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Research Article

The Effect of Addition Recombinant Follicle-Stimulating Hormone (rFSH), Human Menopausal Gonadotropin (hMG), *In Vitro* Fertilization on its Outcomes and Cost-Effectiveness in Young Females

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Abstract

Purpose: In a difficult economic situation forced by the Syrian war, we approached different methods aiming to play important role in cost-effectiveness hence offering the ART service by reducing the cost of drugs by 22%. This research aims to carry out a comparison of the IVF outcomes as well as rates of pregnancy in young females, undergoing COS for IVF/ ICSI, either with the combination of hMG and rFSH or with rFSH using antagonist flexible protocol. The addition of hMG with FSH is likely to result in a significant reduction in the IVF cost.

Patients and Methods: This retrospective research was performed in the British-Syrian Fertility center from 10th April 2018 to 11th May 2021. The target population for this research was females (< 35 years) undergoing OS for ICSI/ IVF along with embryo transfer.

1822 females ≤ 35 years were recruited for this research, such that N = 798 patients received rFSH only Follitrope LG®), whereas N=1024 patients received hMG (IVF-M LG®) and rFSH (Follitrope®).

Results: The outcomes of this research revealed that the pregnancy rates of receivers of hMG + rFSH, and rFSH alone were not different.

However, rFSH alone treatment is expensive. In this regard, the addition of hMG with rFSH is likely to result in a significant reduction in the IVF treatment cost, whoever we could consider another approach by using uhCG instead of rhCG then we would gain reduction of medication cost by 25%, provide similar IVF outcomes for maturation rate, fertilization rate and rate of pregnancy.

Conclusion: Analyzing the outcomes of statistical analysis, it can be stated that the IVF outcomes and rates of pregnancy were similar among individuals treated with rFSH alone, and hMG and rFSH. However, the addition of hMG with rFSH is anticipated to have a significant reduction in the overall cost of treatment. Although using uhCG reduced the cost of hCG injection significantly by ¾ (cost of rhCG equivalent of 4 times of uhCG) the result should be taken into consideration when the decision made which hCG should take Thus, based on outcomes of this research, it can be stated that combination of hMG and rFSH must be utilized, as compared to rFSH alone.

Keywords: *hMG; rFSH; Controlled Ovarian Stimulation; IVF; Cost-Effectiveness; Pregnancy Rate*

Introduction

According to Steptoe, *in vitro* fertilization (IVF), along with the transfer of embryo was utilized for management of bypass infertility in females having bilateral tubal occlusion [1]. By the time, IVF was also used for managing male subfertility, failed ovulation induction, endometriosis, and cervical factor [2]. The lifetime prevalence of infertility in the United Kingdom (UK), defined as at least 1 year of unsuccessful attempts to conceive, has been reported to range between 17.3% and 26.4% [3,4]. Treatment for infertility has a very good prognosis, with 80% - 90% of couples being successful after 1 year and 95% after 2 years. Exogenous gonadotropins have been used to induce ovulation since the first half of the twentieth century, in humans, follicle-stimulating hormone (FSH) and Luteinizing Hormone (LH) act in concert to stimulate folliculogenesis and ovulation [5]. Therefore, these gonadotropins are used in the controlled ovarian stimulation (COS) in order to produce relatively high oocyte number to be used fresh or after cryopreservation to obtain pregnancies [6], recently they have been considered a treatment option for some forms of male hypogonadism with low-to-normal gonadotropin levels, this could be explained by the fact that IVF outcomes are dependent on the functions of recombinant follicle-stimulating hormone (rFSH), human menopausal gonadotropin (hMG), recombinant luteinizing hormone (rLH), and urinary human menopausal gonadotropin (uHMG) are widely used for controlled ovarian stimulation (COS).

The rFSH is administered in doses (100 to 600 IU/day) for ovarian stimulation [7]. As a result, rFSH is essential for the procedure of Controlled Ovarian Stimulation (COS) through assisted reproductive technology (ART). However, studies showed that hMG have higher rates of pregnancy in comparison to the effect of rFSH in GnRH [8-11]. Thus, the GnRH antagonist and agonist were used in COS protocols of COS for Intra-Cytoplasmic Sperm Injection (ICSI), and IVF, and outcomes of some of the randomized controlled trials (RCT) indicated that rFSH and highly purified hMG (hp-hMG) have similar effects in terms of rates of pregnancy, live birth, as well as pregnancy loss [12,13].

