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IVF Sikluslarında Kontrollü Ovaryen Hiperstimulasyonu Uygulanan Hastalarda Yalnız rFSH ile rFSH + rLH Kombinasyon Protokolleri Sonuçlarının Karşılaştırılması

Comparison of The Outcomes of rFSH Alone Versus rFSH + rLH Protocols in Patients Undergoing Controlled Ovarian Hyperstimulation for IVF Cycles

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ÖZ

GİRİŞ ve AMAÇ: *Gonadotropin tedavisi, overyan stimülasyonun temelidir. FSH, antral folliküler büyümenin ana düzenleyicisi iken, LH ise steroidogenezin desteklenmesi ve antral follikül gelişiminde önemli rol oynar. Bununla birlikte, literatürde LH desteğinin, kontrollü ovaryan hiperstimülasyonuna eklenmesi hakkında sınırlı veri bulunmaktadır. Prospektif randomize çalışmamızın amacı, hipofizi baskılanmış normo-gonadotropik ve rFSH ile monoterapiye normal - suboptimal over cevabı olan kadınlarda kontrollü ovaryan hiperstimülasyon sırasında tedaviye rLH eklenmesinin etkinliğini araştırmaktır.*

YÖNTEM ve GEREÇLER: *Çalışmaya yetmiş yedi hasta dahil edildi. IVF tedavisine alınan normal ve azalmış over fonksiyonuna sahip hastalar randomize edildi ve kontrollü overyan hiperstimülasyon esnasında, rFSH ile rFSH + rLH rejimleri prospektif olarak karşılaştırıldı. Çalışmanın birincil sonlanım noktası, toplam metafaz II oosit sayısı olarak kabul edildi.*

BULGULAR: *Çalışmaya dahil olan yetmiş yedi hastadan otuz dokuzu, yalnız FSH (Grup A) ve otuz sekizi de FSH + LH (Grup B) aldı. Tüm yaş grupları içinde değerlendirildiğinde, grup B'de elde edilen metafaz II oosit ve toplam embriyo sayıları grup A'ya göre istatistiksel olarak anlamlı derecede azdı. Otuz beş yaş ve üstü hastalar ayrıca değerlendirildiğinde, metafaz II oosit sayısı, rFSH + rLH alan grupta istatistiksel olarak anlamlı derecede azalmış olarak saptandı. Hem tüm yaş gruplarındaki hastalar, hem de otuz beş yaş ve üstü hastalar değerlendirildiğinde iyi kalitede embriyo sayısı ve klinik gebelik oranları bakımından, her iki grup arasında istatistiksel olarak anlamlı farklılık izlenmedi.*

TARTIŞMA ve SONUÇ: *Çalışmamızda, IVF tedavisinde rFSH + rLH rejiminin, hem normal hem de azalmış over rezervi olan kadınlarda faydalı olmadığı görülmektedir. Bununla birlikte, hasta sayısının daha fazla olduğu prospektif randomize kontrollü çalışmalarının yapılması gerektiğini düşünmekteyiz.*

Anahtar Kelimeler: *luteinizan hormon takviyesi, overyan stimulasyon, rekombinant folikül uyarıcı hormon, rekombinant luteinizan hormon, in vitro fertilizasyon*

ABSTRACT

INTRODUCTION: *Gonadotropin therapy is the mainstay of ovarian stimulation, while FSH is the main regulator of antral follicular growth, LH plays key roles in promoting steroidogenesis and in the development of the leading follicle. However, there is limited data on the use of LH supplementation in controlled ovarian stimulation for IVF. The aim of this prospective randomized study is to investigate the efficacy of the administration of rLH during COH in normogonadotrophic downregulated women, with initial normal - suboptimal ovarian response to monotherapy with rFSH.*

METHODS: *Seventy seven patients were included in the study and two regimens, rFSH and rFSH + rLH, for IVF treatment of women with normal and decreased ovarian function were compared in prospective randomised fashion. Primary end-point of the study was the total number of metaphase II oocytes.*

