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Controlled ovarian hyperstimulation (COH) with sequential hpfsh & hmg versus rec-F.S.H alone in ICSI cycle

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Abstract

Background: In spite of there are several publications on COH protocols evaluating the efficacy of various exogenous gonadotropins, no established protocols exist, and it isn't very clear which is best to the others.
Aims and objectives: The aim of this work is to investigate the sequential use of hpFSH+hHMG vs. rFSH alone on fertility outcome (rate of gestation, abortions and live delivery) in ICSI-cases.
Subjects and methods: This work recruited patients referred for assisted reproduction treatment (ART) cycles to Global Nile Infertility Center. Under supervised of main principal investigator during the period from February, 2020 to February, 2021 according to study protocol.
Result: Clinical pregnancy ratios were 71% . In Group 1,54% in Group-2. Group-1 was detected to have elevated clinical gestation ratios in comparison with other group, more over there was statistical significance0.01.
Conclusion: Hp-HMG adding can be utilized as a choice for correcting of outcomes in those whose respond is unpredictably suboptimal to ovulation inductions with HP-FSH throughout GnRH agonist protocols. The elevated yield of oocyte with r-FSH doesn't lead to high embryos quality. Hp-HMG supplement is a choice to improve IVF outcomes in patient's ovulation inductions with HP-FSH throughout GnRH agonist down-regulations. Mainly, hp-HMG is suggested as it can have an advantageous action on implantations on the particular group but to prone the effectiveness extensive prospective randomized control trials must be performed.

Background

Nowadays, assisted reproductive technology (ART) has been a well-known and high effective treatment for nonfertility. In ART, it is well recognized that the most significant features to maximize the rate of success of in vitro fertilization (IVF) are saving bigger numbers of good oocytes via controlled ovarian hyperstimulation (COH) and creating a receptive endometrium. Consequently, COH have a key role in accomplishing a high ART rate of success [1].

Various researches have confirmed that better outcomes regarding oocyte and quality of embryo, following rate of gestations, and live births is attained when HMG is employed for ovarian stimulations, in comparison to rFSH., But, other researches have revealed that rFSH is as operative as urinary FSH or HMG regarding the number of oocytes and embryos attained and the entire gonadotrophin dosage required [2].
Researches that make a comparison between hpFSH and rFSH found an increasein the ovarian recruitment of follicles in the rFSH-group. Daya revealed that rFSH was more preferred than hpFSH in accordance to the rate of gestation, whereas van Wely et al. showed a borderline a significant change of 5% elevated rate of clinical gestation in females given stimulation with hpFSH in comparison to rFSH. Selman et al. shoed that the mixture of hpFSH/rFSH for ovarian stimulations has a positive outcome on follicular improvement, oocyte quality, embryo improvement, and clinical outcomes in cases with repetitive IVF failure [3].

So far, various gonadotrophin arrangements were presented for controlled ovarian stimulation (COS) in pituitary-suppressed cases experiencing IVF/intra-cytoplasmic sperm injections (IVF/ICSI) procedure, regarding the evidence that each specific case has particular nonfertility causes, demographical and medical parameters require the usage of personalized routines in every case which must be grounded on the physiology of ordinary gestation [4].

Consequently, in spite of there are several publications on

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COH protocols evaluating the efficacy of various exogenous gonadotropins, no established protocols exist, and it isn't very clear which is best to the others. Therefore, the aim of the present work was to evaluate the efficiency of 2 various ovarian stimulating protocols, including hpFSH, HMG vs. R-FSH on oocyte and quality of embryo and IVF treating outcomes in cases experiencing IVF or ICSI [3].

In a new report [5], the commonest procedure of LH supplementations utilized in poor ovarian respond (POR) was HMG+rFSH, shadowed by HMG only, rLH+rFSH and small-dosage HCG+rFSH. But, the usage of LH supplementations throughout ovaries stimulations has long been a disagreement, and there was research have concluded the contradictory fact [6]. The aim of the current work was to evaluate outcome of sequential HPFSH+ hMG versus rFSH only in cases experiencing IVF-ET treatments with agonist protocols.