The explanation of the importance of gonadotropin as having an essential role in OS; therefore, widely utilized for treating infertility [14] is due to its mechanism of action GnRH stimulates FSH and LH secretion from the anterior region of the pituitary gland, which then regulates the processes of follicle development and the process of dominant follicle selection [15]. It is also reported that GnRH antagonists inhibit LH secretion, decreasing rates of pregnancy have been reported concerning the medication dosage [16]. As the levels of endogenous LH are at risk of falling too low, specifically along with the females of advanced reproductive age, LH supplementation effects have been shown to have some effects on the GnRH antagonist protocol which was detectable in older females. This could be explained by the fact that FSH stimulated by GnRH contributes to the regulation of antral follicular growth, whereas, LH is responsible for promoting steroidogenesis, developing leading follicle, and exerting several functions during the natural as well as stimulating cycle. LH binds to LH/hCG receptor (LHCG-R), which is present on granulosa, ovarian theca, luteal cells, and extragonadal tissue. LHCG-R is responsible for the generation of extragonadal effects on the processes of implantation, oviduct regulation, as well as cervical functions regulation [17-21]. Since the last two decades, several researchers have studied the role of exogenous LH supplementation in COS for ART; however, the clinical use of r-LH in OS for ART is still not clear [22,23]. Recently, HMG and rFSH are the two most common gonadotrophins, which are utilized in controlled ovarian stimulation protocols [24]. The exogenous gonadotrophins administration maintains LH and FSH above the critical threshold level is required to stimulate follicle development and to facilitate retrieving multiple oocytes in one IVF cycle [25]. The premature LH surge is suppressed by the administration of GnRH agonist or antagonist; however, the maturation and ovulation of the final oocyte are triggered by either GnRH agonist, or HCG, or both in combination [26].

The conventional protocols for ovarian stimulation are efficient for acquiring desired outcomes of clinical procedures; however, high gonadotrophins dose is likely to give rise to discomfort, and clinical complications, including ovarian torsion, ovarian hyperstimulation syndrome (OHSS), as well as other complications [28]. In recent years, mild stimulation protocols, using lower doses (≤ 150 IU/day), as well as shorter time duration for exogenous gonadotrophins is considered as a safer and affordable option for IVF treatment (Fauser., *et al*. 2010) and (J Martin 2006) [29]. In comparison to conventional stimulation, mild stimulation has lower rates of pregnancy per cycle in older females; however, the cumulative rate of pregnancy for conventional and mild stimulation is comparable [30]. Contradictory opinions on the impacts of mild as well as conventional stimulation, on embryo quality, exist [31]. Therefore, there is a requirement for further research on the advantages and challenges of mild as conventional stimulation protocols.

This retrospective research aimed to examine the outcomes of IVF/ intra-cytoplasmic sperm injection (ICSI) in GnRH antagonist protocol with hMG + rFSH or rFSH only, among younger females.

For hMG we used IVF-M Each vial contains 75 IU or 150 IU of hMG (human menopausal gonadotropin), having equal quantities of FSH (follicle-stimulating hormone) and LH (luteinizing hormone). While for rFSH we used Follitrope Inj. 75 or 150 IU recombinant follicle-stimulating hormone (FSH) lyophilized powder Follitrope Pre-filled Syringe 75, 150, 225 or 300 IU recombinant follicle-stimulating hormone (FSH) liquid.

Safety

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly concerning the number and pattern of adverse events.

Pharmacokinetics

Based on these results, it can be concluded that the test rFSH (Treatment A) is bioequivalent to the reference rFSH and hMG (Treatment B) following a median dose of 225 IU.

Ethics

Independent ethics committee (IEC) or institution Review Board (IRB)

The clinical study protocol, and relevant associated documents, and informed consent forms were reviewed and approved by an Institutional Review Board (Institutional Review Board Services).

The study protocol, any relevant associated documents, and informed consent forms are approved and A non-objection letter from the Syrian authorities was received before the beginning of the study.

Ethical conduct of the study

All clinical work was conducted in compliance with Good Clinical Practices and local regulatory requirements.

