International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Comparing Efficacy and Safety of Recombinant FSH Originator Product with Biosimilar in Women Undergoing Ovarian Stimulation

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Abstract: ***Background: Biosimilar medications have expanded the treatment possibilities within assisted reproductive technology (ART). Real-world data comparing the clinical outcomes of the original follitropin alfa (Gonal-f®) with its biosimilars are essential for enhancing the existing body of evidence to inform clinical decisions regarding drug selection. Aim of the study was to evaluate the efficacy of biosimilar in comparison to recombinant FSH originator product (Gonal F). Methods: This was a Retrospective Observational Study which involved 220 women who underwent IVF treatment for subfertility from Institute of Reproductive Medicine and Women's Health, Madras Medical Mission Hospital, Chennai between the year 2020 to 2022. Stimulation outcomes and Reproductive outcomes were analysed in terms of number of days of stimulation, total dose of rFSH used, number of embryos obtained, number of embryos transferred, clinical pregnancy rate, multiple pregnancy rate and miscarriage rate. Results: There was no significant difference in the number of oocytes retrieved, number of M2 oocytes retrieved, number of embryos per cycle and embryos transferred between Biosimilars and Gonal F groups. Reproductive outcomes were similar in terms of clinical pregnancy rate. Conclusion: rFSH Biosimilar is as effective as the originator product and similar safety profile.***

Keywords: Assisted reproductive technology, follitropin alfa, gonadotropin-releasing hormone antagonist, infertility

1. Introduction

Follicle Stimulating Hormone (FSH) is a hormone secreted by the the anterior pituitiary . It plays an important role in sexual development and function. Physiologically the secretion of FSH is under the control of feedback from various hormones. Gonadotropin Releasing Hormone (GnRH) secreted by the hypothalamus in a pulsatile manner stimulates the Anterior Pituitiary to secrete FSH. FSH secretion is under negative feedback control of estradiol and inhibin[1].

LH also has important role in folliculogenesis. Firstly, it operates within the theca compartment, where it induces androgen production [2]. Secondly, its action commences during the intermediate follicular phase, involving granulosa cells to induce the local production of diverse molecules. These molecules facilitate the growth of granulosa cells, subsequently regulating oocyte maturation[3].

Exogenous preparations of FSH have long been used in the treatment of infertility. FSH products are used to stimulate the growth and maturation of multiple follicles, develop several embryos and thus improve the probability of having a live birth.

In the past, all available FSH preparations were obtained from postmenopausal women urine extracts. These preparations had some drawbacks including batch-to-batch inconsistency, low specific activity and the presence of impurities

Advances in recombinant DNA technology led to the development of highly purified, highly specific recombinant FSH. In September 1997[4] , recombinant FSH Gonal F received the Food and Drug Administration approval for ovulation induction and use in ART. As patents expire on innovator products, there is increasing interest in developing biosimilar products globally.

The FDA describes biosimilars as biologic products that are "highly similar to the reference product not with-standing minor differences in clinically inactive components and that there are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency of the product"[5]

While earlier research has assessed outcomes associated with Gonal F and its biosimilars, there is a lack of data regarding variances in stimulation and reproductive outcomes within real-world scenarios. This study endeavors to address this gap by comparing stimulation and reproductive outcomes in patients administered either Gonal F or its biosimilars within a clinical setting.[6,7,8]

Aim of the study was to evaluate the efficacy of biosimilar in comparison to recombinant FSH originator product (Gonal F).

2. Materials and Methods

This was a Retrospective Observational Study which involved 220 women who underwent IVF treatment for subfertility from Institute of Reproductive Medicine and Women's Health, Madras Medical Mission Hospital, Chennai between the year 2020 to 2022. The study participants were divided into two groups based on administration of either

Gonal-f or its biosimilars with a sample size of 110 for each group.

Primary outcome of the study was number of oocytes retrieved per cycle and number of M2 oocytes retrieved. Secondary outcomes were total dose of gonadotropins, duration of ovarian stimulation, number of embryos obtained per aspirated cycle, moderate or severe ovarian hyperstimulation syndrome (OHSS) rate, clinical pregnancy rate, miscarriage rate and multiple pregnancy rate.

Approval was obtained from the institutional ethics committee. Inclusion Criteria included women who had undergone controlled ovarian stimulation with recombinant FSH for IVF during the study period. Exclusion criteria included women with history of ovarian surgery, severe endometriosis and endocrine disorders.

Data was collected using a structured proforma. Baseline characteristics like age, BMI, years of infertility, AMH and AFC were noted. The stimulation details were documented, encompassing both the total dose of gonadotropins administered and number of days of stimulation. The outcomes of the stimulation process were recorded, including the number of oocytes, metaphase II (M2) oocytes, the quantity of obtained embryos, as well as the results of beta hCG and pregnancy outcomes.