Patients and Methods

The study recruited patients referred for assisted reproduction treatment (ART) cycles to Global Nile Infertility Center. under supervised of main principle investigator during the period from february, 2020 to february, 2021 according to study protocol.This was an observational prospective analysis; this prospective study included a number of 250 females experiencing ICSI cycles.

Ethical approval: Ethical permission was sought from a Local Research Ethics Committee (REC).The pre procedure counseling about potential benefits and risks of all aspects of the study were clearly stated to the participants with giving choice to go through procedure or out of it.

Inclusion criteria: Ages between 20 & 35-yrs, males factors, tubal or non-explained nonfertility, steady mensess cycle from 21 to 35-days, ordinary functions of uterus in accordance to hysteron-salpingography (HSG), hysteroscopy or trans-vaginal ultrasonography (TVUS), ordinary ovaries in accordance to TVUS throughout earlier 6-mths previous to investigation and well-matched with ordinary adnexa and ordinary ovaries anatomy, and serum FSH levels lesser than 8 IU/l the entire number of females revealed non-detectable endometriosis in accordance to signs and clinical examinations in TVUS or diagnosing laparo-scopy, all cases have histories of non-explained sterility and ordinary ovulatory functions and ordinary semen analyzing in accordance to the WHO criteria.

Exclusion criteria for all subjects included: Cases with other ovulation diseases like hypo and hypergonadotropic, hyperprolactinemia, hypogonadism, thyroid diseases, ovarian or adrenal neoplasms, Cushing condition, preceding past of systemic disorders like endocrine and metabolic conditions, preceding past of unsuitable ovarian responding to stimulations with gonadotropin (poor responder) and previous past of more than three non-successful IVF, and any deformity of genitals will be omitted.

Plan of the study: Total no of cases 200 who agreed to participate

Cases have been exposed to:

1. Complete history taking

2. Clinical examinations: General, abdominal, vaginal examination.

Pelvic ultrasound examination: All scans have been done throughout the primary follicular stage of a spontaneous cycle (either preceding or within 3-mths of the treatment cycle).All ultrasound examinations were performed by the same investigator.An Toshiba Digital ; Toshiba Co. Ltd., Japan ultrasound machine with multifrequency tranvaginal probe was used for all ultrasound scans. The vaginal probe frequency was routinely selected at 7.5MHz.

All patients will be subjected to: Base-line FSH, LH, anti-Mullerian hormones (AMH) prolactin, thyroid stimulating hormones and testosterone serum level will be assessed for all cases in their preceding cycles.

The entire cases will be given oral contraceptive from 5th-day of menses cycle andwill undergo pituitary down-regulations given one-time everyday sub-cutaneous doses of 0.1 mg (Decapeptyl) short-acting gonadotropin release hormones (GnRH) analog from the 21st-day of their cycles with oral contra-ceptive pills pre-treatment. All the subsequent gonadotrophins will be used sub-cutaneously by cases. Afterward the stoppage of oral contra-ceptive pills for pituitary suppressions when the blood loss happened, the cases will randomized then separated to 2 equal groups.

Group 1: (100 case) which will receive hp FSH (fostimon ibsa) (150 IU/ampoule)will be initiated on 2nd-day of menses and subsequently afterward 6-day, HMG (meriofert ibsa), 150 Iu, s.c) will be supplemented. Administrations of HCG (chriomon), 10,000 IU i.m. will be performed, founded on ovarian responding as evaluated by consecutive vaginal US till the principal follicle get 1.8 cm diameter.

Group 2: (100 case) will be managed with recombinant FSH alone (Gonal-F)(ferring) (150 IU/ampoule) Vaginal sonographic examination will be done and in situation of suitable responses, the cases will undergo sonographic examination daily till they have at minimum 2 follicles ≥1.8 cm and at minimum 2 additional follicles with >1.7 cm in diameter. Ovulation will be persuaded via administrating of HCG (chriomon), 10,000 IU i.m. Endometrial width will be evaluated on the day of HCG injections. Oocyte pick-up will be done 34 to 36-h subsequent to HCG usage. Afterward the ICSI procedures, embryos will be counted in accordance to the morphologic look of their blastomeres and fragmentations. Embryo transfer will be done on5rd-day of ovum pick-up and 2-3 embryos will be transported per case by the sono-opaque catheter (Cook Medical, Ireland LTD) under sterile condition. In all patients, the luteal stage will be sustained via Prontogest pessary (ibsa) at a dosage of 400 mg/Bid, that will be initiated from the oocyte recovery day.

