Do Different Stimulation Protocols Effect Oocyte Quality and IVF Outcomes in IVF–ET?

Farklı Stimülasyon Protokolleri IVF-ET'de Oosit Kalitesi ve IVF Sonuçlarını Etkiler mi?

Stimülasyon Protokollerinin IVF Sonuçlarına Etkisi / The Effect of Stimulation Protocols on IVF

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Özet

Amaç: Bu çalışma IVF-ET' de hMG ve uFSH protokollerinin oosit maturasyonu ve IVF sonuçlarına etkisini araştırmak amacıyla planlanmıştır. Gereç ve Yöntem: Ankara Üniversitesi Kadın Hastalıkları ve Doğum Kliniğinde IVF bölümüne başvuran 82 hasta çalışmaya alındı. Bütün hastalara uzun protokol GnRHa uygulandı. Ovulasyon indüksiyonu için 59 hasta hMG (grup:1), 23 hasta uFSH (grup:2) kullandı. Maksimum follikül çapı, dominant follikül sayısı, hCG günü endometrium kalınlığı, tedavi süresi, kullanılan gonadotropin miktarı, aspire edilen oosit sayısı ve kalitesi, fertilizasyon oranı, elde edilen embriyo sayı ve kalitesi, transfer edilen embriyo ve siklus başına ve transfer başına gebelik oranlan kaydedildi. Bulgular: Maksimum follikül çapı, dominant follikül sayısı, immature oocyte sayısı hMG alan grupta uFSH grubundan anlamlı olarak fazla bulundu(p<0.05). Diğer parametreler açısından iki grup arasında istatistiksel anlamlı farklılık saptanmadı. Siklus başına gebelik oranı grup 1 ve 2 de sırasıyla % 27.1, % 34.8 idi (p>0.05). Tartışma: Çalışmamızda klinik gebelik oranları açısından hMG veya uFSH kullanan gruplar arasında anlamlı farklılık saptanmamıştır. Gelişmekte olan ülkelerde ovulasyon stimülasyon preparatları hasta özellikleri ve maliyet dikkate alınarak seçilmelidir.

Anahtar Kelimeler

İn Vitro Fertilizasyon; İnsan Menopozal Gonadotropin; İdrar Kökenli Folikül Stimulan Hormon

Abstract

Aim: This study was planned to compare the effect of different stimulation protocols (hMG and uFSH) on oocyte maturation and in vitro fertilization outcomes. Material and Method: Eighty-two patients admitted Ankara University Obstetrics and Gynecology Clinic- IVF Department were included in this retrospective study. All patients used long GnRH agonist protocol. Fifty-nine patients used human menopausal gonadotropin (hMG) (Group 1) and 23 patients used urine derived follicle-stimulating hormone (uFSH) (Group 2) for ovulation induction. Maximum follicle diameter, dominant follicle number, endometrial thickness at human chorionic gonadotropin day, duration of induction, dose of gonadotropin, oocyte number and quality, fertilization rate, embryo number and quality, pregnancy rate per cycles and transfer were reported. Results: Maximum follicle diameter, dominant follicle number, immature oocyte number were significantly higher in hMG group vs. uFSH group (p<0.05). For the other parameters, there were no significant differences between the groups. Pregnancy rate per cycles were 27.1%, 34.8% in Group 1 vs. 2 respectively (p>0.05). Discussion: Clinical pregnancy rate was not significantly different in hMG vs. uFSH group. In developing countries, ovarian stimulation agents should be chosen based on patient characteristics and cost.

Keywords

In Vitro Fertilization; Human Menopausal Gonadotropin; Urine Derived Follicle-Stimulating Hormone

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Introduction

The first in vitro fertilization (IVF) cycles were put into practice in natural cycles [1]. The quality of oocytes and developing preembryos is one of the most important factors determining the success of an IVF treatment. In order to improve the efficacy of the treatment, either more embryos at a time will be transferred or a well-established stimulation protocol and embryo-selection procedure with lower number of transferred embryos is practiced. As ovarian stimulation protocol is one of the eligible factors during an IVF treatment, its embryo quality influencing effects are necessary to know. Controlled ovarian hyperstimulation (COH) has been used to generate multiple follicular growth to obtain an increased quantity of oocytes and a higher pregnancy rates. Different drug protocols have been used, such as clomiphene citrate, human menopausal gonadotropins (hMG), urine derived follicle-stimulating hormone (uFSH), recombinant FSH (rFSH) and LH (Luteinizing hormone). During ovarian stimulation gonadotrophin-releasing hormone (GnRH) analogues are co-administered in order to prevent premature LH surges. Although GnRH antagonist protocols are in common use, standard long protocol GnRH agonist regimen is a well-established strategy for COH. In such a protocol, GnRH agonist administration is primarily followed by 'gonadotropin' with FSH or hMG.

Because of the detrimental effects of high LH activity present in hMG on follicle and oocyte maturation, purified, highly purified and recombinant FSH are in use.

Assisted reproductive techniques are expensive. The costs of medication are especially important for developing countries. Hormonal stimulation covered the main part of the costs per cycle due to the relatively high cost of recombinant technology. Our aim is to test the clinical efficiency of cheaper medications in terms of hMG and FSH.