Subject information and consent

As retrospective study we understand that no need to an informed consent form(s) in Arabic for review apart from the routine consent of IVF treatment. Before initiation of study procedures, the informed consent form was verbally reviewed with subjects, allowing sufficient time for review of the information provided and to answer any question subjects had.

Scope of study

In a difficult economic situation forced by the Syrian war, we approached different methods aiming to play important role in cost-effectiveness hence offering the ART service by reducing the cost of drugs by 22%. This research aims to carry out a comparison of the IVF outcomes as well as rates of pregnancy in young females, undergoing COS for IVF/ICSI, either with the combination of hMG and rFSH or with r FSH using Antagonist protocol (Cetrotide 0.25 mg) in a flexible protocol (from stimulation day 2). The addition of hMG with FSH is likely to result in a significant reduction in the IVF cost. For a literature search, Science Direct, Cochrane Library, and PubMed were searched by using the search terms, hMG, rFSH, expense, cost-effectiveness, and IVF. It was revealed that none of the research had assessed the cost-effectiveness of combining hMG and rFSH, as compared to using rFSH alone. For this reason, this research aims to fill this research gap.

Hypothesis

The following hypotheses are considered for this research:

- H1: There is no significant difference of cost between rFSH alone and hMG with rFSH for IVF outcome and rate of pregnancy.

- Ho: The combination of hMG and rFSH is cost-effective over rFSH only, whereas, the outcome of IVF and rate of pregnancy is similar in both cases.

Objectives of the Study

The research objectives considered for this research are listed below:

- To analyze the pregnancy rate of IVF among the receivers of a combination of hMG +rFSH, and rFSH in IVF OS.
- To assess the pregnancy rate between the receivers of a combination of hMG + rFSH, and rFSH alone in IVF OS.
- To carry out a comparison of the cost-effectiveness of the combination of rFSH + hMG in OS protocols in ICSI/ IVF treatment cycles.

Methodology

This retrospective research was performed in the British-Syrian Fertility centre from April 2018 to May 2021. The target population for this research was females (< 35 years) undergoing OS for ICSI/ IVF along with embryo transfer. Due to Syrian war which impact the availability of medication we had chosen the protocols of HMG + rFSH or rFSH alone. We appreciate this opportunity of research to explain the considerations supporting specific methodology choices made and to clarify the potential impact of these decisions on the outcome of the trial.

The research participants were selected after acquiring informed consent by using inclusion and exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria for this research ascertained the inclusion of infertile 19 to 35 years old females, having a regular menstrual cycle of 25 - 35 days. The females experiencing infertility due to tubal factor, male infertility (including Azoospermia), unknown reasons, or combined factors were eligible for this research. It was also ascertained that females have hormonal profile i.e. LH, normal basal serum E2, P levels, and FSH during the early follicular phase. Additional to Hepatitis B, HIV, FBC as routine check-up according to local health service authority instruction, the females having a poor response to gonadotropin hormone therapy, with a history of POR, and had 3 retrieved ≥ 3 oocytes via conventional stimulation protocol were also eligible for this research. Moreover, females with abnormal ovarian reserve test (presenting > 5 follicles at the time of screening), were also eligible for participation.

Females more than 35 years old, Body Mass Index > 30 kg/m^2, having a history of significant systemic metabolic or endocrine abnormalities, history of uterine, breast, ovarian, pituitary gland, and hypothalamus tumours, positive for syphilis or HIV were excluded from this research. In addition, females having a history of ovarian, or uterine surgical treatment, hypersensitivity to rFSH, history of severe ovarian hyperstimulation symptoms (OHSS) during the IVF cycles were also excluded. Moreover, the females diagnosed with ovarian, uterine, adnexa (hydrosalpinx) abnormalities at the time of screening were also excluded from this research. In addition, the females having a history of more than three consecutive failed cycles was also excluded from this research. In addition, females were also excluded based on lifestyle-related habits.

Research population

N = 1822 females ≤ 35 years were recruited for this research, such that N = 798 patients received rFSH only Follitrope LG®), whereas N = 1024 patients received hMG (IVF-M LG®) and rFSH (Follitrope®).

Primary and secondary outcomes

Primary outcomes included embryological profile, as well as IVF outcomes (total number of oocytes, the total number of matured oocytes, the fertilized egg, and pregnancy outcome).

