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Relative Biopotency Differences between Follitropin Delta and Follitropin Alfa: A Pooled Analysis of Randomized Controlled Trials (RCTs) comparing Gonadotropin Consumption per Oocyte Retrieved

E. Gravotta,[1] J. García-Velasco,[2,3] S. Nelson,[4] E. Bakhtadze Bagci,[5] A. Falahati,[6] G. Griesinger,[7] N. P. Polyzos,[8] R. Lobo[5]

1. Ferring Pharmaceuticals, Global Research and Medical, Roma, Italy; 2. IVIRMA Global Research Alliance, IVI Madrid, Spain; 3. Rey Juan Carlos University, Obstetrics and Gynaecology, Madrid, Spain; 4. University of Glasgow, Obstetrics and Gynaecology at the School of Medicine, Glasgow, United Kingdom; 5. Ferring Pharmaceuticals, Global Research and Medical, Kastrup, Denmark; 6. Ferring Pharmaceuticals Co. Ltd, Biometrics, Tokyo, Japan; 7. University Hospital of Schleswig-Holstein, Gynecological Endocrinology and Reproductive Medicine, Lübeck, Germany; 8. Dexeus Fertility- Dexeus University Hospital, Obstetrics- Gynecology and Reproductive Medicine, Barcelona, Spain.

OBJECTIVE

To assess the relative biopotency of follitropin delta, across individualized and conventional (flexible) dosing regimens, compared with conventionally dosed follitropin alfa, measured by gonadotropin consumption per oocyte retrieved

KEY TAKEAWAYS

1. **These analyses support higher relative biopotency of follitropin delta compared with follitropin alfa, with consistently lower mean gonadotropin consumption per oocyte retrieved across both individualized and flexible (i.e., conventional with dose adjustments) dosing regimens**
2. **Pregnancy rates from first transfer were similar for both gonadotropins, providing reassurance that the potentially higher biopotency of follitropin delta versus follitropin alfa does not reduce overall oocyte quality**
3. **These data may inform dose selection and pharmacoeconomic considerations in clinical practice**

References

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Abbreviations: AFC, antral follicle count; **AMH,** anti-Müllerian hormone; **CI,** confidence interval; **OHSS,** ovarian hyperstimulation syndrome; **RCT,** randomized controlled trial.

Trial registrations: NCT05263388, NCT03809429, NCT01956110, NCT03296527, NCT04773353, NCT06173869

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Contact information: For questions and comments, contact Errica Gravota at errica.gravota@ferring.com.

BACKGROUND

- Follitropin delta is a recombinant follicle-stimulating hormone (rFSH) derived from a human cell line whereas follitropin alfa is derived from a Chinese hamster ovary cell line
- When algorithmically dosed, based on anti-Müllerian hormone (AMH) and bodyweight, follitropin delta has demonstrated efficacy comparable to conventionally dosed follitropin alfa (150 IU/day starting dose), with a favourable safety profile[1–4]
- Previous analysis of >1500 clinical trial participants established that follitropin delta 10 µg provides an ovarian response similar to follitropin alfa 150 IU (11 µg)/day[5]
- Additional RCTs showed that flexible dosing for follitropin delta (starting dose of 10 or 15 µg/day) provides similar oocyte yields to follitropin alfa (starting dose 150 or 225 IU/day)[6,7]
- However, a comparison of mean gonadotropin consumption per oocyte retrieved across dosing strategies has not been performed to quantify relative biopotency

