RESEARCH ARTICLE

Efficacy of Follitropin-A (Gonal-F) Versus Follitropin-B (Puregon) for Controlled Ovarian Stimulation in Women Undergoing *in vitro* fertilization (IVF)

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ABSTRACT

The purpose of this study was to compare the efficacy of two recombinant follicle-stimulating hormone (FSH) on pregnancy rates in infertile patients.

Material and Methods: between 2015-2017, 387 females intended to have in vitro fertilization (IVF) for infertility treatment (226 patients use Gonal-F and 161 using Puregon.

Results: Serum E2 concentration at hCG time was higher with follitropin-a treated patients, and a larger number of retrieved oocyte result in a large number of the transferred embryo, and high pregnancy rate than Follitropin-b treated patients.

Conclusions: Gonal-F (Follitropin-a) is associated with a potential stimulatory effect on ovaries. Puregon (Follitropin-b) was associated with a lower clinical pregnancy rate (PR). E2 level 5-7 days after stimulation can be used as an indicator of the success of IVF.

Keywords: COS, Fertilization, Follitropin-a, Follitropin-b, Gonal-F, IVF, Puregon.

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INTRODUCTION

Infertility is defined clinically as at least 12 months of sexual intercourse without contraception and without accomplishing pregnancy.[1] *In vitro* fertilization (IVF) is a complex series of procedures used to treat fertility or genetic problems and assist with the conception of a child. VF works by utilizing a mix of drugs and surgeries to enable sperm to fertilize an egg and help the prepared egg embed in the uterus. FSH and LH drive Folliculogenesis and steroidogenesis both in a spontaneous menstrual cycle and during ovulation induction.[2]

With recombinant human follicle-stimulating hormone (r-hFSH), controlled ovarian stimulation (COS) with gonadotropins to produce multiple follicular development and high-quality oocytes is the cornerstone of assisted reproductive technology.[3] Controlled ovarian hyperstimulation (COH) is viewed as a key factor in the accomplishment of IVF–embryo transfer. Usually, COH includes the coadministration of GnRH analogs and gonadotropins aiming to prevent the premature increase in LH and to facilitate folliculogenesis and steroidogenesis. At present, several gonadotropin products are classified according to their source and constitution: the urinary hMG and FSH and the recombinant FSH and LH preparations, which contain FSH, LH, or both.[4]

Early recombinant FSH proteins communicated in chinese hamster ovary (CHO) cells are named follitropin alfa or follitropin beta. FSH is composed of two extensively glycosylated protein subunits, and to express recombinant FSH (rFSH) for therapeutic use, the genes encoding the human FSH subunits are introduced into a mammalian cell line from which FSH protein is secreted and purified.[5]

Recombinant innovation has addressed the requirement for an increasingly dependable FSH source. Under proper conditions, the qualities that code for the human FSH alpha and beta subunits are fused into the atomic DNA of a host cell

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by means of a plasmid vector utilizing grafted DNA strings containing the FSH quality and bacterial DNA sections. The subsequent production steps are similar for both preparations. In any case, in spite of a progression of anion and cation trade chromatography steps, hydrophobic chromatography and size exclusion chromatography used to deliver follitropin beta, an immune-affinity venture with a particular monoclonal counter acting agent like the neutralizer utilized for HP-hFSH creation is utilized for follitropin alfa.

Because of the slight contrasts in their creation and purification techniques, the products are not similar, with varieties in posttranslational glycosylation that yield diverse sialic acid corrosive buildup syntheses and distinctive isoelectric coefficients.[6]

Number of eggs, which is obtained from hormonal stimulation accomplished by GnRH analogs, is remaining the main step of successful fertilization. In patients defined "poor responders," the predetermined number of got eggs remains the fundamental issue in optimizing the live birth rates. In fact, as a result of a lower number of oocytes retrieved, there are fewer embryos to select and transfer, and subsequently, these patients have lower pregnancy rates per transfer and lower cumulative pregnancy rates per started cycle compared with normal responders.[7]

Numerous examinations and various meta- analyses looking at changed FSH preparations have yielded conflicting outcomes for ovarian stimulation and pregnancy rate.[8]

The present investigation aimed to evaluate the rate of pregnancy as a comparison between a two novel recombinant human FSH; Follitropin-a (Gonal-F) versus follitropin-b (Puregon). Because of the similarity in the active substance as well as the formulation, Gonal-F treatment (Follitropin-a) was expected to result in efficacy and safety profiles similar to those of Puregon (Follitropin-b).

MATERIAL AND METHODS

This prospective study included 387 females intended to have in vitro fertilization (IVF) for infertility treatment from March 2015 to September 2018 in Iraqi centers. The comparison between two-follitropin preparations was carried out regarding embryo transfer, size of ovum, and morphology of mature oocytes, HCG level before and after administration, basal E2, and pregnancy rate.

Patients

Females were selected according to the included criteria, and some of them are excluded due to associated variable factors, which may affect the outcome of the results.

