3-1-2021

In vitro fertilization cycles stimulated with follitropin delta result in similar embryo development and quality when compared with cycles stimulated with follitropin alfa or follitropin beta

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Objective: To study the impact of follitropin delta for ovarian stimulation on embryo development and quality compared with that of follitropin alfa or beta in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles.
Design: Retrospective cohort study
Setting: University-affiliated, hospital-based fertility clinic
Patient(s): A total of 403 IVF/ICSI cycles were conducted from September 1, 2018 to December 31, 2019. Cycles were grouped on the basis of stimulation with follitropin delta vs. follitropin alfa or beta.
Intervention(s): None.
Main Outcome Measure(s): Embryo parameters and clinical pregnancy and implantation rates.
Result(s): Ovarian stimulation using follitropin delta resulted in no statistically significant difference in day 3 embryo quality between the control group and follitropin delta group (median 0.50 vs. 0.54 for good quality embryos and median 0.25 vs. 0.20 for intermediate quality embryos). Although on initial analysis there was a lower proportion of good quality blastocysts in the follitropin delta group than in the control group (0.11 vs. 0.22), this difference was no longer present when day 3 after fertilization vitrification and transfer cycles were excluded (0.26 vs. 0.33 follitropin delta vs. control). The clinical pregnancy rates and clinical implantation rates were similar in both groups in fresh transfer cycles.
Conclusion(s): Stimulation with follitropin delta in IVF/ICSI cycles resulted in similar embryo development and pregnancy rates compared with those of stimulation with follitropin alfa or beta. (Fertil Steril Rep® 2021;2:30–5. ©2020 by American Society for Reproductive Medicine.)
Key Words: Embryo quality, follitropin delta, intracytoplasmic sperm injection, in vitro fertilization, pregnancy rates

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In recent years, the benefit of an individualized approach to ovarian stimulation in in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) procedures has become evident. There is an increasing trend toward the selection of the starting dose of gonadotropin on the basis of the unique characteristics of each patient with the goal of improving oocyte yield while simultaneously minimizing the associated risks of excessive response and associated sequelae (1).

Follitropin delta is a relatively new recombinant follicle stimulating hormone (FSH) expressed in a human fetal retinal cell line (1). It is administered according to a specific dosing algorithm, taking into account the patient's body weight as well as anti-mullerian

Received August 6, 2020; revised December 2, 2020; accepted December 10, 2020.
All authors have nothing to disclose.
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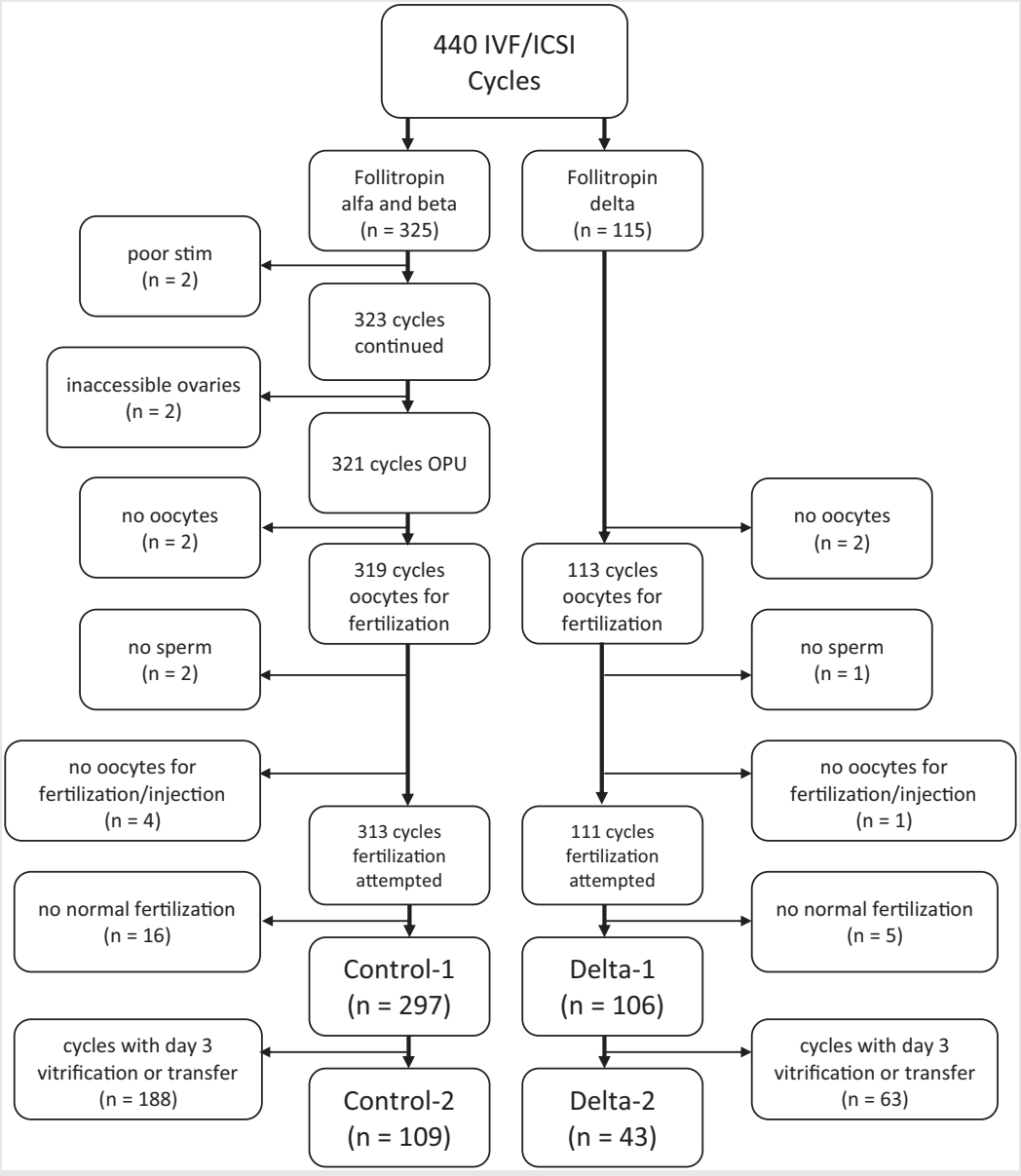
Fertil Steril Rep® Vol. 2, No. 1, March 2021 2666-3341