METHODS

- Two pooled RCT datasets compared follitropin delta with follitropin alfa[1–4,6,7]
  1. **Individualized dosing:** follitropin delta (algorithm-based) versus conventional follitropin alfa (150 IU/day starting dose)[1–4]
  2. **Flexible dosing:** follitropin delta (10 or 15 µg/day starting dose) versus conventional follitropin alfa (150 or 225 IU/day starting dose)[6,7]
- For each trial, the inclusion and exclusion criteria were set according to the gonadotropin starting doses to ensure participant safety[1–4,6,7]
- Mean total dose per oocyte retrieved, and relative potency was calculated using the number of oocytes retrieved per unit dose of gonadotropin. Pregnancy rates with risk differences and confidence intervals (CIs) were calculated
- Oocyte counts were modelled using negative binomial regression with a log link, gonadotropin total dose as a log offset, and covariates; relative biopotency was estimated as the adjusted oocyte yield per unit dose
- Pregnancy outcomes were analysed using multivariable logistic regression adjusted for trial and baseline characteristics. Adjusted rates, 95% CIs, and p-values were obtained from the model, and pooled risk differences with 95% CIs were calculated using the Cochran-Mantel-Haenszel (CMH) method stratified by trial

RESULTS

- Trial participants were women, 18–40 years, BMI 17.5–32 kg/m^2, with either infertility or an infertile male partner, eligible for IVF/ICSI, and were enrolled at specialist reproductive clinics predominantly in Europe and Asia

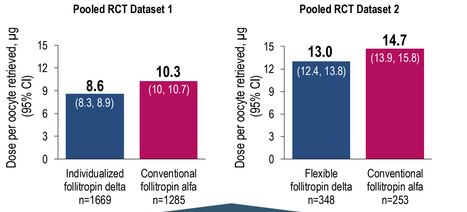
TABLE 1 Demographics and Baseline Characteristics

	Pooled RCT Dataset 1		Pooled RCT Dataset 2	
	Individualized (algorithm-based) follitropin delta n=1669	Conventional follitropin alfa 150 IU / day n=1285	Flexible follitropin delta 10 or 15 µg / day n=348	Conventional follitropin alfa 150 or 225 IU / day n=253
Age, years	32.2 ± 0.10	32.1 ± 0.11	33.6 ± 0.21	33.1 ± 0.24
<35 years	1145 (68.6)	889 (69.2)	190 (54.6)	150 (59.3)
BMI, kg/m^2	23.2 ± 0.08	22.7 ± 0.09	23.7 ± 0.22	23.5 ± 0.22
Primary reason for infertility				
Tubal infertility	380 (22.8)	352 (27.4)	113 (32.5)	116 (45.8)
Unexplained infertility	647 (38.8)	445 (34.6)	108 (31.0)	53 (20.9)
Mild/moderate male factor	341 (20.4)	264 (20.5)	74 (21.3)	37 (14.6)
Severe male factor	262 (15.7)	184 (14.3)	44 (12.6)	40 (15.8)
Endometriosis stage I/II	33 (2.0)	32 (2.5)	9 (2.6)	7 (2.8)
Other reason	6 (0.4)	8 (0.6)	0	0
Duration of infertility, months	38.8 ± 0.70	42.2± 0.82	38.2 ± 1.6	37.5 ± 1.7
AFC	14.9 ± 0.16	14.3 ± 0.18	13.2 ± 0.27	12.9 ± 0.33
Serum AMH, pmol/L	20.7 ± 0.33	22.2 ± 0.49	15.6 ± 0.40	16.1 ± 0.56
AMH <15 pmol/L group	644 (38.6)	498 (38.8)	177 (50.9)	131 (51.8)

Data are mean ± standard deviation or n (%).

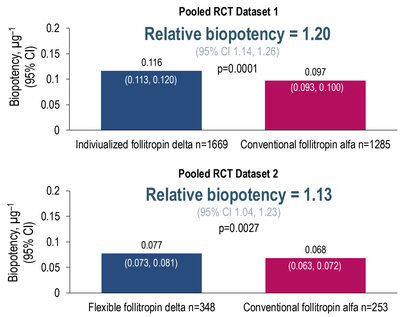
- **Baseline characteristics and infertility history were balanced between comparator groups in each dataset**

FIGURE 1 Mean Gonadotropin Dose per Oocyte Retrieved



- **There was consistently a lower mean gonadotropin consumption per oocyte retrieved with follitropin delta across both individualized and flexible dosing regimens compared with follitropin alfa**

