

The effectiveness of using r-HMG+r-FSH vs. r-FSH alone during COS on ICSI outcome

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Abstract

Controlled ovarian stimulation (COS) has been used during an assisted reproduction cycle to improve the success rate. The gonadotropins which are most frequently used during COS/ICSI cycles are r-FSH and r-HMG (FSH+LH). Over many years, outcomes achieved with using both gonadotropins during COS have been compared and the superiority of using both or only r-FSH is still a controversial topic that necessitates further studying. The aim of this research is to study the effectiveness of adding r-HMG to r-FSH on ICSI outcome in infertile patients who underwent COS. Fifty infertile couples were included who attended fertility clinic due to either female factor or male factor infertility and all of them were treated by ICSI and subjected to COS by r-FSH with or without r-HMG. ICSI outcome was assessed in the form of the total number of retrieved oocytes, FR, CR, embryo quality and chemical PR. The study showed that there was no significant difference between using both gonadotropins or FSH alone regarding the total number of oocytes produced, fertilization rate (FR), cleavage rate (CR), embryos number and quality except pregnancy rate (PR) which was lower with adding r-HMG 41.66% VS 50 % with r-FSH alone. We concluded that the combined use of r-HMG+r-FSH is effective as r-FSH alone in terms of oocytes' and embryos' quality while the effect on PR is still undetermined.

Keywords: COS, r-HMG, r-FSH, ICSI and PR.

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Introduction

The success of any in vitro fertilization (IVF) / intracytoplasmic sperm injection (ICSI) cycle directly depends on the optimization of controlled ovarian stimulation to obtain a sufficient number of oocytes with an excellent quality which would be utilized later on for in vitro insemination to produce good quality embryos and improve the chance of clinical pregnancy^[1]. In the last decade, the number of gonadotropins available for ovulation induction and COS is rapidly expanded^[1]. Recombinant FSH and r-HMG are widely used gonadotropins for ovarian stimulation in assisted reproduction^{[2] [14]}. The effectiveness and the clinical benefits of both gonadotropins are still a matter of debate^{[2] [15]}. FSH is the key gonadotropin that controls the follicular phase and only very little amounts of LH are needed during certain stages of follicular growth and development^[3]. LH exhibit different physiological functions within the ovary. The role of LH in folliculogenesis is still a subject of controversy and it is questionable whether the enhancement of LH activity is an important issue for adequate multi-follicular development^[4]. LH also may enhance embryo implantation depending upon the presence of LH receptors on the uterine endometrium during implantation window^[5]. However, it had been postulated by some studies that exogenous administration of LH (in form of HMG) may adversely affect the pregnancy rate, whereas others failed to detect a detrimental effect^[4]. Although some researchers tried to establish the clinical efficacy of r-HMG VS r-FSH in assisted reproduction^[4], the definitive clinical results on large numbers of patients are still deficient^[4]. The aim of this study is to compare the ICSI treatment results of adding r-HMG with r-FSH during COS to investigate the possible existing differences in the pregnancy rates between both. The study design that we used was the prospective cohort study of the infertile couples were selected randomly from the Fertility Center, Al- Sadr Medical City, Al- Najaf AL-Ashraf /Iraq.

Materials and methods

Fifty sub-fertile couples were included in this study and all of them were treated by intracytoplasmic sperm injection (ICSI). The sub-fertile female and male partners were evaluated respectively depending on history, physical examination, BMI and fertility investigations (cycle day 2 E2, LH, FSH, prolactin, TVUS for endometrial thickness and seminal fluid analysis for the male partner). Pituitary down regulation-COS was started by using r-FSH (Gonal F. 75 iu) +/- r-HMG (Menopur 75 iu) according to the female situations (depending upon the type, duration of infertility, cause of infertility, response to stimulation treatment previous treatment failure and BMI). Strict and serial follow up was done for follicular growth by hormonal assay of E2 and TVUS. Once the number and the size of the follicles were adequate, ovulation is triggered by hCG; Pregnyle 5000 iu*2. 34-36 hours later, oocyte retrieval was done by the gynecologist under GA. Assessment of oocytes maturity by the embryologist was followed and only mature MII oocytes who extrude the second polar body were prepared for ICSI [6]. The seminal fluid was prepared by swim-up from pellet in concomitant with oocyte preparation using only fresh ejaculate. ICSI was done followed by evaluation of fertilization rate, cleavage rate and embryo grading (good (I&II) and bad (III&IV) [7]. Day 3 post-injection, up to 3 good quality embryos were transferred to the uterus under TVUS and local anesthesia with luteal phase support, 14 days later, blood was drawn from the females to assess chemical pregnancy by measuring beta-HCG in the serum.

Inclusion criteria: The age of all females was 35 years old and less, all of them were normal ovulatory attended the fertility clinic either for tubal obstruction or mild-moderate malefactor. **Exclusion criteria:** those females more than 35 years old and those with PCOS, endometriosis, unexplained infertility or with severe male factor infertility. Females were divided into two groups: Group I: Those infertile females which were stimulated by Gonal F. alone (n=38) and Group II: Those infertile females which were stimulated by Gonal F. and Menopur (n=12). The statistical analysis was by SPSS (Version 24.0) using either mean \pm SD for continuous data (An independent sample student t-test) or a total number and percentage for categorical data (Chi-square test) with a significant p-value \leq 0.05.