Whereas, secondary outcomes were analysis of the cost-effectiveness of including hMG and minimal use of rFSH (IVFM + Follitrope) within stimulation protocols for the IVF programs, instead of rFSH (Follitrope) alone.

Treatment regimen

At the second or third day of the treatment cycle, the OS was carried out by injecting 150 - 275 IU urinary FSH (hMG; IVF-M LG®), with 75 iu recombinant FSH (rFSH; Follitrope LG®), per day or 225 - 300 recombinant FSH (rFSH; Follitrope LG®) as starting dose for 5 days. When on transvaginal ultrasound presented that lead follicle's mean diameter was 14 - 15 mm, 0.25 mg of a GnRH antagonist (Cetrotide®) per day was provided to the patients. After GnRH antagonist administration, hMG (IVF-M LG®) administration was adjusted and carried out in FSH/hMG group, and rFSH was continued in FSH alone group. hMG (75 IU) comprising of 75 IU of LH activity and 75 IU FSH; therefore, hMG and rFSH doses were adjusted based on size, and the number of follicles, as well as based on Estradiol level. However, no specific criteria were utilized to determine the selection of FSH or hMG.

After the development of at least two follicles (≥ 16 mm in diameter), egg maturation was triggered by recombinant hCG (Ovitrelle 250®), or hCG injection (PREGNYL® 5,000 or 10,000 IU). After 34 - 35 hours, eggs were retrieved by ultrasound-guided transvaginal egg retrieval process, and ICSI, IVF, or IVF/ICSI combination was performed based on the condition of sperm. Stimulation protocol was used for data stratification. In FSH-hMG group, N = 544, and N = 480 patients were triggered by uHCG, and rHCG, respectively. In addition, in FSH alone group, N = 398 and N = 400 patients were triggered by rHCG and uHCG.

Statistical analysis

The statistical analysis was carried out by using Statistical Package for Social Science (SPSS), version 24.0, after assessing the data for completeness, and correction of errors. The nor-normal distribution of data was confirmed by Shapiro Wilk and Kolmogorov Smirnov tests. The Mann Whitney U test was conducted to compare demographics, and other continuous variables of recipients recruited in both groups. Moreover, the Chi-Squared test was conducted to compare endometrial thickness, triggering medicine, TESA, outcomes of pregnancy, and other categorical variables between the two groups. All statistical tests were performed under a 95% confidence interval.

Results

Characteristics	Attributes	N	%
Factor	Male factor	1054	57.8
	PCOS (Polycystic Ovarian Syndrome)	298	16.4
	Unexplained	470	25.8
TESA (Testicular Sperm Aspiration)	Yes	126	6.9
	No	1696	93.1
Stimulation	rFSH	798	43.8
	hMG+rFSH	1024	56.2
Triggering medicine	rhCG	858	47.1
	uhCG	964	52.9
Endometrial thickness	Favorable	1316	72.2
	unfavorable	506	27.8
Pregnancy outcome	Negative	892	49.0
	Positive	930	51.0

Table 1: *(N = 1822) Cases distribution by factors.*
**Protocol: Antagonist for all cases.*

Results from table 1 show male factor was the predominant factor in N = 1054 (57.8%) cases. This table presented that N = 1024 (56.2%) patients underwent simulation by rFSH, and hMG, and N = 798 (43.8%) received rFSH. The triggering medicine rhCG were provided to n = 858 (47.1%) cases, whereas, uhCG was provided to N = 964 (52.9%) cases. N = 1316 (72.2%) cases were reported to have favorable endometrium thickness, and N = 892 (51%) females were successfully pregnant.

Characteristics	Mean	Std. Error of Mean	M Median	Std. Deviation	Minimum	Maximum
Age(years)	30.076	.1416	31.0	4.2731	19.0	35.0
BMI (kg/m)	25.4219	.15087	24.9	4.55370	0.0	37.8
FSH	6.9531	.06965	6.9	2.10102	4.0	49.0
MII (Metaphase II)	8.6092	.12091	8.0	3.64931	2.0	19.0
2PN (Bipronuclear)	6.4501	.10190	6.0	3.07551	1.0	16.0
Embryos on day 3	5.3019	09326	5.0	2.81479	1.0	16.0
Duration of stimulation (days)	10.3875	.02073	10.0	0.62566	9.0	13.0
Endometrial thickness (mm)	9.8390	.05477	9.6	1.65315	7.0	15.0
Fertilizing rate	0.7545	.00614	0.7500	0.18532	0.20	1.30
Pregnancy rate	0.51	0.017	1.00	.500	-	-