The main inclusion criteria included women with age were between 19–39 years with body mass index (BMI) range between 21–32 kg/m^{2,} women having normal hormonal rhythm with the regular menstrual cycle (25–35 days), normal uterine cavity as confirmed by intrauterine ultrasound and normal morphological ovaries.

The exclusion criteria included a previous reproductive trial (surgical or hormonal), endometriosis, sever ovarian hyperstimulation, polycystic ovarian disease, hypothalamic or pituitary disorder, and hyperprolactinemia.

Study design

The eligible participants were randomized into a two-treatment group to receive either Gonal-F or Puregon. Age and weight for both groups was recorded, and endometrial thickness was confirmed by transvaginal ultrasound (endometrial thickness of < 5 mm) supplemented with serum E concentration (< 150 pmol/L) where necessary. FSH for both groups was administered as a daily bases dose. The first group was administered 150 IU Gonal-F, and the second group was administered Puregon 50 IU. The patients were investigated 7 days after FSH administration to assess follicular development and growth and patient response to COS.

All patients were administered hCG 10,000 IU at the time when at least three follicles are more than 18 mm recognized by transvaginal ultrasound with no more than 24 days of ovarian stimulation. Patient inappropriately stimulated (follicles less than 18mm) were excluded. Serum E2 concentration was measured on the day of hCG administration, and subsequent measurements were done on day 5 or 7.

Oocytes were retrieved 34–36 hours after induction of ovulation, and microinjection was done after 24 hours of the meiotic stage.

Progesterone was given as suppositories 400 mg daily for 14 days, and patient follow-up was done by intrauterine and hormonal assessment.

Statistical analysis

Study groups were compared with respect to all variables; the mean value was expressed as the mean ± standard deviation (SD). Using Independent sample t-test and Chi square test compared categorical variables. The p-value < 0.05 was considered as statistically significant. For statistical analysis, IBM SPSS version 22 was used.

RESULTS

Three hundred and eighty-seven women were involved in this study, a 226 were used Gonal-F and 161 using Puregon. There was no significant change between the two groups in age and weight (p = 0.876 and 0.271 respectively). For all patients, the baseline serum E2 concentration was measured; there was no significant difference between the study groups (p = 0.415), suggesting adequate randomization of the studied population (Table 1).

The range of the days from the beginning of stimulation to the time of matured follicles recognition for the entire patient was 18.2 ± 5.2, although it was longer in Gonal-F, but no significant variability between both groups (p = 0.296).

The serum concentration of E2 at the time of ovulation (at hCG) was significantly higher in the Gonal-F group indicating higher ovarian response (p = 0.04592).

Follicles with size ≥18mm was 33% higher in Gonal-F group in comparison to the Puregon group (p = 0.0423)

The higher ovarian stimulation observed by Gonal-F was supported by a significantly more substantial number of the

retrieved oocyte with a subsequent significant large number of Embryo transferred (p = 0.00519, 0.012) subsequently.

The total number of successful IVF was 142 (36.69%) patients, and the percentages of women with an ongoing pregnancy and live-born children within study groups were significantly higher in protocol using Follitropin-a 106 (46.90%) in comparison to that using Follitropin-b 36 (22.36%) (p = 0.0002) (Table 1).

The 5-7 days of E2 level after fertilization was assessed for the entire patients, a significantly higher serum concentration of E2 was found in on going pregnant patient in comparison to the failed IVF patients (p = 0.035). No significant variability in E2 serum concentration was found between two groups in ongoing pregnant women (p = 0.46) (Table 2).

DISCUSSION

The adequate randomization of the studied population is supported by no difference in age, weight, baseline E2, and duration of stimulation.

In this study, we found that E2 concentration at hCG time was higher with Follitropin-a treated patients, and more significant number of retrieved oocyte results in large number of transferred embryo and high pregnancy rate than Follitropin-b treated patients.

The serum estradiol (E2) level is utilized to assess follicle development. In pre-menopausal women, granulosa cells in the follicles mainly secrete E2.

As these cells isolate and multiply inside a follicle, expanding in number as the follicle develops, the E2 level additionally increments. Consequently, the E2 level is a good index for follicles development.[9] Additionally, N. Siddhartha *et al.* and Siddhartha Nagireddy *et al.* proposed higher E2 levels upon the arrival day of the ovulation trigger would anticipate expanded oocyte yield after COH.

E2 levels in the scope of 3000–4000 pg/mL would most likely predict increases in the rate of fertilization and pregnancies in ICSI cycles.[10,11] E2 levels, in combination with age and FSH, can be used to predict outcomes during an ongoing IVF cycle. E2 levels correlated with increasing live birth rates per cycle.[12] The elevation of serum E2 concentration throughout the process of stimulation is directly associated with IVF outcome.[13] In contrast, Matal *et al.* supported that serum estradiol does not exert any positive or negative influence on IVF outcome, whereas estradiol per mature follicle and retrieved oocytes do have an impact.