Outcome measures: Rates of gestation, implantations, clinical gestation, clinical pregnancy with embryonic heart beats and rate of constant gestation were the major outcomes gages.

Rate of gestation: Number of cases with serum β-hCG > 20-mIU/ml on 14th-day afterward OPU per the entire cases num-

ber.

Rate of implantations: Number of pregnancy sacs detected per the number of embryos transported. Clinical gestation: a gestation detected via ultrasonography visualizations of one or more gestation sacs or conclusive clinical gestation signs. It comprises ectopic gestation. Ongoing gestation was described as gestation going on beyond the 20th- week of pregnancy.

Statistical analysis: Collected data have been analyzed via windows IBM-SPSS-19. Quantitative data have been introduced in terms of mean and standard deviation (SD), whereas qualitative data have been introduced in terms of frequency distributions. Chi square testing, test was utilized to make a comparison among percentages. Mann-Whitney, kruskal Wallis testing and Student t-testing have been employed used to match means. Multi-regression analyzing was utilized to find out the joint influence of various nondependent parameters on the target (dependent variable) and Odds ratngio was calculated for factors predicting pregnancy outcome.

Results

Baseline features in this work, a number of 250-cases have been evaluated for suitability. Lastly, afterward administrations of deacetyl (0.1 mg daily) for down-regulating treatment,200-cases were randomly separated into 2 groups: HP-FSH+HMG group (n=100) received fostimon + meriofert and rFSH group (n=100) received .gonal f (Figure 1). Base-line demographical parameters and hormone levels at the start of ovulation in-

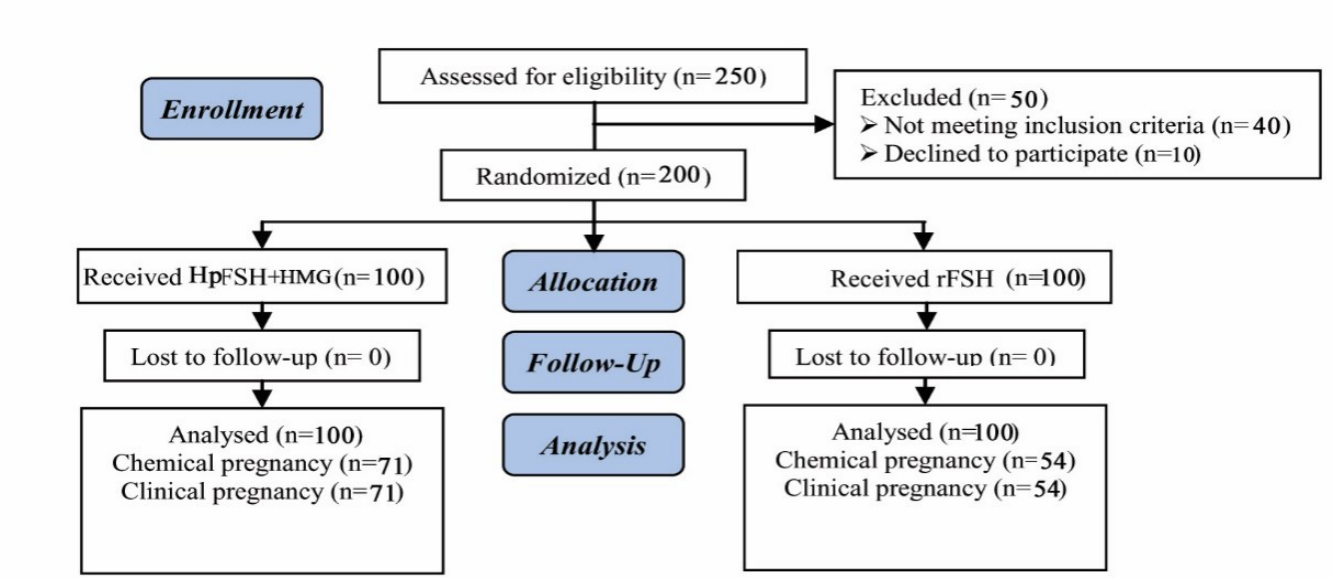

Table 1: *Comparing among the study groups in accordance to history and examination.*