Table 2*: Distribution of (N = 1822) cases by demographics and other factors.*

The mean age of the receivers was 30.07 ± 4.27 years, whereas BMI levels were 25.42 ± 4.55 Kg/m^2 (Table 2). The Patient's data reported that the mean values for Metaphase II (MII) and FSH were 8.61 ± 3.65, and 6.95 ± 2.10, whereas, the mean value of 2PN was 6.45 ± 3.07. Moreover, the mean endometrial thickness in all patients was 9.84 ± 1.65 mm. Table 2 also shows that ten days was reported to be the median duration of stimulation, and the median number of embryos were three to five. Overall, the rates of maturation and fertilization were 67%, and 75%, whereas, rate of pregnancy was 51%.

Characteristics	Attributes	Stimulation with rFSH, N+ (%)	Stimulation with rFSH+hMG, N+ (%)	0R	P-value
Factor	Male factor	426 (53.4)	628 (61.3)	-	.008
	PCOS	126 (15.8)	172 (16.8)		
	Unexplained	246 (30.8)	224 (21.9)		
TESA	No	746 (93.5)	950 (92.8)	1.117	.675
	Yes	52 (6.5)	74 (7.2)		
Triggering medicine	rhCG	378 (47.4)	480 (46.9)	1.020	.882
	uhCG	420 (52.6)	544 (53.1)		
Endometrial thickness	Unfavorable	234 (29.3)	272 (26.6)	1.147	.356
	Favorable	564 (70.7)	752 (73.4)		
Result	Negative	384 (48.1)	508 (49.6)	.042	.656
	Positive	414 (51.9)	516 (50.4)		

Table 3: *Statistical analysis of the factor conditions using chi-square test. Statistical analysis were achieved by SPSS and p-value less than 0.05 was considered significant.*

**0dds ratios were generated for dichotomous variables.*

The chi-square test revealed that N = 628 (61.3%) of the cases which had received simulation rFSH + hMG had male factor with p-value = 0.008. The statistical analysis revealed that PCOS was the least common factor contributing to infertility in both groups. Table 3 also shows that endometrial thickness, triggering medicine, TESA, and results of pregnancy possessed no significant association with the stimulated medicines (rFSH, or combination of rFSH and hMG). However, the recipients of hMG + rFSH were found to have a higher favorable endometrial thickness, N = 752 (73.4%), as compared to rFSH alone, having N = 564 (70.7%). The receivers of hMG + rFSH also possessed slightly higher levels of TESA, as compared to the other group.

Characteristic	Stimulation with rFSH		Stimulation with hMG +rFSH		p-value
	Mean	SD	Mean	SD	
Age (years)	30.04	4.19	30.11	4.34	.502
BMI (kg/m^3)	25.64	4.72	25.26	4.42	.156
FSH	6.94	2.60	6.96	1.62	.199
MII	8.43	3.72	8.75	3.59	.072
PN2	6.44	3.14	6.46	3.03	.572
Embryos on day 3	5.65	2.89	5.03	2.72	.004
Duration of stimulation (days)	10.38	0.55	10.39	0.68	.394
Endometrial thickness (mm)	9.83	1.69	9.85	1.63	.951
Fertilizing rate	0.77	0.18	0.74	0.19	.167
Pregnancy rate	0.52	0.50	0.50	0.50	.656

Table 4: *Statistical analysis of the effect of characteristics using Mann Whitney U test. Statistical analysis was achieved by SPSS and p-value less than 0.05 was considered significant.*

Group 1 = Stimulation with rFSH. Group 2 = Stimulation with rFSH + hMG.

Mann Whitney U test performed.

Table 4 shows that age BMI levels, 2PN, MII, and FSH concentrations, simulation duration, rate of fertilization, the thickness of endometrial, and rates of pregnancy were not found to possess statistically significant differences, based on stimulation medicines ($p > .050$, for all variables). On the other hand, the receivers of rFSH were successful in achieving the high number of embryos, as compared to the other group ($p = 0.004$).

