Clinical outcomes of ovarian stimulation with follitropin delta in a mixed regimen with HP-hMG: a real-world retrospective analysis

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ABSTRACT

Introduction: Optimising controlled ovarian stimulation (COS) procedures for in vitro fertilisation (IVF) requires an assessment of the patients' medical history, ovarian reserve, prognostic factors and resources to personalise the treatment plan. Treatment personalisation in IVF is increasingly recognised as being vital in providing a balance of efficacy and safety for patients undergoing the COS procedure. In this study, we aimed to assess the efficacy of an ovarian stimulation protocol employing a personalised dosing algorithm for a novel recombinant FSH (rFSH) derived from a human cell-line - follitropin delta, in a mixed gonadotrophin regimen with human menotrophin (HP-HMG). The main outcome of interest in this study is clinical pregnancy rate (CPR) per embryo transfer cycle.

Materials and Methods: In this single-centre, retrospective, non-interventional study of 20 infertility patients, each individual was provided with a personalised COS regimen based on her ovarian reserve biomarker—serum anti-Mullerian hormone (AMH) and body weight, in a gonadotrophin-receptor hormone (GnRH) antagonist protocol. Personalised dosing of follitropin delta was co-administered with 75 IU of HP-hMG during the COS duration until the final oocyte maturation trigger injection. Ovarian response, pregnancy and safety outcomes resulting from this procedure were assessed and reported here.

Results: Following a mean COS duration of 11 days and 50% of patients who underwent frozen embryo transfers, the CPR per started cycle was 70%. The observed CPR from this study was higher than that reported in the follitropin delta Phase 3 studies using rFSH monotherapy stimulation, and additionally showed no incidents of cycle cancellations and no iatrogenic safety risks such as ovarian hyperstimulation syndrome.

Conclusion: The present study provides a first glimpse into the favourable benefit: risk profile of a mixed protocol regimen using follitropin delta combined with HP-hMG in a cohort of Asian patients in Malaysia.

KEYWORDS:
Assisted reproductive technique, follicle stimulating hormone (FSH), follitropin delta, in vitro fertilisation (IVF), menotropins, ovarian stimulation

INTRODUCTION

The aim of controlled ovarian stimulation (COS) with gonadotrophins for in vitro fertilisation (IVF)/intracytoplasmic sperm injection (IVF/ICSI) is to obtain an adequate number of competent oocytes, leading to improved pregnancy outcomes with minimum risks for the women. However, individual variability in the ovarian and endocrine responses is a well-recognised phenomenon in patients undergoing COS who are given standard doses of recombinant follicle-stimulating hormone (rFSH). This is due to differences in each woman's functional ovarian reserve, genetics and ovarian ageing.[1] It is therefore important to individualise gonadotrophin dosing to tailor the ovarian stimulation according to each patient's profile. The aim of this is to improve the predictability of the ovarian response as well as to eliminate iatrogenic risks, such as ovarian hyperstimulation syndrome (OHSS) or cycle cancellations due to poor response.[2,3]

Follitropin delta (FE 999049, Rekovelle®) is the first recombinant human FSH expressed from a human cell line (PER.C6), resulting in improved stability and higher biopotency compared to other existing rFSH preparations.[4] A unique feature of follitropin delta is its' dosing algorithm which enables treatment personalisation for each individual based on the serum biomarker anti-Mullerian hormone (AMH) and body weight.[4-6] Importantly, this dosing algorithm which was developed specifically for follitropin delta, has been validated in large clinical trials in both the Asian and Caucasian populations.[7,8]

The aim of this non-interventional study is to retrospectively assess the preliminary clinical outcomes resulting from a 'mixed protocol' COS treatment using a combined stimulation with an individualised dosing regimen of follitropin delta and highly purified human menotrophin (HP-hMG) (Menopur®) in the local clinical setting with Asian patients.

The rationale for using a mixed protocol regimen with HP-hMG in COS is due to its evidence of improved clinical outcomes among patients with decreased ovarian reserve or in patients with inadequate response in previous cycles.[9,10] Specifically, HP-hMG (Menopur®) is the only FDA-approved menotrophin with a robust evidence base for application in COS, which provides hCG-driven LH activity during ovarian stimulation and is associated with a higher proportion of mature oocytes and top-quality embryos.[9-15]

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MATERIALS AND METHODS

This was a single-centre, retrospective case series study assessing the efficacy and safety of follitropin delta (Rekovelle®) in combination with HP-hMG (Menopur®) for COS among infertile women aged ≥18 years, who visited the Sunfert International Fertility Centre from July 2021 to February 2023. This study was carried out in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and is approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH). All women were provided written informed consent as part of the retrospective recruitment process. Women were recruited only after the decision to treat with follitropin delta had been made and there was no interference with routine clinical procedures. All data were collected as part of routine clinical practice.