RESULTS: *Of the 77 patients, 39 received FSH alone (Group A) and 38 received FSH + LH (Group B). When all age groups were evaluated, number of metaphase II oocytes and total embryos were statistically significantly decreased in group B compared to groups A ($p< 0.01$). Particularly, in the subgroup of patients aged 35 years and over, number of metaphase II oocytes were statistically significantly decreased in group B compared to group A ($p< 0.005$). The number of good quality embryos and clinical pregnancy rates did not differ significantly between the two groups either in all age groups and patients aged ≥35.*

DISCUSSION and CONCLUSION: *rFSH+rLH regimen appears not to be beneficial for the IVF treatment of women either with normal and decreased ovarian reserve. It should be considered however, to prove the efficacy, larger scale prospective randomized control trials should be conducted.*

Keywords: *luteinizing hormone supplementation, ovarian stimulation, recombinant follicle-stimulating hormone, recombinant luteinizing hormone, in vitro fertilization*

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INTRODUCTION

Controlled ovarian hyperstimulation (COH) is the multiple follicular developments aimed at getting the number of oocytes needed to perform IVF and plays an important role also in achieving optimal endometrial development (1). Gonadotropin therapy is the mainstay of ovarian stimulation. Whereas FSH is the main regulator of antral follicular growth, LH plays key roles in promoting steroidogenesis and in the development of the leading follicle (2). Moreover, LH exerts different functions during the different stages of both natural and stimulated cycles (3). According to 'two cell two gonadotropin' model, LH stimulates theca cells thereby advancing androgen production, and FSH governs the proliferation of granulosa cells (GCs) and promotes E2 synthesis (4). LH upregulates E2 output and aromatase CYP19 mRNA expression (5,6). Moreover, it cooperates with FSH in inducing local production of androgen, inhibin B, and growth factors (7).

In long protocol, pituitary downregulation with a GnRH-a is initially achieved. Multifollicular development is then stimulated through administration of exogenous gonadotrophins. This treatment is effective in modulating endogenous LH activity and preventing the onset of a spontaneous LH surge during COH. After pituitary suppression, residual circulating levels of endogenous LH are usually adequate to support multiple follicular growth and oocyte development (8). Nevertheless, in a subset of normogonadotrophic patients, the ovarian response to this association is suboptimal and this may be due to a profound suppression of endogenous LH in some women whose activity may fall below an hypothetical threshold value. Thus, it could be hypothesized that those subjects may benefit from the use of LH-containing gonadotrophin preparations (9).

There is limited data on the use of LH supplementation in ovarian stimulation for IVF. No clear picture emerges regarding the clinical use of recombinant human LH (rLH) in this situation (10). In some normogonadotropic patients, when suppressed LH concentration occurred with GnRH analog, it may be expected that successful completion of folliculogenesis may be established with LH supplementation and those subjects may benefit from the use of LH-containing gonadotrophin preparations (11). rLH gives the opportunity to personalize COH protocols by administering the two gonadotrophins independently. The aim of this prospective randomized study is to investigate the efficacy of rHL administration during COH in normogonadotropic downregulated women of all ages and 35 years of age & older.

METHODS

A total of seventy-seven patients treated at the Zekai Tahir Burak Women's Health Education and Research Hospital, IVF department, between 1 December 2004 and 30 April 2006 and who previously diagnosed with tubal factor, cervical factor, unexplained female infertility, male infertility were enrolled in this study. The study was approved by the ethical committee of our hospital.

Inclusion criteria were: (i) patients aged ≥20 and ≤40; (ii) body mass index between 19 and 28 kg/m2; (iii) baseline FSH <12 U/L; (iv) primer or secondary infertility with normo-ovulatory cycles (21-35 days) (v) the presence of both ovaries and uterine cavity capable of sustaining a pregnancy. Patients were excluded if they met any of the following criteria: (i) history of clinically severe systemic disease and any contraindication for pregnancy (ii) polycystic ovary or an ovarian cyst of unknown etiology; (iii) smoking more than 10 cigarettes/day.