Results

Table (1) shows the means of age, BMI, duration and the type of infertility in both groups. There were no significant statistical differences regarding these parameters between both groups. P-value > 0.05.

Table (1): A comparison between both groups regarding age, BMI, duration and type of infertility.

Parameter	G-I (N=38) Mean \pm SD	G-II (N=12) Mean \pm SD	P-value
Age (years)	27.42 \pm 3.9	29.66 \pm 3.9	0.09
BMI (Kg/m ²)	27.62 \pm 4.3	28.52 \pm 6.7	0.58
Duration(years)	7.74 \pm 3.7	8.5 \pm 5.0	0.41
Primary infertility	27	7	0.41
Secondary infertility	11	5	

Table (2) shows the types of induction protocols that were used during COH and the total dose of gonadotropins. Two protocols were used: antagonist protocol and agonist protocol. There was no statistical difference regarding them at p-value = 0.18 and.

Table (2): A comparison between the two groups regarding stimulation protocols and total dose of gonadotropins.

Protocol	G-I (Total no.)	G-II (Total no.)	Total	P-value
Antagonist	13	4	17	0.19
Agonist	25	8	33	
Total	38	12	50	
Total dose of gonadotropin (IU)	Mean±SD 1595.65±393.7	Mean±SD 1843.75±914.9		0.18

Table (3) compares the CD2 hormonal profile and endometrial thickness (ET) in both groups. There was no significant statistical variation regarding cycle day 2 E2, LH, FSH, prolactin and ET between females in both groups (p-value = 0.80 , 0.30 , 0.13, 0.91 and 0.92) respectively.

Table (3): A comparison of cycle day 2 hormones and endometrial thickness between the studied groups.

Parameter	G-I(n=38) Mean±SD	G-II (n=12) Mean±SD	P-value
E2 (pg/ml)	35.08±15.61	33.7±16.6	0.80
LH (IU/L)	4.7±9.01	2.04±1.19	0.30
FSH (IU/L)	5.01±1.8	7.5±10.10	0.13
Prolactin (ng/l)	18.9±12.3	19.4±16.7	0.91
ET (mm)	3.4±0.86	3.5±1.0	0.92

Table (4) demonstrates the total number of retrieved oocytes and maturity between both groups with no significant difference at a p-value of more than 0.05.

Table (4): A comparison between both groups regarding the number of oocytes and maturity.

Parameter	G-I Mean±SD	G-II Mean±SD	P-value
To. No. of oocytes	8.8± 5.6	8.4 ± 5.6	0.84
Mature oocytes	7.5 ± 5.1	7.2 ± 4.5	0.89
Immature oocytes	1.2 ± 2.2	1.1± 1.3	0.90

The effect on fertilization rate (FR), cleavage rate (CR) and embryo quality (good or bad) can be demonstrated in the table (5). There was no significant statistical difference in both groups regarding FR and CR, embryos number and quality.

Table (5): A comparison of FR, CR, mean total no. of embryos and their quality between our studied groups.

Parameter	G-I Mean±SD	G-II Mean±SD	P-value
FR	75.4±26.00	75.2±18.2	0.98
CR	95.2±16.3	97.7±7.55	0.62
To. No. of embryos	5.1±4.2	5.00±2.5	0.90
To. No. of good quality embryos	4.6±3.6	4.5±2.5	0.98
To. No. of bad quality embryos	0.5±1.1	0.3±0.5	0.70

While the pregnancy rate comparison was assessed in the table (6). It was higher in the females who stimulated by r-FSH alone 50% VS 41.66%, p-value= 0.61.

Table (6): Pregnancy rate comparison between the studied groups.

Parameter	G-I	G-II	P-value
Pregnant	19 (50%)	5 (41.66%)	0.61
Non-pregnant	19	7	
Total	38	12	

Discussion

The role of both FSH and LH in ovarian stimulation, follicular growth and maturation were proposed by Balasch in 1959 who demonstrated that both of them are necessary for follicular maturation with evidence that a moderate quantity of LH may be advantageous for ovulation induction ^[4]. LH stimulates theca cell to produce androgens which are subsequently transformed into estrogens in granulosa cells and have a positive effect on oocyte development ^[4]. A relationship has been suggested between an elevated LH level and potentially detrimental effects on embryo quality during the time of follicular development in the peri-ovulatory phase ^[4]. An ampoule of HMG preparation contained approximately 75 IU of FSH and 75 IU of LH, so it will be considered one of the sources of exogenous LH. HMG started to be used during ovulation induction/COS to get a better pregnancy rate in assisted cycles ^{[8] [9]}. As some studies had been demonstrated that the LH activity within HMG negatively affects follicular development and embryo implantation. So, its usage gradually either replaced by FSH or being in combination with FSH ^[10].

The current study demonstrated that using r-HMG plus r-FSH during the ICSI cycle has the same fertility outcomes in form oocysts' and embryos' quality, F and CR, the exception is PR which showed to be lower. Similar results were obtained by different studies ^{[4] [9] [11] [12] [13]}. So, we can conclude that despite lower PR, adding r-HMG to r-FSH for COS during the ICSI cycle has the same clinical outcome with no superiority of one regime over the other in terms of oocytes' and embryos' quality.

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