Material and Method

This study was conducted at Ankara University Obstetrics and Gynecology Clinic- IVF Department with 82 patients. The study protocol was approved by the institutional review board. We included all our first IVF cycles. Control and study groups were similar with regard to infertility etiology (Tubal factor, endometriosis, male infertility and unexplained infertility). Exclusion criteria were advanced age and repeated implantation failure.

Patients received long term down-regulation with GnRH agonist and controlled ovarian hyperstimulation with 150-300IU/day hMG (n=59) or 150-300IU/day uFSH (n=23).

Oocyte retrieval was performed 35–36 h after the hCG injection by transvaginal ultrasound-guided double lumen needle aspiration. ICSI was performed only in cases with severe male factor or previous fertilization failure. Ultrasound guidance was used for all embryo transfers, which were performed 2 or 3 days post-oocyte retrieval, Day 2 and Day 3 embryo transfers were equally distributed in the two groups. Luteal phase support with intravaginal progesterone and intramuscular hCG was initiated after oocyte retrieval.

The primary outcome measure was oocyte maturity and clinical pregnancy. Clinical pregnancy was defined as the presence of gestational sac with fetal heart beat detection at 6–7 weeks of gestation. Secondary outcome measures were duration of stimulation, total dose of ampules, endometrial thickness on day of hCG administration, maximum diameter of dominant follicles, number of dominant follicles, oocyte retrieved and embryos, and fertilization rates.

Student-t test, chi-square test, Mann Whitney U test were used for statistical analysis. Statistical significance was accepted when $p < 0.05$.

Results

Baseline characteristics and clinical and laboratory outcomes of the patients analyzed are shown in Table 1, Table 2 shows oocyte maturation characteristics. No significant differences were observed between the two groups regarding baseline characteristics (age, infertility duration). Control and study groups were similar with regard to infertility etiology (Tubal factor, endometriosis, male infertility and unexplained infertility).

Table 1. Clinical and laboratory parameters

	Group 1 (hMG)	Group 2 (FSH)	p
	n: 59	n:23	
Age	33.1 ± 5.3	34.3 ± 4.6	> 0.05
Infertility duration (years)	8.1 ± 5.5	8.5 ±4.6	> 0.05
Stimulation day	10.7 ± 2.3	10.3 ± 2.4	> 0.05
Number of ampoules	36.9 ± 13.3	38.0± 16.7	> 0.05
Endometrial thickness (mm)	9.7± 1.9	9.3 ± 2.2	> 0.05
Max. follicle diameter	20.0 ± 2.9	17.9 ± 2.6	< 0.05
Number of dominant follicle	5.1 ± 2.6	3.3 ± 2.4	< 0.05
Number of retrieved oocyte	8.6 ± 5.8	10.2 ± 7.1	> 0.05
Fertilization rate (%)	49.2	43.1	> 0.05
Abnormal fertilization	2.68	1.96	> 0.05
Number of embryos	4.1±3.7	4.1 ± 4.8	> 0.05
Number of transferred embryos	2.7± 1.6	2.5±1.7	> 0.05
Pregnancy rate (%)	27.1	34.8	> 0.05

Table 2. Oocyte maturity in two groups

	Immature	Intermediate	Mature	Post-mature
Group 1	% 4.34	% 33.75	% 53.02	% 8.87
Group 2	% 0.56	% 32.85	% 59.56	% 6.46
p	< 0.05	>0.05	>0.05	>0.05

No significant differences were found between the two groups in stimulation duration, total dose of ampoules, endometrial thickness on day of hCG administration, number of retrieved oocytes, fertilization rate, number of embryos and number of transferred embryos ($p>0.05$). Maximum follicle diameter was 20.0 ± 2.9 mm in group 1, and 17.9 ± 2.6 mm in group 2. Maximum follicle diameter, dominant follicle number, immature oocyte number were significantly higher in hMG group vs. uFSH group ($p<0.05$). Immature oocyte ratio was 4.34% and 0.56%, in both groups, respectively ($p<0.05$). Table 3 and 4 summarizes the grading of embryos. We found no difference between the groups. Pregnancy rate per cycles were 27.1%, 34.8% in Group 1 vs. 2, respectively ($p>0.05$).

Discussion

The clinical impact of different stimulation protocols, analysis of ovarian stimulation on quality of oocytes and developing

Table 3. Embryo quality in two groups

	2 pn	gr 1	gr 2	gr3	gr 4
Group 1 (%)	9.56	49.62	27.16	6.89	6.74
Group 2 (%)	7.91	33.82	39.57	10.14	
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

pn:Pronucleus;
gr: grade

Table 4. Transferred embryo quality in two groups

	2 pn	gr 1	gr 2	gr 3	gr 4
Group 1(%)	8.84	55.93	24	5.15	6.06
Group 2(%)	5	43.33	40	6.66	5
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

embryos has been studied.