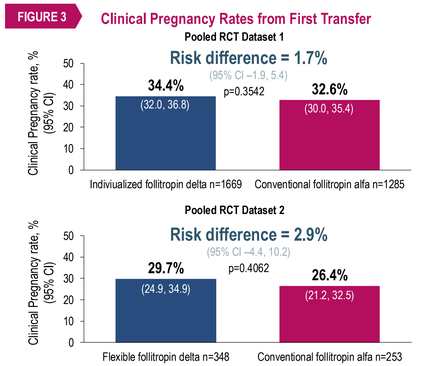
FIGURE 2 Modelled Relative Biopotency per Oocyte Retrieved



Relative biopotency was estimated using a negative binomial regression model with a log link, adjustment for trial and baseline covariates, and total gonadotropin dose as a log offset.
P-value for testing the null hypothesis of no treatment difference in relative biopotency was derived from the negative binomial regression model.

- **There was consistently a higher ovarian response per unit dose with follitropin delta across both individualized and flexible dosing strategies compared with follitropin alfa**

FIGURE 3 Clinical Pregnancy Rates from First Transfer



P-value for testing the null hypothesis of no treatment difference was based on the logistic regression model.

- **Pregnancy rates from first transfer were similar between follitropin delta and follitropin alfa**

TABLE 2 Gonadotropin Treatment, Oocyte Yield and Fertilization Rate

	Pooled RCT Dataset 1		Pooled RCT Dataset 2	
	Individualized (algorithm-based) follitropin delta n=1669	Conventional follitropin alfa 150 IU / day n=1285	Flexible follitropin delta 10 or 15 µg / day n=348	Conventional follitropin alfa 150 or 225 IU / day n=253
Gonadotropin treatment				
Duration of gonadotropin treatment, days	9.2 ± 0.05	8.8 ± 0.05	9.8 ± 0.10	9.9 ± 0.10
Gonadotropin total dose, µg	89.9 ± 0.69	108.0 ± 1.0	148.1 ± 1.99	162.4 ± 2.6
Gonadotropin daily dose, µg	9.8 ± 0.06	12.1 ± 0.05	15.1 ± 0.12	16.3 ± 0.16
Oocyte yield and fertilization rate				
Oocyte yield	9.8 ± 0.14	10.7 ± 0.19	11.3 ± 0.30	11.2 ± 0.37
Fertilization rate relative to oocytes retrieved, %	58.1 ± 0.61 [n=1599]	60.0 ± 0.65 [n=1252]	56.3 ± 1.2 [n=346]	60.1 ± 1.4 [n=247]
Fertilization rate relative to MII* oocytes, %	74.1 ± 0.73 [n=1023]	75.8 ± 0.80 [n=840]	70.9 ± 1.8 [n=188]	75.4 ± 2.2 [n=110]

Data are mean ± standard deviation or n (%).
*MII oocytes were assessed for participants with intracytoplasmic sperm injection method of fertilization.

- **Mean daily and total gonadotropin dose was consistently lower with follitropin delta**

CLINICAL IMPLICATIONS

- The numerically lower total microgram dose with follitropin delta using different dosing strategies across pooled RCT datasets supports previous findings on differential biopotency of follitropin delta and follitropin alfa[5,8]
- The two rFSH preparations are not biologically inter-changeable between 1 µg of each preparation. The Steelman-Pohley bioassay in rats under-estimates the *in vivo* potency of follitropin delta in humans,[8] therefore it is dosed in micrograms

LIMITATIONS

- Direct comparisons between the two pooled analyses should be made with caution due to the differences between trial populations
  - Trials with the higher fixed gonadotropin starting doses (follitropin delta 15 µg and follitropin alfa 225 IU) excluded potential high responders
- The trials were not originally designed to compare the clinical biopotency of the gonadotropins
- Ongoing pregnancy rates, cumulative pregnancy rates and live birth rates were not available for all the pooled RCTs

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