All patients underwent a GnRH-a long protocol for COH, pituitary desensitization was induced with the administration of Leuprolide acetate (Lucrin, Abbott) or Triptorelin acetate (Decapeptyl, Ferring) in the luteal phase of the previous menstrual cycle. Patients were randomized in two groups and rFSH (Gonal F, Serono) was administered on day 2 or day 3 of the menstrual cycle and a daily dose of 225 IU of rFSH was administered subcutaneously in both groups. Serum E2 concentrations were measured and follicular growth was monitored with transvaginal scan beginning on the seventh or eighth day of the stimulation based on the current

clinical practice at our hospital. On the eighth day, a fixed daily dose of 75 IU of rLH was administered with rFSH concomitantly in the second group. The choice of the eighth day of stimulation for starting the rLH administration also derives from the data suggesting that during the middle to late follicular phase, LH plays a key role in the stimulation and modulation of the follicular function (12). The ovulatory dose [10.000 IU intramuscularly (i.m.)] of hCG (Profasi; Serono) was administered when three follicles showed a mean diameter of at least 17 mm. Oocytes were retrieved by transvaginal ultrasound-guided aspiration thirty-six hours after the hCG injection. Luteal phase support was provided with vaginal progesterone (Crinone 8% gel, Serono), two applicators/day. A pregnancy test was done fourteen days after embryo transfer. A beta hCG level of 5 mIU/ml was considered positive. Clinical pregnancy was defined as the visualization of fetal heart activity on ultrasonographic examination. Pregnancies progressing beyond the 12th week of gestation were considered ongoing.

The primary end-point of the study was the number of metaphase II oocytes retrieved. Secondary end-points were the number of total oocytes retrieved, number of embryos, number of good quality embryos, clinical pregnancy rate, embryo implantation rate, miscarriage rate, duration of stimulation, total number of r-FSH units used, estradiol concentrations on the hCG-administered day, endometrial thickness on the hCG-administered day.

All statistical analyses were performed with Statistical Package version 12.0 (SPSS, Chicago). Data were expressed as the mean±SD. Student's t-test, chi-square test and Fisher's exact test were used to compare clinical outcome between the groups. Results were considered significant at the 5% level (p-value <0.05). Randomization to study treatments was performed via a computer-generated random number list.

RESULTS

A total of seventy-seven patients were enrolled in the study, of whom thirty-nine patients were assigned to the rFSH alone group (Group A) and remaining thirty-eight patients who received rFSH and r- LH were in the second group (Group B). Demographical properties and laboratory findings of each group were demonstrated in Table 1. Baseline characteristics of patients in the two treatment groups were similar. Ovarian stimulation characteristics were also similar in the two treatment groups except for estradiol concentration on the day of hCG and the number of rFSH ampoules which was used more often in rFSH + rLH versus r-FSH alone recipients. Ovarian stimulation characteristics were summarized in Table 2. The number of metaphase II oocytes and total embryos were statistically significantly decreased in group B compared to group A. Other parameters were similar among the groups and no statistically significant difference was found (Table 3).

Table 1. Baseline patient characteristics and demographic data

	rFSH (n=39)	**rFSH + rLH (n=38)**
Age, years	32.2 ± 6.1	31.4 ± 4.1
BMI, kg/m²	24.3 ± 4.7	24.7 ± 5.0
Basal FSH value, IU/L	7.24 ± 1.0	7.36 ± 1.5
Basal LH value, IU/L	5.98 ± 3.2	4.87 ± 1.6
Basal E2 value, pgr/mL	38.8 ± 9.0	41.1 ± 13.5
Aetiology	**n (%)**	**n (%)**
Male Factor	24 (61.5)	24 (63.2)
Female Factor	5 (12.7)	8 (21.0)
Male+Female	1 (2.6)	2 (5.3)
Unexplained infertility	9 (23.2)	4 (10.5)