https://doi.org/10.1016/j.xfre.2020.12.002

hormone (AMH) levels before treatment (1, 2). Follitropin delta was shown to be noninferior in terms of ongoing pregnancy and implantation rates when compared with conventional ovarian stimulation in the ESTHER-1 trial. Potentially improved safety was also noted, with more women responding within target, fewer poor responses, and fewer excessive responses (1). The differing glycosylation profile of this preparation has resulted in lower clearance and higher ovarian response in humans compared with other recombinant FSH preparations (1, 3, 4). However, this increase in oocyte yield may not have translated into an increased number of blastocysts (3). Follitropin alfa and follitropin beta have been available for use in clinical practice in North America since 2004. Although there are some differences between their pharmacokinetics, in clinical trials, these 2 medications showed similar safety and efficacy (5–9).

Since the introduction of follitropin delta into clinical practice, a variety of parameters, specifically related to stimulation response as well as the effect on the risk of ovarian hyperstimulation syndrome, have been assessed (10, 11). The resulting embryo quality has not, however, been reported to date. In this study, we aimed to assess the embryo quality

FIGURE 1



Flow chart of the cycles excluded from the initial sample to form the study and control cohorts. IVF/ICSI = in vitro fertilization/intracytoplasmic sperm injection; OPU = oocyte pick-up.

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and development associated with the use of follitropin delta for stimulation in IVF/ICSI as compared with the use of follitropin alfa or beta. We anticipated that embryo and blastocyst quality after stimulation with follitropin delta would not differ significantly from that of cycles employing follitropin alfa or beta.

MATERIALS AND METHODS

A retrospective cohort study was performed at The Fertility Clinic in London, Ontario, Canada, a hospital-based, university-affiliated fertility clinic. The study included all IVF/ICSI cycles from September 1, 2018 to December 31, 2019. Ethics approval was provided by the Western University Health Sciences Research Ethics board under project ID number 115800. All IVF/ICSI cycles in which follitropin delta (Rekovelle, FE 999049; Ferring Pharmaceuticals, St. Prex, Switzerland) was used for ovarian stimulation were identified as the exposure cohort (Delta-1). The start date of follitropin delta use in our center was September 1, 2018; all remaining IVF/ICSI cycles from September 1, 2018 to December 31, 2019 were then identified as the control cohort (Control-1), including cycles stimulated with follitropin alfa (Gonal-F; Merck KgaA, Darmstadt, Germany) and follitropin beta (Puregon; MSD, Darmstadt, Germany). Cycles that did not result in embryos were excluded (Fig. 1).