All patients in this study who fulfilled the criteria for ovarian stimulation with a gonadotropin-releasing hormone (GnRH) antagonist protocol were treated with a mixed protocol regimen combining HP-hMG (Menopur®) with a fixed personalised daily subcutaneous dose of follitropin delta.

Two separate syringes were used to co-administer both types of gonadotrophins to all patients - HP-hMG in combination with follitropin delta, with follitropin delta administered at personalised doses determined by an established algorithm based on body weight and serum AMH level.[6] The dose of follitropin delta for each patient may also be conveniently calculated using its online calculator (https://dosedelta.ferring.com/appStart). In contrast to other gonadotrophins, follitropin delta is dosed in µg units instead of International Unit (IU) - which provides a better expression of the biopotency of this new rFSH. As this was a real-world study, physicians were allowed to adjust the doses of gonadotrophins during COS based on clinical discretion. In the case of follitropin delta, any deviation within ± 0.66µg of the calculated dose is considered to be within the range of the drugs' algorithm. The reason for choosing the value of ± 0.66µg is because this corresponds to two minor dial clicks on the Rekovelle® prefilled pen.

All serum AMH measurements were performed within the Sunfert International Fertility centre using the automated Elecsys AMH immunoassay (Roche) as routine baseline clinical evaluation before COS. AMH measurements for all patients are within 12 months prior to the date of starting COS to be considered valid.

Gonadotropin therapy was initiated on day-2 of the menstrual cycle. A gonadotropin-releasing hormone (GnRH) antagonist was initiated on day-6 of stimulation and continued throughout the remainder of stimulation. The response to stimulation was monitored via transvaginal ultrasound (TVUS). HP-hMG (Menopur®) was initiated from day-1 of stimulation at a dose of 75IU, with adjustments of the menotrophin dosing permitted from day-6 of the stimulation cycle. HP-hMG was administered concomitantly with an individualised dose of follitropin delta calculated from the dosing algorithm. In contrast to HP-hMG, no dose adjustments were permitted for follitropin delta throughout the stimulation cycle.

The choice of triggering medication was decided based on serum estradiol (E2) levels; hCG 5,000–10,000 IU was administered if E2 <15,000pmol/L, and GnRH agonist 0.2 mg triptorelin acetate (Decapeptyl®) was given if E2 ≥15,000 pmol/L. A dual trigger of subcutaneous 1,000 IU hCG plus SC 0.2 mg triptorelin acetate may also be administered in patients with low serum LH levels (≤1.0mIU/ml) at the day of trigger. Oocyte retrieval was scheduled 36 hours (±1 hour) after triggering final follicular maturation and injected with ejaculated sperm from a partner. When frozen transfer was indicated, all embryos were cultured to blastocysts, and pre-implantation genetic testing (PGT) for aneuploidy (PGT-A) or monogenic disease (PGT-M) was conducted in cases planned for PGT. All usable blastocysts were cryopreserved for future use. Usable blastocysts are defined as grade 3CC and above according to the modified Gardner grading criteria for blastocyst scoring. Any embryos with a grading of at least one X is not considered usable (Table I). Top-quality blastocysts are defined as those with blastocyst expansion and hatching status 4-6, inner cell mass (ICM) grade A or B, and trophectoderm (TE) grade A or B.

In the frozen cycles, one or two blastocysts could be transferred according to the discretion of the treating physician. The number of thawed blastocysts transfer was determined by age and blastocyst quality, with transfers limited to either one or two blastocysts.

Both natural cycle and programmed regimens were allowed. Daily vaginal progesterone insert (VPI) was prescribed for luteal phase support, with oral dydrogesterone 10 mg tds, according to routine practice of each physician.

The main outcome of interest in this real-world study was clinical pregnancy rate (CPR) at the first transfer cycle. Clinical pregnancy was defined as a pregnancy documented by transvaginal ultrasonography (TVUS) at 6-8 gestational weeks, showing a gestational sac inside the uterus sac with evidence of a fetal heartbeat, excluding all ectopic and biochemical pregnancies. Clinical pregnancy rate was defined as the number of clinical pregnancies divided by the number of embryo transfer cycles. Implantation rate is defined as the number of intrauterine gestational sac(s) (IUGS) observed through TVUS at 3–5 weeks post-transfer divided by the number of embryos transferred.

