the number of $\geq$14 mm stimulated follicles, the number of oocytes retrieved, and the number of MII oocytes. Stimulation with follitropin delta in the second cycle resulted in a 42% increase in day 3 embryo yield and an approximate two-fold rise in good-quality blastocysts at days 5–6 compared with the preceding follitropin alpha cycle (IRRs: 1.42 and 1.90, respectively). An incremental increase was also observed in total stimulated follicles (+16%, IRR: 1.16; p = 0.043), whereas the increases in follicles $\geq$14 mm, total oocytes retrieved, and matured oocytes retrieved (IRRs: 1.12, 1.11, and 1.22, respectively) did not reach statistical significance.

4. Discussion

This study evaluated the embryological outcomes of IVF cycles stimulated with the combination of follitropin delta and CC in a cohort of women who previously had suboptimal responses to stimulation with follitropin alpha. Using a pre-post study design, we observed an improvement in embryology outcomes, including a significant increase in the number of day 3 embryos, day 5–6 embryos, and good-quality blastocysts from follitropin delta plus CC cycles compared to follitropin alpha cycles. These findings suggest that follitropin delta may offer advantages in embryology quality over conventional gonadotropins, particularly in patients who have previously demonstrated suboptimal responses to ovarian stimulation.

The study results are consistent with previous findings, which indicate that follitropin delta produced superior embryological outcomes compared to traditional gonadotropins. Prior RCTs documented that follitropin delta provided comparable pregnancy rates to follitropin alpha while reducing the occurrence of OHSS through its tailored dosing approach [9,23].

The findings of this study differed from certain other meta-analyses, indicating no substantial difference in blastocyst quantities between follitropin delta and conventional gonadotropins [8]. Therefore, these improvements in embryological outcomes may be attributed to the pre-post design of this study, wherein each participant acted as their own control, thereby reducing interpatient variability. Moreover, our cohort comprised women who had previously shown a suboptimal response to follitropin alpha, indicating that follitropin delta may be particularly beneficial for this subgroup.

A plausible explanation for the increase in the number of high-quality blastocysts in our study is the enhanced follicular recruitment and synchronization noted with follitropin delta plus CC. Prior pharmacokinetic investigations have shown that follitropin delta demonstrated reduced FSH clearance and prolonged action compared to recombinant FSH sourced from Chinese hamster ovary cells [4]. This pharmacodynamic profile may have resulted in more uniform follicles.

The pre-post design used in this study represents a major strength since this design facilitated a direct comparison of ovarian stimulation regimens within the same woman. This design clarified the impact of alterations in

Table 2. Ovarian stimulation characteristics in the two cycles of the included women.

Treatment outcomes	Follitropin alpha cycle	Follitropin delta and CC cycle	*p*
Initial rFSH dose (IU)	300 [300–300]	NA	NA
Total rLH dose (IU)	750 [450–750]	NA	NA
Total rFSH dose (IU)	3000 [2475–3000]	180 [180–198] µg(2)	0.408(1)
Duration of ovarian stimulation (days)	10 [8–10]	10 [10–11]	0.004(1)
Estradiol level at the trigger day (pmol/L)	1775.0 [1216.0–2890.0]	2058.0 [1478.5–2758.0]	0.357(1)

Values are presented as the median [IQR] as appropriate.

LH, luteinizing hormone; rFSH, recombinant follicle-stimulating hormone; rLH, recombinant luteinizing hormone.

(1): Wilcoxon-signed rank paired test.

(2): 10 µg follitropin delta was equivalent to 150 IU follitropin alpha [19].

NA, not applicable.

Table 3. Embryology outcomes in the two cycles of the included women.

Embryology outcomes	Follitropin alpha cycle	Follitropin delta and CC cycle	*p*
Number of stimulated follicles	6 [4–10]	7 [5–11]	0.042
Number of stimulated follicles ≥14 mm	4 [3–7]	5 [3–8]	0.211
Number of oocytes retrieved	4 [2–7]	4 [2–7]	0.313
Fertilization rate	3 [1–5]	3 [2–6]	0.159
Number of total day 3 embryos	2 [1–3]	2 [1–5]	0.028
Number of total day 5–6 embryos	2 [1–3]	2 [1–5]	0.055
Number of day 5–6 good quality embryos	0 [0–1]	0 [0–1]	0.021

Data are presented as the median and interquartile range [IQR].

Statistical tests were Student's paired *t*-test or Wilcoxon signed rank test, depending on the distribution of the difference between the two cycles of each outcome.

Table 4. The differences in embryology outcomes between the two cycles.

Embryonic outcomes	Coefficients	IRR	95% CI IRR	*p**
Number of stimulated follicles	0.145	1.16	1.01–1.33	0.043
Number of stimulated follicles ≥14 mm	0.112	1.12	0.90–1.39	0.307
Number of oocyte retrieved	0.109	1.11	0.88–1.41	0.371
Number of MII oocyte	0.196	1.22	0.92–1.60	0.165
Number of total day 3 embryos	0.348	1.42	1.07–1.88	0.018
Number of total day 5–6 embryos	0.302	1.35	1.06–1.72	0.017
Number of day 5–6 good quality embryos	0.641	1.90	1.08–3.33	0.028

*: Multivariable mixed-effect model adjusted for female age, female body mass index, type of infertility, duration of infertility, AMH, and time interval between the two cycles.