A number of studies have shown that increased concentrations of LH during the follicular phase of the menstrual cycle may be associated with reduced rates of fertilization and implantation and increased miscarriage rates [2]. Especially for the patients with PCOS with high levels of LH, there are studies comparing FSH and hMG [3, 4] Westergaard et al. [5] found no detrimental effect of the LH activity of HMG on the clinical outcome of FVF in GnRHa down-regulated normogonadotrophic women.

In the present study, we compared the effect of different stimulation protocols (hMG and FSH) on oocyte maturation and in vitro fertilization outcomes. We found significantly higher maximum follicle diameter, dominant follicle number, immature oocyte number in hMG group compared with FSH group.

Placido et al [6] revealed a significant increase in the number of oocytes in patients with ovarian steady response who received rLH in the course of ovarian stimulation, when compared with those undergoing an increase in rFSH dose. Bjercke et al [7] tested the clinical efficiency of recombinant FSH and highly purified human menotrophin in terms of pregnancy and live birth rates during the first treatment cycle of IVF or ICSI. In the study of Bjercke et al [7] similar pregnancy and live birth rates were observed with hMG and rFSH. Compared to hMG, treatment cycles with rFSH were characterized by significantly shorter stimulation, lower gonadotrophin consumption, and increased number of oocytes and embryos. Andersen et al [8] revealed that superiority of highly purified-hMG over recombinant FSH in ongoing pregnancy rate could not be concluded.

We also found no significant differences between the two groups in stimulation duration, total dose of ampoules. Our results are in agreement with the other studies [9].

Van Wely et al [10] made a review of studies comparing recombinant gonadotrophin with urinary gonadotrophins (hMG, purified FSH, highly purified FSH) for ovarian hyperstimulation in IVF and ICSI cycles and revealed that live births are similar irrespective of the gonadotrophin used.

Kumbak et al[11] found recombinant LH supplementation in agonist long ART cycles to have a detrimental effect on the oocyte quality, without a beneficial or adverse effect on the embryo quality in normoresponder women <40 years. They also stated that inclusion of rLH during stimulation in antagonist ART cycles, on the other hand, is neither favourable nor deleterious for the oocyte or the embryo quality in normoresponder women <40 years.

As a conclusion, although we had a limited number of patients, clinical pregnancy rate was not significantly different in hMG vs. FSH group. Parallel with Cochrane review [10], based on our results any type of gonadotrophin can be chosen depending on the situations eg. cost, patient characteristics. Larger studies are needed to clarify our results.

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Competing interests

The authors declare that they have no competing interests.

References

1. Fatemi HM, Blockeel C, Devroey P. Ovarian stimulation: today and tomorrow. Current pharmaceutical biotechnology. 2012 ;13(3):392-7.1.
2. Regan L, Owen EJ, Jacobs HS. Hypersecretion of luteinising hormone, infertility, and miscarriage. Lancet 1990;336(8724):1141-4.
3. Larsen T, Larsen JF, Schioler V, Bostofte E, Felding C. Comparison of urinary human follicle-stimulating hormone and human menopausal gonadotropin for ovarian stimulation in polycystic ovarian syndrome. Fertility and sterility 1990;53(3):426-31.
4. Figen Turkcapar A, Seckin B, Onalan G, Ozdener T, Batioglu S. Human Menopausal Gonadotropin versus Recombinant FSH in Polycystic Ovary Syndrome Patients Undergoing In Vitro Fertilization. International journal of fertility & sterility 2013;6(4):238-43.
5. Westergaard LG, Erb K, Laursen S, Rasmussen PE, Rex S. The effect of human menopausal gonadotrophin and highly purified, urine-derived follicle stimulating hormone on the outcome of in-vitro fertilization in down-regulated normogonadotrophic women. Human reproduction 1996;11(6):1209-13.
6. De Placido G, Alviggi C, Perino A, Strina I, Lisi F, Fasolino A et al. Recombinant human LH supplementation versus recombinant human FSH (rFSH) step-up protocol during controlled ovarian stimulation in normogonadotrophic women with initial inadequate ovarian response to rFSH. A multicentre, prospective, randomized controlled trial. Human reproduction 2005;20(2):390-6.
7. Bjercke S, Tanbo T, Abyholm T, Omland A, Opoien HK, Fedorcsak P. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing their first treatment cycle of IVF or ICSI. Acta obstetricia et gynecologica Scandinavica 2010;89(8):1053-60.
8. Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Human reproduction 2006;21(12):3217-27.
9. Edelstein MC, Brzyski RG, Jones GS, Simonetti S, Muasher SJ. Equivalency of human menopausal gonadotropin and follicle-stimulating hormone stimulation after gonadotropin-releasing hormone agonist suppression. Fertility and sterility 1990;53(1):103-6.
10. van Wely M, Kwan I, Burt AL, Thomas J, Vail A, Van der Veen F et al. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. The Cochrane database of systematic reviews 2011, DOI: 10.1002/14651858.CD005354.pub2(2):CD005354.
11. Kumbak B, Kahraman S. Effect Of Combining Recombinant FSH With Recombinant LH On Oocyte And Embryo Quality In GnRH Agonist Long And Antagonist Cycles. Journal of Turkish German Gynecological Assocociation 2008; 9:120-126.

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