Table 5 data show that among the recipients, unexplained factor possessed association with infertility in rFSH group, whereas, male factor was the reason for infertility in hMG + rFSH group. The rFSH alone retrieved the higher number of oocytes, i.e. 12.71 ± 5.01 alone, as compared to hMG + rFSH, who were reported to retrieve 13.56 ± 5.17 oocytes ($p = 0.009$). Table 5 also presented that thickness of endometrial, result of pregnancy, and TESA was not reported to possess association with the patients receiving rhCG or uhCG.

Table 6 shows the Mann Whitney U test and found that individuals triggered by rhCG had lower MII, and 2PN, (7.19 ± 3.212 and 5.65 ± 2.96), as compared to hMG + rFSH (8.55 ± 3.41 and 6.64 ± 3.17) ($p < 0.001$). However, the case is opposite for 2PN ($p < .001$), and MII ($p < .002$), for the cases in which ovulation was triggered by uhCG. Table 6 revealed no statistically significant differences between other continuous variables in both groups.

	Characteristics	Attributes	rFSH alone N + (%)	hMG + rFSH N + (%)	OR	p-value
rhCG (n = 858)	Factor	Male factor	186 (49.2%)	264 (55%)	-	.001
		PCOS	48 (12.7%)	104 (21.7%)		
		Unexplained	144 (38.1%)	112 (23.3%)		
	TESA	No	358 (94.7%)	446 (92.9%)	1.365	.448
		Yes	20 (5.3%)	34 (7.1%)		
	Endometrial thickness	Unfavorable	102 (27%)	136 (28.3%)	0.935	.757
		Favorable	276 (73%)	344 (71.7%)		
	Result	Negative	204 (54%)	288 (60%)	0.782	.210
		Positive	174 (46%)	192 (40%)		
uhCG (n = 964)	Factor	Male factor	240 (57.1%)	364 (66.9%)	-	.067
		PCOS	78 (18,6%)	68 (12.5%)		
		Unexplained	102 (24.3%)	112 (20.6%)		
	TESA	No	388 (92.4%)	504 (92.6%)	0.962	.912
		Yes	32 (7.6%)	40 (7.4%)		
	Endometrial thickness	Unfavorable	132 (31.4%)	136 (25%)	1.375	.118
		Favorable	288 (6.6%)	408 (75%)		
	Result	Negative	180 (42.9%)	220 (40.4%)	1.105	.593
		Positive	240 (57.1%)	324 (59.6%)		

Table 5: *Chi-square test for assessing association between variables in (rFSH/ hMG + rFSH) in recipients of rhCG and uHCG. Statistical analysis was achieved by SPSS and p-value less than 0.05 was considered significant.*

**Odds ratios were generated for dichotomous variables.*

**Chi-square test was done.*

	Characteristics	Stimulation with rFSH		Stimulation with hMG + rFSH		p-value
		Mean	SD	Mean	SD	
rhCG (n = 429)	Age (years)	30.22	4.03	30.30	4.07	.568
	BMI (Kg/m^2)	25.78	4.28	25.82	4.03	.838
	FSH	6.77	1.52	6.84	1.65	.541
	MII	7.19	3.21	8.55	3.41	**<.001**
	PN2	5.65	2.96	6.64	3.17	**<.001**
	Embryos on day 3	5.00	2.72	5.28	2.83	.194
	Duration of stimulation	10.32	.50	10.30	0.54	.427
	Endometrial thickness	9.68	1.61	9.75	1.53	.819
	Fertilizing rate	0.79	0.21	0.77	0.21	.668
	Pregnancy rate	0.46	0.50	0.40	0.49	.210
uhCG (n = 482)	Age (years)	29.87	4.32	29.93	4.57	.673
	BMI (Kg/m^2)	25.51	5.09	24.76	4.68	.091
	FSH	7.09	3.27	7.08	1.57	.250
	MII	9.54	3.80	8.93	3.73	.119
	PN2	7.14	3.13	6.30	2.90	**.002**
	Embryos on day 3	6.23	2.92	4.82	2.62	**<.001**
	Duration of stimulation	10.44	0.58	10.47	0.78	.695
	Endometrial thickness	9.97	1.75	9.93	1.70	.889
	Fertilizing rate	0.75	0.16	0.72	0.16	.096
	Pregnancy rate	0.57	0.50	0.60	0.49	.594