History and examination	Group 1 Fostomin plus meriofert No=100		Group 2 Gonal f No=100		Test of Sig.	p
	No.	%	No.	%		
Age (years) 20-25 25-30 ≥ 30	 76 15 9	 76 15 9	 26 34 40	 26 34 40	χ^2=51.4	0.001*
Min. – Max. Mean ± SD. Median (IQR)	21-37 26.3±3.1 25(25)		22-39 29.7±4.8 29(25-34)		t=5.9	0.001*
BMI (kg/m²) Normal (18.5 - 24.9) Overweight (25-29.9) Obese (≥ 30)	 10 53 37	 10 53 37	 12 61 27	 12 61 27	χ^2=2.3	0.3
Min. – Max. Mean ± SD. Median (IQR)	24.5-32.6 28.3±2.6 27.7(26.1-31.1)		24.3-32.9 28.4±2.2 29.1(26.8-30.07)		t=0.3	0.7
Type of infertility Primary Secondary	 50 50	 50% 50%	 48 52	 48 52	χ^2=0.08	0.7
Male Female Both Unexplained	29 55 0 16	29 55 0 16	18 68 2 12	18 68 2 12	χ^2=6.5	0.09
Duration of infertility (years) Min. – Max. Mean ± SD. Median (IQR)	1-16 6.4±3.4 6(4-9)		2-15 6.5±3.1 6(5-8)		T=0.1	0.9

t: Student t-testing. *χ2: Chi square testing.*

Table 2: *Comparison between the study groups regarding treatment endometrial thickness.*

Treatment endometrial thickness (mm)	Group 1 Fostomin plus meriofert No=100	Group 2 Gonal f No=100	t	p
Pre				
Min. – Max.	8.0 – 9.0	8.0 – 9.0	0.2	0.7
Mean ± SD.	8.4 ± 0.5	8.4 ± 0.4		
Median (IQR)	8(8-9)	8(8-9)		
Post				
Min. – Max.	10.0 – 11.0	9.0 – 11.0	4.8	0.001*
Mean ± SD.	10.4 ± 0.4	10.03 ± 0.6		
Median (IQR)	10(10-11)	10(10)		
t_1 (p_0)	29.6 (<0.001*)	20.7 (<0.001*)		

ductions treatment were shown in (Table 1); this table shows that there is insignificant difference between two groups as regards age, BMI, Type of infertility, menses, ovarian volume, ovary pathology and endometriosis.

Chemical gestation: Positive serum β-subunit Human Chorionic Gonadotropin (β-hCG) in 5-6-wks afterward LMP last menstrual period or 13th to 15th- day afterward ET.

Clinical pregnancy: Number of sacs in ultrasonography for the total number of IVF cycles.

Clinical pregnancy ratios were 71%. in Group 1,54% in Group-2. Group-1 has been detected to have high clinical gestation ratios in comparison with other group, more over there was statistical significance 0.01

Both treating protocols have been matched in regard to the cases' demographical parameters (ages, parity, BMI, type and duration of infertility), the cycle features (number of gonadotropins utilized, endometrial width) and the cycle outcome (amount of oocytes retrieved, rate of fertilizations, best embryos quality, clinical gestation and rate of live births, rate of miscarriages, and rate of implantations). In the current work, 100-cases have been treated by hp-FSH+ hp-HMG (Group-1), 100-cases given r-FSH. (Group-2)

Discussion

Nowadays different gonadotropins arrangements like human menopausal gonadotropins (HMG) involving both FSH, LH activity, and recombinant FSH (rFSH) arrangements are utilized in controlled ovarian stimulations (COS) in suppressed pituitary cases experiencing IvF/ICSI treatment some evidences propose that administering drugs with LH activity in cases experiencing IVF may advance IVF outcomes by means of FSH only [7]. Some researchers have revealed lesser estradiol biosyn-thesis, lesser oocyte and embryo yields, and an elevated incidence of early gestation losing in normo-gonadotrophic females downregulated with a GnRH agonist and motivated with highly rFSH in comparison to females motivated with hMG or in a mixture with FSH. Highly purified-HMG (HP-HMG) and rFsH were extensively employed for different stimulations in infertile females experiencing ART. But, the influence of various gonadotropins arrangements on females, who experienced COS in invitro fertilization embryo transfers (IVT-ET) of controversial 2 metanalyses concluded slightly elevated rates of live births when utilizing HMG for COS as compared to rFsH in low doses GnRH versus extended protocols.