The appropriate size of follicles at the time of oocyte retrieval paly an important role in IVF success.[15]

Overall, mature oocytes are most likely present in Follicles with size of at least 12–22 mm on the day of oocyte retrieval, while post-mature oocytes are mainly present in larger follicles. In general, most centers hCG admiration is initiated once follicle size reached more than 17mm in diameter. Hu X *et al.* indicated that proper follicular maturation and peak E2 level result in better implantation and pregnancy rate.[16] This was consistent with this study, a high serum concentration of E2 at hCG indicate a proper maturation and large number of mature follicles were recognized (Follitropin-a) in comparison to low serum concentration (Follitropin-b).

The number of retrieved oocyte is not significantly effect the treatment outcome, although, the gold standard oocytes number will be 5–15, this is associated with high pregnancy rate after IVF.[17] In this study, the number of retrieved oocytes were significantly higher in Follitropin-a treated patient and was within the acceptable range for higher rate of pregnancy outcome.

Past studies regarding to stimulation outcome of follitropin alfa or follitropin beta indicating that Gonal-F and Puregon may be equally suitable for use in ovarian stimulation for IVF.[18] In the other hand, Raoul Orvieto *et al* conclude that the use of follitropin-beta was associated with a tendency toward a lower clinical pregnancy rate (PR), and with significantly higher E2 levels despite the use of significantly lower total

Table 1: Comparison between Follitropin-a and follitropin-b efficacy for women undergoing IVF

Parameter	*Total (n = 387)*	*Follitropin-a (n = 226)*	*Follitropin-b (n = 161)*	*p-value*
Age	28.7 ± 5.8	29.6 ± 6.0	27.4 ± 5.4	0.876
Weight	72.3 ± 10.9	71.6 ± 9.3	74.3 ± 15.0	0.271
Baseline of E_2	49.6 ± 22.7	54.7 ± 25.0	46.8 ± 21.6	0.41591
Days ST	18.2 ± 5.2	18.9 ± 5.4	17.2 ± 4.8	0.296
At HCG	1784.6 ± 893.3	1956.5 ± 943.7	1498.1 ± 734.1	0.04592*
Size of follicles ≥ 18 mm	59.5%	76 %	43%	0.0223*
No. of retrieved oocyte	8.8 ± 5.8	10.3 ± 6.1	6.3 ± 4.6	0.00519*
No. of Embryo transferred	2.6 ± 1.4	3.1 ± 1.1	1.9 ± 1.6	0.012*
No. Of successful IVF	142 /387 (36.69%)	106/226 (46.90%)	36/161 (22.36%)	0.0002*

* Significant

Table 2: Comparison of E2 level 5 to 7 days after fertilization

Group	*Parameters*	*E2 AF 5 or 7 days*	*p-value*
All women (Pregnancy outcome)	The success of IVF (conception)	1580.4 ± 1253.3	0.035*
	Failure of IVF (conception)	982.8 ± 650.6	
Successful IVF (conception) Between-group	Follitropin-a (n=106)	883.3 ± 812.8	0.46
	Follitropin-b (n = 36)	679.7 ± 523.7	

* Significant

gonadotropin dose.[19] *Samuel C Pang* observed no statistically significant differences in the number of mature follicles or oocytes retrieved and the number of clinical pregnancies was also similar between follitropin a and follitropin b,[20] this isn't reliable with N L Vuong *et al* which saw that Corifollitropin alfa is an alluring alternative for ladies since it lessens the burden of COS treatment, and is better for human services experts since it requires less staff assets for medication organization and observing while at the same time giving proportionate results.[21]

In this study, the rate of successful IVF and pregnancy outcome with lived delivery was higher in Gonal-F. This result could be related to both longer stimulatory days and; although not significant; higher E2 baseline in Gonal-F in comparison to the Puregon or could be due to the different biochemical properties of both product. Otherwise, the higher stimulatory effect of Gonal-F is confirmed by large number of matured follicles (>18mm in diameter) and number of retrieved oocytes.

Suneeta mittal *et al* and Sudha Prasad *et al* confirm that Estradiol level on down-regulated day 2 of menstrual cycle and up-regulation on the day of trigger was found to have a significant impact on the success of IVF and Serum estradiol elevation on 5-7 day is an important predictor for IVF success.[22,23] In the current study, the 5-7 day serum level of E2 concentration can be used as indicator for the success of IVF as result of significant high concentration in patient bearing fetus the entire patient and a no significant variability between two groups.

LIMITATIONS

This study has various confinements that ought to be recognized. The first is the small data included in our study. Large scald data could result in suspected change in the significances. The second is the male factor should be included in the study. Male sperm should be studied carefully to exclude any morphological or viability character could affect the result.

CONCLUSION

Gonal-F (Follitropin-a) is associated with potential stimulatory effect on ovaries. Puregon (Follitropin-b) was associated with lower clinical pregnancy rate (PR). E2 level 5-7 days after stimulation can be used as indicator for the success of IVF.

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