All statistical analyses were performed using SPSS software (version 22.0, SPSS Inc). All numeric data are presented as the mean value ± standard deviation. The variables Age (Years) , BMI (Kg/m²), Years of Infertility, AMH , AFC , number of days of stimulation ,total dose of gonadotropins , number of oocytes retrieved , number of M2 oocytes retrieved , number of embryos obtained and number of embryos transferred were not normally distributed in the 2 subgroups of the variable Group. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. Chi-squared test was used to explore the association between the groups and clinical pregnancy rate. Fisher's exact test was used to explore the association between the groups and pregnancy outcome. Differences between the values were considered statistically significant when $p< 0.05$.

3. Results

A total of 220 subfertile women who underwent controlled ovarian stimulation with recombinant FSH were included in the analysis. There were 110 women in the biosimilar group and 110 women in the originator group.

Baseline characteristics of the study group are presented in table 1. The mean Age (Years) of the study group was 31.56 Age (Years) ± 4.45 years. The mean age (Years) in the Biosimilar Group was 31.58 (4.04). The mean age (Years) in the Gonal-F group was 31.54 (4.84). There was no significant difference between the groups in terms of age.

The mean BMI (Kg/m²) of the study group was 26.15 ± 3.86.The mean BMI (Kg/m²) in the Biosimilar group was 25.94 (3.36). The mean BMI (Kg/m²) in the Gonal-F group was 26.36 (4.30). There was no significant difference between the groups in terms of BMI (Kg/m²) ($p = 0.649$).

The mean Years of Infertility of the study group was 6.39 ± 4.01. The mean Years of Infertility in the Biosimilar group was 6.70 (3.92). The mean Years of Infertility in the Gonal-F group was 6.09 (4.08).

The mean AMH of the study group was 3.08 ± 1.70. The mean AMH in the Biosimilar group was 2.96 (1.50). The mean AMH in the Gonal-F group was 3.20 (1.88). There was no significant difference between the groups in terms of AMH ($p = 0.622$).
The mean AFC of the study group was 13.99 ± 7.57. The mean AFC in the Biosimilar group was 13.83 (6.96). The mean AFC in the Gonal-F group was 14.15 (8.16). There was no significant difference between the groups in terms of AFC ($p = 0.934$).

Table 1: Demographic and baseline clinical characteristics of the study population

Parameters	Group		p value
	Biosimilar (n = 110)	Gonal-F (n = 110)	
Age (Years)	31.58 ± 4.04	31.54 ± 4.84	0.857
BMI (Kg/m²)	25.94 ± 3.36	26.36 ± 4.30	0.649
Years of Infertility	6.70 ± 3.92	6.09 ± 4.08	0.132
AMH	2.96 ± 1.50	3.20 ± 1.88	0.622
AFC	13.83 ± 6.96	14.15 ± 8.16	0.934

Table 2 presents details of ovarian stimulation, encompassing the duration of stimulation and the dosage of gonadotropins administered. The mean of Days of Stimulation of the study group was 10.86 (1.35). The mean Days of Stimulation in the Biosimilar group was 10.97 (1.35). The mean Days of Stimulation in the Gonal-F group was 10.75 (1.34). There was no significant difference between the groups in terms of Days of Stimulation ($p = 0.197$). The mean of Dose of the study group was 2800.54 (1114.43). The mean Dose in the Biosimilar group was 2753.90 (1035.15). The mean Dose in the Gonal-F group was 2847.17 (1191.38). There was no significant difference between the groups in terms of Dose ($p = 0.427$)

Table 2: Comparison of the 2 Subgroups of the Variable Group in Terms of Ovarian Stimulation parameters (n = 220)

Parameters	Biosimilar	Gonal-F	p value
Days of Stimulation	10.97 (1.35)	10.75 (1.34)	0.197
Dosage of gonadotropins	2753.90 (1035.15)	2847.17 (1191.38)	0.427

While the average count of retrieved oocytes and M2 oocytes was similar between the biosimilars and Gonal F groups, there was a slight increase in the number within the biosimilar cohort. The average of Oocytes Retrieved was 8.09 (5.69). In the Biosimilar group, the mean of Oocytes Retrieved was 8.59 (6.43), while in the Gonal-F group, it was 7.58 (4.81). The analysis revealed no significant difference between the groups concerning the number of Oocytes Retrieved ($p = 0.265$).The mean (SD) of the Number of M2 Oocytes in the Biosimilar group was 6.74 (4.97), while in the Gonal-F group, it was 6.14 (4.27). There was no significant difference between the groups concerning the Number of M2 Oocytes ($p = 0.454$). Same has been represented in table 3.

Table 3: Comparison of the 2 Subgroups in terms of Number of retrieved oocytes and M2 oocytes

Parameters	Biosimilar	Gonal-F	P value
Oocytes Retrieved	8.59 (6.43)	7.58 (4.81).	0.265
M2 oocytes	6.74 (4.97)	6.14 (4.27)	0.454

Reproductive outcomes between the two study groups are compared in Table 4. Average number of embryos obtained per cycle and average number of embryos transferred was comparable in the Biosimilar group and Gonal-F group. The clinical pregnancy rate was significantly higher in the biosimilar group compared to the Gonal-F group.