RESULTS

Baseline Characteristics

A total of 20 patients who attended the Sunfert International Fertility Centre between July 2021 and February 2023 were included in this analysis of our first experience with the novel rFSH follitropin delta used in a mixed protocol stimulation (Table II). Their mean age was 35.2 years; four (20.0%) patients were aged ≥40 years. A majority of subjects were of Chinese ethnicity (80.0%). The study subjects' mean serum AMH level was 26.0±14.71pmol/L, with a mean antral follicle count of 13.0±4.35. Out of this total cohort, two women (10%) were at risk of a hyporesponse to ovarian stimulation on the basis of their low serum AMH level <15pmol/L, while a total of 5 (25%) women were considered high-responders based on their AMH level ≥35pmol/L. The most predominant aetiology for infertility was polycystic ovary syndrome

Table I: The modified Gardner classification scheme (ICM – inner cell mass)

ICM grade	Description	Usability
A	Many cells forming a large compacted ICM	Yes
B	Moderate number of ICM cells, moderate ICM compaction	Yes
C	Few ICM cells, limited ICM compaction or ICM poorly distinguished	Yes
X	No ICM visible or degenerate ICM	No

Table Ib: The modified Gardner classification scheme (TE – trophectoderm)

TE grade	Description	Usability
A	Many cells forming a cohesive TE network (>80 TE cells)	Yes
B	Moderate number of TE cells forming a cohesive network (40-80 cells), some gaps or large TE cells may be apparent	Yes
C	Few TE cells (15-40), large TE cells, irregular network, some unclear TE cell boundaries	Yes
X	Very few TE cells (<15), unclear TE cell boundaries, degenerative or fragmented TE	No

Table II: Demographics and baseline characteristics

Characteristic	
Total number of patients	20
Age (years)	35.2±4.47
Women < 35 years (n, %)	9 (45.0%)
Women 35–40 years (n, %)	12 (60.0%)
Women > 40 years (n, %)	3 (15%)
Race:	
Malay (n, %)	2 (10.0%)
Chinese (n, %)	16 (80.0%)
Indian (n, %)	1 (5.0%)
Others (n, %)	1 (5.0%)
Body weight (kg)	58.3±8.22
BMI (kg/m^2)	23.4±3.67
AMH (pmol/L)	26.0±14.71
AMH (pmol/L)	20.1 (16.0 - 32.7)
AFC - for both ovaries (n)	13.0±4.35
Infertility history	
Duration of infertility (mo)	54.0±32.31
Primary infertility	11/20 (55.0%)
Primary etiology	
Tubal infertility (%)	3/20 (15.0%)
Male infertility (%)	3/20 (15.0%)
Unexplained (%)	3/20 (15.0%)
PCOS (%)	5/20 (25.0%)
Endometriosis (%)	1/20 (5.0%)
Others (%)	4/20 (20.0%)
Smoking (n, %)	1/20 (5.0%)
Number of first IVF/ICSI cycles	16/20 (80.0%)
Number of repeat IVF/ICSI cycles (non-naïve)	4/20 (20.0%)

Values are mean±SD, median (interquartile range), or number (percentage), unless stated otherwise.

(Rotterdam criteria) (25.0%); followed by aetiology classified as 'others' (20%). Of the women classified under 'others', one was a potential carrier of a monogenic disorder, one had endometrial cancer, one had unexplained anovulation and another had a bicornuate uterus. Most women (80.0%) were undergoing their first assisted reproductive technology (ART) cycle. None of the subjects had oral contraceptive (OCP) pre-treatment prior to their IVF/ICSI cycle.

Ovarian Response and Safety

All patients were administered follitropin delta in combination with HP-hMG in a mixed protocol stimulation regimen. With regards to follitropin delta, a majority of patients (75%) were dosed according to the specified dosing algorithm, while most of the remaining subjects (20%) were administered an average of 20% higher doses than recommended by the algorithm (range Δ 13.4-23.8µg).

A majority of subjects (95.2%) started with HP-hMG from Day-1 of stimulation, with mean daily dose of HP-hMG administered per subject of 65.2±10.94IU (Table III). The mean duration of ovarian stimulation was 11.0±1.16 days. As this was a mixed stimulation regimen, the mean total dose of follitropin delta co-administered was 96.6±28.2µg, which is approximately equivalent to 1449.0IU of gonadotrophin. Depending on follicular development, some patients were administered a step-down dosing of HP-hMG to mitigate the risk of hyperstimulation (75 IU every alternate