All cycles involved controlled ovarian stimulation using recombinant FSH with gonadotropin-releasing hormone (GnRH) antagonist, long GnRH agonist, or flare GnRH agonist protocols. Growth hormone 3.33 mg daily for 9 days was used during stimulation as an adjunct treatment for patients with a history of prior inadequate ovarian response. The follitropin preparation used in the cycle was based on health care provider preference. Menotropin was added in certain cycles on the basis of patient history, recombinant FSH used, and practitioner preference. Follitropin alfa and beta were dosed taking into account the patient's age, weight, baseline FSH level, and prior history. Follitropin delta was dosed using the patient's weight in kilograms and the AMH level. Ultrasound monitoring was started on day 4 or 5 of stimulation until the lead follicles reached 17–18 mm in diameter. Final oocyte maturation was triggered with recombinant human chorionic gonadotropin or GnRH agonist, and oocyte retrieval was performed 36–37 hours later. Conventional IVF or ICSI were performed according to standard protocols. The method of oocyte fertilization used was based on practitioner preference and previous patient history, with only a small number of cycles using insemination through standard IVF (4 in the Delta-1 group and 15 in the Control-1 group). The criteria for the extended culture of embryos consisted of the presence of ≥ 4 good quality embryos on day 3. Embryo transfers were performed on day 3 or day 5 under ultrasound guidance. Generally, only embryos that reached the blastocyst stage by day 5 or 6 were cryopreserved.

The demographic data were collected from paper-based patient treatment records. For the purposes of analysis, the patient's body mass index was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30.0 kg/m^2). An ovarian reserve category was assigned on the basis of the total number of antral follicles measured by ultrasound on day 2 or 3 of the cycle as follows: low (0–8 antral follicles), medium (9–19 antral follicles), and high (≥ 20 antral follicles).

The outcome data were collected from paper-based embryology laboratory records. The primary outcome was embryo quality. The quality of embryos on day 3 after fertilization and of blastocysts on days 5 and 6 were categorized according to the system used in our clinic, largely on the basis of the Istanbul consensus recommendations (12), taking into account the cell number and grade of each embryo on days 2 and 3 after fertilization and the Gardner grade (13) of each blastocyst on day 5 and 6 (Table 1). Secondary outcomes included the clinical pregnancy rates and clinical implantation rates. Clinical pregnancy was defined as the presence of a gestational sac on transvaginal ultrasound on luteal day 40. The clinical pregnancy rate was calculated per fresh transfer on day 3 or day 5 after fertilization. The clinical implantation rate was defined as the number of clinical pregnancies per total number of fresh embryos transferred on either day 3 or day 5. Live birth rates were not a part of the study objective.

Continuous variables were summarized using medians (interquartile ranges [IQRs]), and group comparisons were examined using Mann-Whitney *U* tests. Categorical variables were summarized using frequencies (%), and group comparisons were examined using chi-square tests (or exact chi-square tests, when appropriate). Analyses of covariance and logistic regression models were conducted to examine group differences for continuous and dichotomous outcomes, respectively, while also controlling for potential confounding variables, including etiology of infertility

TABLE 1

Ranking of the embryo quality on day 3 after fertilization and ranking of the blastocyst quality on day 5/6 after fertilization.

Day 3 embryo quality ranking

Embryo characteristic	Good	Intermediate	Poor
Day 2 cell number	3–5	2, >5	Non-division
Day 3 cell number	6–10	6–10, >10	<6 cells
Embryo grade (fragmentation)	G1–G2	G1–G2	G3–G6
Cleavage rate[a]	Appropriate	Appropriate Too slow/fast	Arrested Too slow/fast

Day 5/6 blastocyst quality ranking

Embryo characteristic	Good	Poor	Arrested
Day 5 (ET) stage[b]	≥ early blastocysts	Morula	Cleavage
Day 5/6 stage	≥3 blastocysts	≤2 blastocysts Morula	Cleavage
ICM grade	A/B	C	—
TE grade	A/B/C	A/B/C	—

ET = embryo transfer.
[a] An appropriate cleavage rate was defined as an increase of ≥3 cells and ≤7 cells from day 2 to 3. An increase of <3 cells from day 2 to 3 was considered too slow. Embryos that had the same cell number on day 2 and 3 were classified as "Arrested."
[b] Only embryos that were transferred on day 5 were subjected to the day 5 (ET) stage quality categories. All other embryos were either frozen or discarded on day 5 or 6 and follow the day 5/6 stage grading scheme.