Table 2. Ovarian stimulation characteristics

	r-FSH (n=39)	**r-FSH + r-LH (n=38)**	**P value**
Duration of stimulation, days	9.8 ± 1.2	10.5 ± 1.4	NS
Number of r-FSH ampoules, n	28.4 ± 4.7	34.8 ± 8.7	0.001
Number of r-LH ampoules, n	-	6.0 ± 1.8	-
Estradiol concentration on day of hCG administration, pg/ml	2543 ± 1289	1772 ± 786	0.04
Number of ≥18 mm follicules on day of hCG administration	1.7 ± 1.5	1.6 ± 1.2	NS
Endometrial thickness on day of hCG administration, mm	9.7 ± 2.4	10.6 ± 2.1	NS

NS= Not statistically significant

Table 3. Ovarian stimulation and embryo transfer outcomes

	r-FSH (n=39)	r-FSH + r-LH (n=38)	P value
Total oocytes, n	10.7 ± 4.7	8.0 ± 4.3	NS
Metaphase II oocytes, n	9.1 ± 3.4	6.4 ± 4.0	0.01
Total embryos, n	6.1 ± 3.3	4.1 ± 2.2	0.04
High quality embryos, n	1.8 ± 1.5	2.2 ± 1.2	NS
Transferred embryos, n	3.2 ± 1.4	2.8 ± 1.1	NS
Implantation rate, (%)	12.2	12.7	NS
Biochemical pregnancy rate, (%)	38.5	36.8	NS
Clinical pregnancy rate, (%)	30.8	31.5	NS

NS= Not statistically significant

On the other hand, if we evaluated the subpopulation of patients separately who were at the age of 35 or over, there were 18 and 12 patients in group A and B, respectively. In this age-specific subgroup, the number of metaphase II oocytes were statistically significantly decreased in group B compared to group A ($p< 0.005$), besides that the number of good quality embryos and clinical pregnancy rates did not differ significantly between the group A and B (Table 4).

Table 4. Specific subgroup analysis of patients aged ≥35 years

	r-FSH (n=18)	r-FSH + r-LH (n=12)	P value
Metaphase II oocytes, n	9.8 ± 4.8	4.5 ± 2.4	0.005
High quality embryos, n	1.8 ± 1.2	2.1 ± 1.5	NS
Transferred embryos, n	2.7 ± 1.0	2.5 ± 1.1	NS
Implantation rate, (%)	11.9	11.6	NS
Biochemical pregnancy rate, (%)	36.5	35.8	NS
Clinical pregnancy rate, (%)	33.0	33.0	NS

NS= Not statistically significant

DISCUSSION

According to the two cell, two gonadotropin theory, both FSH and LH are required for folliculogenesis. FSH plays an important role in follicular development by inducing aromatase enzyme activity and allowing LH receptors to be expressed in granulosa cells (13). it is accepted that in the late stages of follicular development, granulosa cells become responsive to LH stimulation and show the effects of LH on both the theca and granulosa cells(14). It is known that many physiological effects, such as the stimulation of the activity of the enzyme aromatase, are also supported by LH via the emergence of LH receptors in the granulosa cells at midfollicular period(15). 'Long protocol' is effective in achieving endogenous LH activity modulation and in preventing premature LH surge. Following the hypophysial suppression, residual LH activity in circulation is usually sufficient for follicular development. However, in some patient populations, excessive ovarian suppression results due to the use of GnRH agonists. This leads to severe endogenous LH activity suppression and degree of LH is thought to fall below the threshold required for follicular maturation. It is assumed that these patients may benefit from the use of exogenous LH (16-20). As undesirable effects caused by the presence of LH activity have been demonstrated during the early follicular phase, rLH has begun to be used in the late period of the follicular phase. The onset of rLH is often considered to be between the sixth and eighth day of stimulation in many studies. Tarlatzis et al. started r-LH administration when the largest follicle reached 14 mm in diameter in their study (21).