IRR, incidence rate ratio.

gonadotropin regimen on embryological outcomes by removing interpatient variability. To our knowledge, this was the first pre-post study to evaluate the effectiveness of follitropin delta, combined with CC, in patients who had previously responded suboptimally to follitropin alpha.

This research has some limitations. The primary limitation of this study is its modest sample size. A post hoc power analysis suggests that this study was underpowered, particularly for detecting small to moderate effects (data not shown). Consequently, while we observed a statistically significant increase in the number of high-quality embryos, the precise magnitude of this effect should be interpreted with caution, as it may represent an overestimation of the actual impact. Our analysis involved assessing seven related embryological outcomes. While a strict statistical correction (e.g., Bonferroni) was not applied due to the highly correlated nature of these endpoints within a single biological pathway, we acknowledge that this approach carries a potential risk of an inflated Type I error. Therefore, our findings should be considered exploratory and hypothesis-generating, underscoring the urgent need for larger, prospective randomized trials to confirm these promising results and provide a more precise estimate of the treatment effect.

Another limitation of our study is the retrospective pre-post design. Although the mixed-effects models in our research minimize interpatient variability, it is susceptible to a potential cycle sequence effect from the initial stimula-

tion cycle. Although we managed to adjust for this effect by adding the time interval between cycles as a covariate, we cannot completely exclude the possibility that prior ovarian stimulation influenced the outcomes of the second cycle.

The lack of an external control group was also a limitation of the study. A comparative analysis with women who received follitropin alpha in their second cycle would yield a more thorough evaluation of the relative efficacy of follitropin delta combined with CC. A parallel design was necessary to compare outcomes as study participants transitioned from follitropin delta cycles to follitropin alpha cycles. Nevertheless, our within-subject comparison mitigated numerous confounding variables that commonly influence parallel-group research, including baseline ovarian reserve and individual heterogeneity in response to gonadotropins.

This study was limited in that it focused solely on embryological outcomes and did not provide evidence on pregnancy outcomes, including live birth rates. Although improved embryo quality was a beneficial aspect, it remained uncertain if these improvements could be translated into improved pregnancy outcomes. Hence, further research investigating implantation rates, clinical pregnancy rates, ongoing pregnancy rates, and live birth rates [24,25] is essential to ascertain the comprehensive clinical effects of follitropin delta plus CC.

One of the statistical issues with modeling count outcomes is the presence of zero-inflation and overdispersion. To confirm the robustness of this key finding on the day 5 good-quality embryo outcome, a sensitivity analysis using a zero-inflated negative binomial (ZINB) model was performed. This model yielded a result (IRR: 2.00; 95% CI 1.11–3.59), which was highly consistent with that of the ZIP model. Therefore, the more parsimonious ZIP model was retained for the final analysis based on its lower AIC. Our study investigated seven downstream embryological outcomes of an IVF cycle. A strict statistical correction (e.g., Bonferroni) was not applied, as formal correlation analysis confirmed that the seven outcomes are highly interdependent (e.g., Spearman's r $>$0.80 between sequential endpoints), violating the assumption of independence required for such corrections.

The findings of this study have numerous clinical implications. Indeed, a key finding of this study was that the second cycle, combining follitropin delta and CC, resulted in a statistically significant increase in the number of total day 3 embryos and, most notably, a nearly two-fold increase in the rate of good-quality day 5–6 embryos (IRR: 1.90). While this did not stem from a significantly larger pool of retrieved oocytes, the downstream improvement in embryo yield is of high clinical relevance. The value of each additional embryo, particularly at the blastocyst stage, is well-established. Large-scale data show a direct correlation between the number of usable blastocysts and the cumulative live birth rate, with each additional blastocyst providing a patient with an extra, distinct opportunity for transfer and conception [26]. Thus, the enhanced ability to generate high-quality blastocysts, as observed in our study, represents a clinically significant outcome that can potentially improve the overall chance of success for each patient from a single stimulation cycle. Another important clinical consideration is the potential safety benefits of follitropin delta combined with CC. Previous studies have reported a lower risk of OHSS with follitropin delta compared to conventional gonadotropins [9]. Although our study did not specifically assess OHSS incidence, the use of follitropin delta, which allows for individualized dosing regimens, may contribute to a safer approach to ovarian stimulation [9].

5. Conclusions

In summary, this study provides novel insights into the use of a combination of the follitropin delta and CC in women undergoing IVF with a prior suboptimal response to follitropin alpha. The findings suggest that follitropin delta combined with CC may result in better embryo quality, potentially improving IVF success rates in this specific population.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conception and design: HDT, STT and TNT; Administrative support: DKN; Provision of study materials or patients: TNT and STT; Collection and assembly of data: HDT, NNN, TTV and PNM; Data analysis and interpretation: HTMP, TQV, TVT, HHS and DKN. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All participants had provided written informed consent of their clinical data to be used for research purposes, in accordance with the ethical principles delineated in the Declaration of Helsinki. This study received approval from the Institutional Ethics Committee of the Vietnam Military Medical University under approval number 01/2024/CNChT-HĐĐĐ dated August 6, 2024.

Acknowledgment

The authors wish to thank all staffs at the Military Institute of Clinical Embryology and Histology for helping the data collection.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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