A study of clinic trail phase-III including 939-cases as well concluded that the rate of clinical gestation didn't vary among r-hFsH + rLH and rFsH alone (14.1% versur 16.8% pualue 0.32 correspondingly)

Researches that make a comparison between hpFSH and rFSH found an increasein the ovarian recruitment of follicles in the rFSH-group. Daya revealed that rFSH was more preferred than hpFSH in accordance to the rate of gestation, whereas van Wely et al. showed a borderline a significant change of 5% elevated rate of clinical gestation in females given stimulation with hpFSH in comparison to rFSH. Selman et al. shoed that the mixture of hpFSH/rFSH for ovarian stimulations has a positive outcome on follicular improvement, oocyte quality, embryo improvement, and clinical outcomes in cases with repetitive IVF failure [16]. The current work matched clinical gestational outcome in cases experiencing IVF/ICSI cycles via either sequential HPFSH & HMG. or rFSH only for COS. The entire cases were pituitary suppressed via GnRH agonist protocols and little doses of gonadotropin. The current work is suggestive for higher number of embryos transferred and elevated rate of clinical gestation that led to elevated rate live births in favor of sequential HPFSH & HMG regimens.

A nonsignificant change was found regarding the demographical and baseline parameters among the study groups. In rFSH-group, the P-level on the HCG trigger day was high significantly in comparison to that of HP-HMG+rFSH-group (4.3±2.2 versus 3.8±1.7 nmol/L, P-value<0.001. The rate of fertilizations in rFSH-group was low significantly as compared to second group (69.2% versus 73.9%, P-value<0.001). Concurrently, the percentages of cycles with new embryo transfers in rFSH-group was as well low significantly as compared to the second group (49.6% versus 57.5%, P-value=0.007). However, no change was found regarding the rates of cleavages, implantations, clinical pregnancies and ovarian hyper-stimulation syndromes (OHSS) among the study groups. These results have led to the suggestion that the dominance of hMG initiates from its LH contents,

Table 3: *Comparison between the two treatment groups regarding ovulation.*

Data	Group 1 Fostomin plus meriofert No=100	Group 2 Gonal f No=100	t	p
Oocyte Min. – Max. Mean ± SD. Median (IQR)	2-47 16.6±10.2 14(9-23)	0-36 15.7±9.5 14(8-23)	0.6	0.5
M2 Min. – Max. Mean ± SD. Median (IQR)	2-40 12.9±8.6 11(7-17)	0-28 11.6±7.3 12(4-17)	1.1	0.2
Embryo Min. – Max. Mean ± SD. Median (IQR)	0-37 9.3±7.9 5(4-13)	0-26 7.9±5.7 7.5(4-10)	1.4	0.1

Table 4: *Comparing among the 2 treatment groups regarding chemical gestation, clinical pregnancy and miscarriage.*

Clinical pregnancy	Group 1 Fostomin plus meriofert N=100	Group 2 Gonal f N=100	χ^2	P
Positive	71(71%)	54(54%)	6.1	0.01*
Negative	29(29%)	46(46%)		
Chemical Pregnancy				
Yes	75(75%)	59(59%)	5.7	0.01*
No	25(25%)	41(41%)		

P-value refers to Mann-Whitney test or Chi-squared test, when appropriate.

Table 5: *Total dose of GNH and clinical pregnancy.*

Clinical pregnancy	Positive	Negative
Fostomin	2440.1±788.8	3258.6±1065.8
Meriofert	2176.05±772.7	2984.2±1234.5
Gonal F	2805.5±1000.7	2967.3±1193.2

Table 6: *Univariate regression analysis of GNH effect on clinical pregnancy.*

GNH	Odds ratio	95% CI for Odds	P
Fostomin plus meriofert	2.08	1.1-3.7	0.01*
Gonal f	0.47	0.26-0.86	0.01*

consequently addition of recombinant LH to conventionally rFSH cycles can lead to a similar outcome [8]. This conception was lately evaluated by in vitro investigations. The hMG revealed 2 kinds of LH activity, one is resulting from LH and the second, that is as well recognized to be stronger, comes from hCG contents [8].