Table III: Ovarian response and pregnancy outcomes

Total patients	20
Duration of stimulation (days)	11.0±1.16
Average daily dose of follitropin delta (mcg)	9.0±2.50
Average total dose of follitropin delta (mcg)	96.6±28.18
Women dosed according to follitropin delta algorithm	15/20 (75%)
Average daily dose of HP-hMG (IU)	65.2±10.94
Average total dose of HP-hMG (IU)	714.3±137.52
Percentage starting HP-hMG from D1 of OS	20/20 (95.2%)
No of cancelled cycles (n, %)	0/20 (0%)
Triggering of final oocytes maturation	
hCG	11/20 (52.4%)
GnRHa	10/20 (47.6%)
No of oocytes retrieved (n)	13.2±6.43
Poor responders (< 4 oocytes) (n, %)	0/20 (0%)
Excessive responders (≥ 20 oocytes) (n, %)	3/20 (15.0%)
Target ovarian response (8–14 oocytes) (n, %)	14/20 (70.0%)
No of MII oocytes (n)	10.8±5.23
Type of fertilization	
IVF	0
ICSI	21
Fertilization rate (%)	67.9±19.93
Blastulation rate (%)	62.6±25.42
Blastocysts:	
Total (n)	5.3±3.52
Top quality (n)	2.4±1.75
≥ 2 cryopreserved blastocysts per cycle start (n, %)	18/20 (90.0%)
No of patients who have undergone embryo transfers (n):	10
Fresh	0
Frozen	10
Average number of embryos per-transfer (n)	1.1±0.32
Implantation rate (%)	72.7%
Clinical pregnancy rate per transferred cycle (n, %)	7/10 (70.0%)
OHSS - any grade (n)	0/20 (0%)

Values are mean±SD, median (interquartile range), or number (percentage), unless stated otherwise.

day). If we consider the total dose of gonadotrophin used in this real-world analysis, the sum of the combined administration of both follitropin delta and HP-hMG over an average 11 days of ovarian stimulation is significantly lower than the dosing employed in a conventional protocol ovarian stimulation in our clinic (3164.1±456.08IU vs. 2162.7±469.42 IU; p<0.0001; 95% confidence interval 679.0911, 1323.7089) (Table IV). This comparison of gonadotrophin dose consumption was based on analysis of our historical records of patients with similar baseline characteristics (follow up from Aug 2021-Jan 2023) as a control group reference.

All fertilisation was done by ICSI and resulting embryos were cultured to stage Day 5/6 blastocysts. All blastocysts were vitrified according to standard clinic procedures. At the point of reporting, a total of 10 subjects underwent frozen blastocysts transfer.

For the main outcome of interest in this real-world study, CPR at the first transfer cycle was 70.0% (Table III); most were singleton pregnancies, except for one live birth resulting in twins (from double embryo transfer). Embryos implantation rate (IR) was also similar at 70.0%. In terms of other secondary outcomes, the mean number of total oocytes and metaphase II (MII) oocytes retrieved were 13.2±6.43 and 10.8±5.23, respectively. There were no cycle cancellations (either owing to hyporesponsiveness or risk of hyperstimulation), and no incident ovarian hyperstimulation syndrome (OHSS) among the subjects. Fertilisation and blastulation rates were 62.2%±18.21 and 63.9%±24.11, respectively. Eighteen patients (90%) had at least two or more cryopreserved blastocysts resulting from their first COS cycle.

DISCUSSION

This study represents the first real-world analysis of a combined stimulation protocol with follitropin delta and HP-hMG in a Malaysian population of patients with infertility. In the pivotal Phase III trials - ESTHER-1 and GRAPE, conducted in Caucasian and Asian subjects, respectively, the CPR in these studies were 34.9% and 36.1%.[7,8] The observed CPR per transfer cycle in this study was 70%, which was approximately double the rates reported in the aforementioned trials. There were several salient differences in the protocol and patient populations in both ESTHER-1 and GRAPE compared to our study. In brief, in both of these trials, follitropin delta was administered as a monotherapy COS for a non-inferiority efficacy comparison with conventional rFSH follitropin alfa,[7,8] whereas we employed the mixed protocol stimulation in our study. Pregnancy outcomes were reported following a fresh transfer cycle of either Day 5 (ESTHER-1) or Day 3 (GRAPE) embryos; but in our study, CPR was reported solely from frozen transfer cycles of Day 5/6 blastocysts. Additionally, the mean age of the patients in our study was higher (35.2 years vs. 31.1 years) with a lower median serum AMH (20.1pmol/L vs. 23.4pmol/L) compared to the Asian GRAPE study.[7] This was

Table IV: Comparison of baseline characteristics and ovarian response with historical control group