LH supplementation for the patients without hypogonadotropic hypogonadism (group 1 according to WHO classification) in ovarian hyperstimulation remains a controversial issue. The debate about issue has been further exacerbated by the introduction of recombinant FSH preparations that do not contain LH activity and the clinical use of GnRH agonists that cause the suppression of endogenous LH activity. Approximately 10–12% of patients do not respond to currently-used ovarian stimulation protocols, and this is thought to be due

to lack of LH (22). As a result, LH supplementation during ovarian stimulation for IVF is part of the treatment protocol at many IVF centres. Besides that the main question is 'which specific patient groups might benefit from LH supplementation (23).

In our study, we sought to determine the impact of LH supplementation on GnRH-a cycles. Supplementation of 75 IU rLH during the mid-follicular phase of ovarian stimulation had negative effects on primary outcome, the number of metaphase II oocytes retrieved, when all age groups were considered (9.1 ± 3.4 vs 6.4 ± 4.0, p-value < 0.01). Furthermore, LH supplementation had no significant effect on the secondary outcomes, the number of high-quality embryos and clinical pregnancy rates, in all age groups. In this study, it was demonstrated that adding 75 IU / day rLH to the stimulation protocol had negative results in terms of metaphase II oocyte count when the subgroup of patients aged 35 years and over was assessed (9.8 ± 4.8 vs 4.5 ± 2.4, p value < 0.005), however secondary outcomes, number of high-quality embryos and clinical pregnancy rates, in both groups were similar and no statistically significant difference was found in patients aged 35 years and over.

In a study published by De Placido, the addition of hMG containing FSH and LH (at a rate of 1/1) to the stimulation protocol in normo-ovulatory normogonadotropic patients who respond poorly to exogenous r-FSH administration improved IVF outcomes (19). Marrs and colleagues reported that adding r-LH to the protocol did not produce a significant difference on the metaphase II oocytes and clinical pregnancy rates in patients who were stimulated with FSH following pituitary suppression in a study involving 121 patients over 35 years of age, in addition, there was no significant difference between the groups under the age of 35 (24). In a recently published study by Voung et all, which involved 240 patients of whom 120 patients were assigned to the rFSH+rLH group and 120 to the rFSH group, the number of metaphase 2 oocytes, number of good quality embryos and live birth rate did not differ significantly between two groups. In particular, Lehert and colleagues analyzed 40 RCTs in which the relative performance of r-FSH and r-FSH + r-LH regimens was comparatively assessed. The meta-analysis did not find a difference in the number of retrieved oocytes between the two treatments in the overall population, but did find a higher number of retrieved oocytes in poor responder cycles where the r-FSH/r-LH was used (25, 26).

Humaidan et al. reported a statistically significant high implantation and clinical pregnancy rates in patients over 35 years of age who underwent r-LH supplementation in a study of 231 controlled ovarian hyperstimulation cycles (27). In similar studies by Matorras et al. and Bosch et al. reported that patients over 35 years of age had better implantation and/or ongoing pregnancy rates when LH supplementation was added to the ovarian hyperstimulation protocol (28, 29). According to a consensus on LH supplementation among IVF experts patients for whom a benefit of LH supplementation has been confirmed include those with a history of poor response to ovarian stimulation and suboptimal ovarian response in the current treatment cycle (30). Furthermore, it has been noted that patients aged ≥35 years may obtain benefit from LH supplementation. In a recently published study involving 137 patients concluded that r-LH addition could be used as an option for the correction of results in those whose response is unexpectedly suboptimal to ovulation induction with r-FSH during GnRH agonist protocol (31).

In conclusion, supplementation of 75 IU rLH during the mid-follicular phase of ovarian stimulation had negative effects on the number of metaphase II oocytes, both in all age groups of patients and in patients aged 35 years and over. We also found that no statistically significant benefit was obtained when evaluated in terms of clinical pregnancy rate and the number of high-quality of embryos in patients aged 35 years and over. Although our study has a randomized design, improving the robustness of the findings, the small sample size means that it may have only been possible to detect the most common adverse events. In this regard, further larger scale prospective randomized control trials should be conducted and

it cannot be excluded that, following larger randomized trials, further indications for selective LH addition will be identified.

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