It was found that LH and hCG bond to a similar receptor, the luteinizing hormone chorionic gonadotrophin receptors as they are ≥80 percent of amino acids order [9]. In contrast, LH-CGR respond contrarily to LH and hCG which led to dissimilar influences of each molecule in human physiology throughout both follicle progress and 1st-trimester of gestation [10].

Our result approve the suggestion that treating by hMG plus hPFSH can attain a similar result in the oocytes number, M2-oocyte number and embryo quality, but a statistical change was found in chemical and clinical pregnancies and rate of live births with a better embryo quality in the 1st-group (.HPFSH & HMG). This variance has leveled due to the entire number and embryo quality that is high in HPFSH & HMG groups, while the embryo quality variance in the 2 groups was nonsignificant. Research matching the influence of rFSH-only versus hp-hMG plus rFSH versus LH plus rFSH arrangements in IVF/ICSI via an extended GnRH-a protocols. In the hp-HMG plusrFSH group has lesser retrieved oocytes number in comparison to FSH-only-group and rLH + rFSH group, whereas high purified hMG treatments cause an elevated rate of implantations and PR in fresh cycle / initiated cycle (p-value< 0.05), in comparison to rFSH. Cycle outcome for 7 < AFC< 20 cases were equivalent. Rate of Live births and clinical gestation were all better in r-FSH + hp-HMG group in comparison to r-FSH + r- LH group and r-FSH groups but there was nonsignificant change Barri P, et al., (11) Economical Analyzing of the Gonadotropin managements HP-hMG and rFSH for ART in France: A Markov Model Analysis Appl Health Econ Health Policy 2018. In the current work we didn't recorded the costs of each IVF cycle via HPFSH & HMG or rFSH only. But given the lesser number of medications given in hMG preparations and consecutive usage with HPFSH it looks that this regimen will lesser cost than rFSH only. Upcoming researches are necessary to precisely evaluate each regimen cost. Self-injection pen kind of rFSH was extensively

utilized and it was revealed to progress the case's suitability [12].

As compared to everyday administrations of short-acting GnRHa, a solo administration of long-acting GnRHa may append these benefits by decreasing the injection number in COH [13]. In the extended protocol, the combinations of longacting GnRHa with self-injection pen kind rFSH may decrease the number and the costs of hospital visits to have injections of GnRHa and gonadotrophins. Taken together, a solo administration of longacting GnRHa in combining with self-injecting pen kind of rFSH may significantly advance the case's suitability and ease. In cases given rFSH alone, the retrieved follicles number was high significantly in comparison to rFSH+HP-HMG group, , that was in agreement with literature [14].

One probable clarification for the higher retrieved oocytes number in the rFSH-group was the superior potency of rFSH in comparison to HMG. Moreover, numerous preceding studies have recommended that 75-units of HMG were corresponding to 56-units FSH activity. However, the cumulative oocytes number in rFSH-group didn't translate into a growing. In contrast, the produced embryos number in the 2 groups was identical, as the high number of produced embryos in the rFSH-group was counterbalance by a low rate of fertilizatios. The above results were in accordance to a preceding study, that the LH supplementations may decrease the retrieved oocyte number, whereas advance oocyte quality [15].

Conclusion

Hp-HMG additions can be utilized as a choice for the corrections of consequences in those whose responding is unpredictably suboptimal to ovulation inductions with HP-FSH throughout GnRH agonist protocols. The elevated yield of oocyte with r-FSH doesn't lead to elevated embryos quality. Hp-HMG supplementations is a choice to improve ICSI outcomes in case's ovulation inductions with HP-FSH throughout GnRH agonist downregulation. Principally, hp-HMG is suggested as it can have a advantageous action on implantations on the particular group but to prone the effectiveness wide prospective randomized control trials must be performed.

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Conflict of interest: It must be noticed that there was noassociation among the authors and anyorganization or institution. The Authors reportno declarations of interest.

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