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TABLE 2

Demographic characteristics of patients treated with follitropin alfa or beta (Control-1 group) or follitropin delta (Delta-1 group).

Characteristic	Control-1	Delta-1	*P* value
Number of cycles included[a]	297	106	
Patient characteristics	n (%)	n (%)	
Mean age in years	33.91 (SD 4.04)	34.27 (SD 4.59)	.409
Nulliparous	169 (56.9)	47 (44.3)	.026
Prior IVF	94 (31.6)	30 (28.3)	.521
BMI category			
Low (<18.5 kg/m^2)	2 (0.7)	1 (0.9)	.909
Normal (18.5–24.9 kg/m^2)	134 (45.1)	44 (41.5)	
Overweight (25.0–29.9 kg/m^2)	64 (21.5)	23 (21.7)	
Obese (≥30.0 kg/m^2)	97 (32.7)	38 (35.8)	
Ovarian reserve category			
Low (AFC 0 to 8)	59 (19.9)	19 (17.9)	.418
Medium (AFC 9 to 19)	135 (45.5)	56 (52.8)	
High (AFC ≥20)	103 (34.7)	31 (29.2)	
Etiology of infertility			
Idiopathic	27 (9.1)	13 (12.3)	.348
Tubal factor	32 (10.8)	13 (12.3)	.676
Male factor	134 (45.1)	31 (29.2)	.004
Endometriosis stage I and II	11 (3.7)	6 (5.7)	.403
Endometriosis stage III and IV	20 (6.7)	12 (11.3)	.134
Ovulatory disorder	13 (4.4)	2 (1.9)	.372
Decreased ovarian reserve	46 (15.5)	23 (21.7)	.145
Donor sperm	29 (9.8)	13 (12.3)	.470
PCOS	49 (16.5)	10 (9.4)	.077
Advanced maternal age	124 (41.8)	56 (52.8)	.049
Uterine factor	4 (1.3)	1 (0.9)	1.000
Stimulation cycle characteristics			
Mean length of stimulation (days)	9.95 (SD 1.70)	9.92 (SD 1.51)	.784
Mean total dose follitropin	1951 IU (SD 849)	132 μg (SD 245)	—
Use of menotropin	295 (99.3)	71 (67.0)	<.001
Use of growth hormone	79 (26.6)	16 (15.1)	.017
Mean number of follicles ≥15 mm	8.42 (SD 4.64)	7.41 (SD 3.43)	.179
Mean number of follicles ≥18 mm	3.94 (SD 2.14)	3.60 (SD 1.87)	.209
Mean number of follicles ≥20 mm	1.47 (SD 1.23)	1.41 (SD 1.13)	.925
Mean E2 levels at the trigger day (pmol/L)	7520 (SD 4424)	6448 (SD 3507)	.050
Mean number of oocytes retrieved	12.3 (SD 7.7)	10.4 (SD 6.1)	.033
Proportion of normal fertilization[b]	0.760 (SD 0.207)	0.732 (SD 0.240)	.490
Proportion of fresh transfers on day 3	167 (64.2)	62 (61.4)	.614

Note: Data are presented as number (%). AFC = antral follicle count; BMI = body mass index; E_2 = estradiol; IVF = in vitro fertilization; PCOS = polycystic ovary syndrome; SD = standard deviation.
[a] Cycles were excluded from analysis if no oocytes were retrieved or if no fertilization took place.
[b] The proportion of normal fertilization was calculated per injected oocytes for intracytoplasmic sperm injection cycles and per oocytes retrieved for IVF cycles.

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(with advanced maternal age included), use of growth hormone, use of menotropin, body mass index, ovarian reserve, as well as whether a previous treatment cycle had taken place. The initial analysis included both the full study cohort (Delta-1) and the full control cohort (Control-1). A secondary analysis was performed excluding cycles where embryos were transferred or vitrified on day 3 after fertilization. This was done to accurately assess the blastocyst development quality in both the study group (Delta-2) and the control group (Control-2). All analyses were conducted using SPSS v26 (IBM Corp., Armonk, NY), and *P* values <.05 were considered statistically significant.