Table 4: Comparison of the 2 Subgroups of the Variable Group in Terms of Reproductive Outcomes

Parameters	Biosimilar	Gonal-F	P value
Embryos obtained per cycle	5.65 (4.26)	5.16 (3.62)	0.385
Number of Embryos transferred	3.53 (2.07)	3.56 (2.32)	0.626
Clinical pregnancy Rate	53 (48.2%)	33 (30.0%)	0.006

The results of comparison of pregnancy outcomes between biosimilar and gonal F group is depicted in table 5. The rates of multiple pregnancies are also comparable between the two groups .Similarly miscarriage rate was comparable between the two groups.

Table 5: Association Between Group and Pregnancy Outcome (n = 87)

Pregnancy Outcome	Group			Fisher's Exact Test	
	Biosimilar	Gonal-F	Total	$\chi 2$	P Value
Single	30 (55.6%)	17 (51.5%)	47 (54.0%)	3.761	0.840
Twins	15 (27.8%)	11 (33.3%)	26 (29.9%)		
Quadruplet	0 (0.0%)	1 (3.0%)	1 (1.1%)		
Triplet	1 (1.9%)	0 (0.0%)	1 (1.1%)		
Ectopic	2 (3.7%)	0 (0.0%)	2 (2.3%)		
Biochemical	3 (5.6%)	2 (6.1%)	5 (5.7%)		
Abortion	3 (5.6%)	2 (6.1%)	5 (5.7%)		
Total	54 (100.0%)	33 (100.0%)	87 (100.0%)		

No cases of moderate or severe OHSS was reported in either group.

4. Discussion

Human FSH has been a crucial medication in assisted reproductive technology (ART) for many years. Recombinant human FSH (r-hFSH), developed through recombinant DNA technology, is extensively utilized to stimulate ovulation in individuals undergoing controlled ovarian stimulation for ART procedures. Among the r-hFSH preparations, Gonal-f (follitropin alpha) is a frequently prescribed fertility drug. It received approval from the European Medicines Agency (EMA) in 1995[6] and the United States Food and Drug Administration (US FDA) in 1997[9] for inducing multifollicular development in women undergoing assisted reproductive technology (ART) procedures[10].

Follicle-stimulating hormone (FSH) treatment constitutes a significant portion of the expenses linked with assisted reproductive technology (ART)[11]. Recognizing this financial aspect, biosimilar versions of r-hFSH have been introduced into clinical practice. These biosimilars are considered vital for enhancing patient access to biological therapies. Presently, several licensed biosimilars for follitropin, are utilized in clinical settings worldwide.

Bemfola®, the initial r-hFSH alpha biosimilar, debuted in Europe in 2014. It has been observed to yield similar clinical benefit rates as Gonal-f® across all patient subpopulations, according to findings from the real-world study of assisted reproductive technology (ART) in France (REOLA) clinical trials. The REOLA trial also showcased hat biosimilar r-hFSH can be equally effective as the original r-hFSH in real-world scenarios.[12]

However, there is a requirement for comparative efficacy and safety data derived from real-world clinical practice. This information is crucial to aid decision-making regarding the adoption and transition to biosimilars from the originator molecule.

In our study, we discovered that biosimilars, when compared to Gonal-F, showed comparability in terms of both the number of oocytes retrieved and the number of M2 oocytes retrieved. These findings align with those reported in a study by Nayana Hitesh Patel et al.[13], which also demonstrated a similar number of oocytes retrieved between biosimilars and Gonal F. In a multicenter phase 3 study conducted by Zarema Barakhoeva et al., similar numbers of oocytes were reported in both the biosimilar and Gonal-F groups[14].

We also observed that the number of embryos obtained and the number of embryos transferred were similar in both groups.

Clinical pregnancy rates are commonly regarded as a reliable indicator of treatment efficacy. Our findings suggest that the clinical pregnancy rate was significantly higher in the biosimilar group compared to Gonal F group. However, it's worth noting that biosimilars exhibited a substantially higher clinical pregnancy rate. These findings are in contrast to those reported in a retrospective study by Van den Haute L et al., where comparable clinical pregnancy rates were observed between the biosimilar and Gonal-F groups[15]. A prospective observational phase IV study on the utilization of biosimilar follitropin Alfa r-hFSH in assisted reproductive technology by Griesinger G et al. also indicated comparable pregnancy rates[16]. Furthermore, our study findings contrast with study

by Strowitzki T et al that demonstrated a higher clinical pregnancy rate with Gonal F[17].

The miscarriage rate and multiple pregnancy rate was also comparable between the two groups.This is aligned with the findings seen in study by Nayana Hitesh Patel et al[13].

In conclusion we found that rFSH Biosimilars when compared to the originator product are equally effective in terms of number of oocytes retrieved, embryos obtained and clinical pregnancy rate. They therefore can be an effective alternative to Gonal F in ovarian stimulation. Additional randomized controlled trials (RCTs) are necessary to compare Biosimilars with Gonal F in order to further substantiate their effectiveness and safety.

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