**Group 1 = stimulation with rFSH, group 2 = stimulation with hMG + rFSH*

*** Mann Whitney U test was done*

Table 6: *Comparison between groups in terms of baseline characteristics as well as IVF outcomes split by rhCG and uHCG. Statistical analysis was achieved by SPSS and p-value less than 0.05 was considered significant.*

Discussion and Recommendations

To date, there is no established proof as to which gonadotropin is further successful when performing controlled ovarian stimulation (COS) in human IVF. However, patient groups in those studies are highly variable, and, as far as we know, no prior report shows the effects of these treatments compared over long-term follow-ups in a specific patient group (with a higher number of previous trials). The present study aims to assess the IVF outcomes of rFSH, rFSH + HMG replacement therapies administered and to reveal other finical factors.

Live birth is the outcome of interest to couples seeking infertility treatment and is now considered the most relevant outcome for couples undergoing ART rather than the number of oocytes retrieved. Ongoing pregnancy represents an appropriate primary endpoint for efficacy trials in ART as it is a practical surrogate for live birth (Arce., *et al*. 2005). We do not consider the slightly higher number of oocytes retrieved and MII in the rFSH+hMG group (G2) as an expression of enhanced efficiency of hMG or a protocol-driven finding. As known the presence of LH-activity in the HP-hMG preparation results in a more selective follicle recruitment process than an FSH-only gonadotrophin (Smitz., *et al.* 2007). The number of oocytes retrieved in the rFSH-hMG group is caused by the modulating effect of LH-activity. hence, rFSH-hMG is not to be viewed as less or more efficient; particularly as no difference between 8.83 and 8.75 oocytes (average number of oocytes retrieved with rFSH and rFSH-hMG, respectively) is irrelevant about pregnancy rates.

The outcomes of this research revealed that the pregnancy rates of receivers of hMG + rFSH, and rFSH alone were not different; however, the triggering medicine rhCG or uhCG we found to have significant impacts. The outcomes of this research are similar to the research conducted by [7,8], which indicated that rFSH, and rFSH and hMG have similar effects on the rates of pregnancy. The research outcomes also indicated differences in IVF outcomes, such that when the analysis was carried out based on triggering medicine, recipients of rhCG had higher PN2, MII, and oocytes. However, the recipients of uhCG were reported to have higher PN2 and the number of embryos on the third day in group A (rFSH only) while PN2 and embryos on day 3 are higher in group B (rFSH + hMG) to the recipient of rhCG. Thus, the analysis of cases revealed that uhCG recipients had a greater number of embryos, whereas, rhCG recipients had a higher number of oocytes, presenting that various IVF outcome parameters were significant for both groups. The IVF outcomes for receivers of hMG + rFSH, and rFSH alone were almost similar.

However, rFSH alone treatment is expensive. In this regard, the addition of hMG with rFSH is likely to result in a significant reduction in the IVF treatment cost (reduction of medication cost by 25%, if we add the cost of uhCG which is significantly less than rhCG), and provide similar IVF outcomes, and rate of pregnancy.

Based on the outcomes of this research, there is a requirement to conduct further research to examine the clear benefits of prescribing the combination of hMG and rFSH instead of rFSH alone. In addition, this research had recruited the participants from one region; therefore, future researches must be carried out in different regions for assessing the generalizability of outcomes of this research.

Conclusion

Analyzing the outcomes of statistical analysis, it can be stated that the IVF outcomes and rates of pregnancy were similar among individuals treated with rFSH alone, and hMG and rFSH. However, the addition of hMG with rFSH is anticipated to have a significant reduction in the overall cost of treatment. Although using uhCG reduced the cost of hCG injection significantly by ¾ (cost of rHCG equivalent of 4times of uhCG) the result should be taken into consideration when the decision made which hCG should take Thus, based on outcomes of this research, it can be stated that combination of hMG and rFSH must be utilized, as compared to rFSH alone.

Limitations of the Study

This research was carried out in a single centre, and the participants were not randomized, which is a potential limitation of this research. Moreover, the sample population considered for this research was not scientifically calculated by the researcher. In addition, this research only emphasized the advantages of hMG + rFSH and rFSH alone and did not compare the side effects, which hinders the generalizability of research outcomes.

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