RESULTS

A total of 440 IVF/ICSI cycles were identified during the study period: 115 with follitropin delta and 325 with either follitropin alfa or beta used for stimulation. Once exclusion criteria were considered, 106 Delta-1 group cycles and 297 Control-1 group cycles were included (Fig. 1). Demographic characteristics of the 2 groups are listed in Table 2. The cohorts differed significantly in the proportion of cycles with a diagnosis of male factor infertility (29.2% in Delta-1 vs. 45.1% in Control-1, *P*=.004) as well as in the incidence of advanced maternal age in each group (52.8% in Delta-1 vs. 41.8% in Control-1, *P*=.049). More women with cycles in the control group were nulliparous (56.9% in Control-1 vs. 44.3% in Delta-1, *P*=.026), and more cycles in the control group utilized growth hormone (26.6% in Control-1 vs. 15.1% in Delta-1, *P*=.017) and menotropin (99.3% in Control-1 vs. 67.0% in Delta-1, *P*<.001). In the Control-1 group, 31.6% of the women had undergone a previous cycle of IVF compared with 28.3% of women in the Delta-1 group (*P*=.521). The mean number of oocytes retrieved was higher in the Control-1 group than in the Delta-1 group (12.3 ± 7.7 vs. 10.4 ± 6.1 [±SD], respectively; *P*=.033). There were no differences between the groups in the mean length of stimulation; numbers of follicles ≥15 mm, ≥18 mm, and ≥20

TABLE 3

Median proportions of good, intermediate, and poor-quality embryos on day 3 after fertilization and proportions of good, poor, and arrested blastocysts on days 5 and 6 after fertilization.

Outcome variable				Analysis of Covariance[a]	
Primary analysis day 3 embryo stage	**Control-1**	**Delta-1**	***P* value**	**B(SE) (95% CI)**	***P* value**
Cycles included	297	106			
Good embryos (IQR)	0.54 (0.33–0.75)	0.50 (0.31–0.75)	.746	—	—
Intermediate embryos (IQR)	0.20 (0.00–0.36)	0.25 (0.00–0.40)	.338	—	—
Poor embryos (IQR)	0.14 (0.00–0.33)	0.05 (0.00–0.25)	.119	—	—
Secondary analysis day 3 embryo stage	**Control-2**	**Delta-2**			
Cycles included	109	43			
Good embryos (IQR)	0.67 (0.50–0.80)	0.60 (0.44–0.75)	.156	—	—
Intermediate embryos (IQR)	0.20 (0.10–0.31)	0.29 (0.00–0.38)	.146	—	—
Poor embryos (IQR)	0.10 (0.00–0.17)	0.11 (0.00–0.20)	.852	—	—
Primary analysis blastocyst stage	**Control-1**	**Delta-1**			
Cycles included	247	79			
Good blastocysts (IQR)	0.22 (0.00–0.50)	0.11 (0.00–0.38)	.026	−0.11(0.04) (−0.19, −0.03)	.008
Poor blastocysts (IQR)	0.38 (0.13–0.57)	0.40 (0.25–0.67)	.137	—	—
Arrested blastocysts (IQR)	0.25 (0.00–0.50)	0.22 (0.00–0.60)	.858	—	—
Secondary analysis blastocyst stage	**Control-2**	**Delta-2**			
Cycles included[b]	108	40			
Good blastocysts (IQR)	0.33 (0.17–0.56)	0.26 (0.13–0.48)	.121	—	—
Poor blastocysts (IQR)	0.40 (0.26–0.55)	0.40 (0.38–0.60)	.127	—	—
Arrested blastocysts (IQR)	0.17 (0.07–0.35)	0.19 (0.10–0.43)	.512	—	—
Pregnancy outcomes	**Control**	**Delta**			
Fresh transfer cycles day 3	167	62			
Clinical pregnancy (% per fresh transfer)	35.3	38.7	.636	—	—
Mean clinical implantation (% per embryo transferred)	25.1 (SD 37.1)	26.6 (SD 37.0)	.697	—	—
Fresh transfer cycles day 5	93	39			
Clinical pregnancy (% per fresh transfer)	37.6	38.5	.929	—	—
Mean clinical implantation (% per embryo transferred)	36.6 (SD 47.9)	38.5 (SD 49.3)	.859	—	—

Note: Data are presented as medians with interquartile ranges (IQR). CI = confidence interval; SD = standard deviation; SE = standard error.

[a] Analysis of covariance was performed taking into account the following control variables: etiology of infertility (presence of endometriosis, ovulatory disorder, polycystic ovarian syndrome, advanced maternal age), previous in vitro fertilization attempt, use of growth hormone, use of menotropin, body mass index, and the ovarian reserve category.