	Control group	Study group	P valuea	95% CI
Total number of patients	15	20		
Age (years)	33.7±2.46	35.2±4.47	0.2501	-1.1068, 4.1068
Women < 35 years (n, %)	10 (66.7%)	9 (45.0%)		
Women ≥ 35 years (n, %)	5 (33.3%)	12 (60.0%)		
Women ≥ 40 years (n, %)	0 (0%)	3 (15%)		
Body weight (kg)	57.2±7.8	58.3±8.22	0.6915	-6.6903, 4.4903
BMI (kg/m2)	22.1±3.1	23.4±3.67	0.2765	-3.6903, 1.0903
AMH (pmol/L)	27.1±16.7	26.0±14.71	0.8376	-9.7305, 11.9305
AMH (pmol/L) median	21.5 (1.7 - 52.0)	20.1 (16.0 - 32.7)		
AFC - for both ovaries (n)	13.3±5.20	13.0±4.35	0.8538	-2.9865, 3.5865
Duration of infertility (mo)	44.9±26.88	54.0±32.31	0.3829	-30.0352, 11.8352
Duration of stimulation (days)	10.8±0.83	11.0±1.16	0.5746	-0.9178, 0.5178
Average daily dose of gonadotrophin (Control Group: rFSH±hMG or rLH; Study Group: follitropin delta + HP-HMG) (IU)	325.8±43.00	210.6±37.36	<0.0001	87.5072, 142.8928
Average total dose of gonadotrophin (Control Group: rFSH±hMG or rLH; Study Group: follitropin delta + HP-HMG) (IU) (IU)	3164.1±456.08	2162.7±469.42	<0.0001	679.0911, 1323.7089
No of oocytes retrieved (n)	13.3±7.60	13.2±6.43	0.9667	-4.7300, 4.9300
No of MII oocytes (n)	12.1±6.96	10.8±5.23	0.5319	-2.8868, 5.4868
Fertilization rate (%)	66.3±20.26	67.9±19.93	0.8169	-15.5475, 12.3475
Top quality blastocysts (n)	2.3±2.24	2.4±1.75	0.8829	-1.4709, 1.2709

Values are mean±SD, median (interquartile range), or number (percentage), unless stated otherwise.
[a] Two-tailed P value, unpaired t-test.

because the eligibility criteria for patients enrolled in GRAPE was limited to women between 20 and 40 years of age[7], whereas we included subjects ≥40 years old as this was reflective of real-world clinical situation.

Although the mixed protocol stimulation regimen in this study is similar to another trial, registered as the Menopur and Rekovelle Combined Study (MARCS) (NCT03483545), the mean number of top-quality blastocysts in this study was lower at 2.4±1.75, compared with 4.9±3.9 from MARCS.[16] This could be attributed to the higher average daily dose of HP-hMG used in the MARCS trial, which was 133.64±41.12IU vs. 65.2±10.94IU used in this study.[16] Nonetheless, there was a reported OHSS rate of 9.3% among the cohort in MARCS,[16] while there were none in our study, which suggests a lower dose regimen of HP-hMG in our protocol may be a safer approach. The MARCS study did not report on pregnancy outcomes so comparison of this endpoints is not possible.

The gonadotrophin dosing administered from the currently described protocol is 32% lower than our conventional protocol which typically employs between 225 and 300IU/day per COS cycle. Despite this reduced dosage regimen based on the dosing algorithm, there was no compromise on the ovarian response and clinical outcomes as compared to our historical controls with similar baseline characteristics (Table IV). The implication of this finding is that this protocol may be a more efficient and cost-effective methodology for ovarian stimulation.

Overall, despite the more advanced maternal age among our patients (mean age 35.2±4.47) vs. ESTHER-1 (33.4±3.9), GRAPE (31.1±3.7) and MARCS (34.05±3.47),[7-8,16] the resulting stimulation outcomes from this mixed protocol regimen was reassuring and was demonstrated to be safe and efficacious in our local clinical setting with an Asian patient population even at a lower dose of rFSH. Although the use of lower doses of rFSH in IVF/ICSI seems counterintuitive to most clinicians, especially in patients of older age, the present study provides preliminary information that a more personalised dosing regimen based on each patients' ovarian reserve and body weight would not only avoid wastage from overconsumption of gonadotrophins, but it is also markedly safer and provides excellent pregnancy outcomes.

CONCLUSION

Employing a mixed protocol COS regimen with individualised dosing of follitropin delta in combination with HP-hMG results in a good majority of our subjects achieving CPR, without any safety incident of OHSS. By using the validated dosing algorithm for follitropin delta, the total dose of gonadotrophin administered in this protocol was lower than conventional protocol; and thus represents a more resource-efficient, personalised and potentially safer treatment approach for our patients seeking IVF/ICSI treatment.

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