[b] Secondary analysis was performed after the exclusion of cycles in which day 3 vitrification or transfer occurred.

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mm; mean estradiol level on the trigger day; or proportion of normal fertilization. An equal proportion of fresh transfers occurred on day 3 after fertilization in both the Control-1 and Delta-1 groups (Table 2).

No significant differences were identified between the Delta-1 and Control-1 groups in terms of the proportion of good-, intermediate-, and poor-quality embryos on day 3 after fertilization (Table 3). There were also no significant differences between cohorts in the proportions of poor and arrested blastocysts (day 5 and 6 after fertilization). A significant difference was noted in the proportion of good quality blastocysts, with the Delta-1 group having a lower proportion compared with the Control-1 group (median 0.11 vs. 0.22, respectively; $P=.026$). This difference persisted even when controlling for potential confounding variables (Table 3). Clinical pregnancy and clinical implantation indices for both day 3 and day 5 fresh embryo transfers did not differ between the Control-1 and Delta-1 groups (Table 3).

For the secondary analysis, once day 3 after fertilization embryo transfer and vitrification cycles were excluded, the Delta-2 group included 43 cycles and the Control-2 group included 109 cycles (Fig. 1). There were no significant differences between the groups in the quality of embryos on day 3 after fertilization as well as at the blastocyst level (Table 3).

DISCUSSION

Our results suggest there was no difference in the embryo quality associated with IVF/ICSI cycles in which follitropin delta was used for stimulation as compared with cycles in which follitropins alfa or beta were used. The clinical pregnancy indices with fresh transfer were comparable. The ESTHER-1 trial showed an improved safety profile with follitropin delta, with fewer excessive stimulation responses and fewer measures taken to prevent ovarian hyperstimulation syndrome (1, 10, 11). Our findings of equivalent cycle

outcomes contribute to the evidence on follitropin delta and support its position as an important alternative stimulation medication.

The findings of equivalent clinical implantation and clinical pregnancy indices between the 2 groups are consistent with the findings of ESTHER-1, where similar efficacy was reported between follitropin delta and follitropin alfa in ongoing implantation rates, ongoing pregnancy rates, and live birth rates. In that study, however, oocyte yield was equivalent between the groups under comparison (1). A randomized, controlled, multicenter trial in 2014 found that although a positive relationship existed between the dose of follitropin delta administered and the number of oocytes retrieved, this did not translate into an increase in the number of blastocysts (3). Oocyte yield is, therefore, not necessarily a useful parameter for evaluating the performance of follitropin delta. The difference between the 2 groups in the number of oocytes retrieved was not reflective of the sample as cycles in which no oocytes were retrieved were excluded. The wide variation between groups in the use of menotropin was explained largely by possible differences in physician preference. Menotropin was not routinely used in cycles stimulated with follitropin delta.

Follitropin delta has a lower clearance compared with that of follitropin alfa, which is likely related to differences in glycosylation patterns, but a similar absolute bioavailability (4, 14). In addition, its in vitro potency at the human FSH receptor was the same as that of follitropin alfa (14). These pharmacodynamic traits may explain why the outcome parameters associated with the use of this medication have been equivalent to those of follitropin alfa, whereas the lower clearance and individualized dosing may contribute to the improved safety profile.

Our study was retrospective in design and consisted of a relatively small sample size. The study cohorts differed significantly in their demographic characteristics, and efforts were made to control for these differences when a difference in outcomes was observed. The ovarian reserve categories were based on antral follicle counts at the start of each stimulation cycle as AMH serum levels were unfortunately not available for all patients in the study. This could be considered a limitation because AMH is a better predictor of ovarian response (15, 16), and it is used in the formal dosing of follitropin delta (1). The significant proportion of embryos that were either transferred or vitrified on day 3 after fertilization affected the evaluation of resulting blastocyst number and quality; secondary analysis was performed to account for this, albeit with a smaller sample size. A significant strength of our study was that it contributed important information on the quality of embryos and blastocysts associated with the use of follitropin delta for stimulation, a parameter that has not previously been reported.

In conclusion, stimulation with follitropin delta in IVF/ICSI cycles was associated with comparable embryo quality, clinical implantation, and clinical pregnancy incidence as compared to stimulation with follitropin alfa or beta. Further study of this association, with a greater number of cycles, in the future would be interesting to determine whether these results can be reproduced.

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