CLINICAL STUDY

Is Follicular Aspiration Preventive for Severe Ovarian Hyperstimulation Syndrome?

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Abstract

Objective: To evaluate the practice of follicular aspiration in prevention of severe ovarian hyperstimulation syndrome (OHSS) in couples with nonobstructive azoospermia stimulated for intracytoplasmic sperm injection (ICSI) and testicular sperm extraction (TESE) without success in obtaining sperm with the TESE.
Materials and Methods: Couples infertile due to non-obstructive azoospermia were evaluated retrospectively. Thirty-two stimulated patients in whom follicular aspiration was not performed since no sperm was found in the TESE and 28 stimulated patients in whom follicular aspiration was performed but no fertilization was achieved were conducted as study and control group respectively. The patients were evaluated by age, ultrasonographic appearance of the ovaries, induction period, total gonadotrophin dose, estradiol level on the day of human chorionic gonadotrophin (hCG) and the number of follicles with greater than a 15 mm diameter for the risk of OHSS. Controlled ovarian hyperstimulation (COH) was performed with midluteal long gonadotrophin releasing hormone agonist protocol (leuprolide acetate 500 μg/day, hMG/FSH 225 IU/day). The severe early OHSS rates of the two groups were compared.
Results: There is no patient, has complication with OHSS in group with follicular aspiration, whereas three patients (9.4%) had severe OHSS in group without follicular aspiration. Although, severe OHSS incidence was not statistically different between the two groups (p=0.241), follicular aspiration decreased the severe OHSS incidence (OR: 0.509; 95% CI: 0.394-0.657).
Discussion: Our results indicate that severe OHSS incidence tend to be higher in group without follicular aspiration, but it's not statistically significant. Follicular aspiration may be planned individually especially for patients having high risk for OHSS. Further studies with larger cohorts are needed to investigate the impact of follicular aspiration in prevention of OHSS.

Keywords: follicular aspiration, ovarian hyperstimulation syndrome, testicular sperm extraction

Özet

Folikül Aspirasyonu, Ciddi Ovaryen Hiperstimülasyon Sendromuna Karşı Koruyucu mu?

Amaç: Non-obstrüktif azoospermi nedeni ile intrasitoplazmik sperm enjeksiyonu (ICSI) ve testiküler sperm ekstraksiyonu (TESE) planlanan ve kontrollü ovaryen hiperstimülasyon uygulanan fakat TESE'de sperm bulunmayan infertil çiftlerde ciddi OHSS'yi engellemede folikül aspirasyonun yerini belirlemek.
Materyal ve Metot: Non-obstrüktif azoospermili infertil çiftler retrospektif olarak değerlendirildi. Kontrollü ovaryen hiperstimülasyon uygulanmış fakat TESE'de sperm bulunamadığı için folikül aspirasyonu yapılmamış 32 hasta ile kontrollü ovaryen hiperstimülasyon uygulanmış, folikül aspirasyonu yapılmış ancak fertilizasyon elde edilememiş 28 hasta sırası ile çalışma ve kontrol gruplarına dahil edildi. Hastalar ovaryen hiperstimülasyon sendromu (OHSS) riski açısından yaş, overlerin ultrasonografik görünümü, indüksiyon süresi, toplam gonadotropin dozu, insan koryonik gonadotropininin (hCG) gününde östradiol seviyesi ve çapı 15 mm'nin üzerindeki toplam folikül sayısı ile değerlendirildi. Kontrollü ovaryen hiperstimülasyon ortalüteal uzun gonadotropin salgılayıcı hormon agonisti (löprolid asetat 500 μg/gün, hMG/FSH 225 IU/gün) protokolü ile uygulandı. Gruplar arasında ciddi erken OHSS oranları karşılaştırıldı.
Sonuçlar: Folikül aspirasyonu yapılan grupta hiçbir hasta ciddi OHSS ile komplike olmazken, folikül aspirasyonu yapılmayan grupta üç hastada (%9.4) ciddi OHSS tespit edildi. İki grup arasında ciddi OHSS oranları açısından istatistiksel olarak

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anlamlı bir farklılık bulunmasa da (p=0.241), folikül aspirasyonu ciddi OHSS oranını düşürmüştür (OO: 0.509; %95 GA: 0.394-0.657).

Tartışma: Çalışmamızda ciddi OHSS oranı, folikül aspirasyonu yapılmayan grupta daha yüksek olarak tespit edilse de istatistiksel olarak anlamlı bir fark bulunmamıştır. Folikül aspirasyonu, özellikle OHSS riski yüksek hastalarda planlanabilir. Folikül aspirasyonunun OHSS'yi engellemedeki yerini belirlemek için daha fazla hasta ile yapılmış çalışmalara ihtiyaç vardır.

Anahtar sözcükler: folikül aspirasyonu, ovaryen hiperstimülasyon sendromu, testiküler sperm ekstraksiyonu

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation in women receiving fertility treatment. The severe OHSS rates vary between 0.1-4% in different studies (1,2). Although a rare complication, it can be mortal.

It is thought that OHSS may be triggered by the exogenous or endogenous human chorionic gonadotrophin (hCG) stimulation (3,4). Other widely accepted risk factors are a high serum estradiol level, presence of multiple immature follicles (5) and presence of polycystic ovarian syndrome (PCOS) (6). OHSS risk also increases in conceptual cycles.

The pathophysiology of OHSS is still obscure, so, there is no consensus about its prevention and treatment. Up to date many preventive measures such as cycle cancellation, coasting (7), embryo cryopreservation (8), intravenous albumin during or after oocyte pick up (9), laparoscopic ovarian diatermia (10), follicular aspiration before or early after hCG administration (11,12) have been investigated by the clinicians.

To our knowledge, there is no study in the literature evaluating the need of follicular aspiration to prevent OHSS in nonobstructive azoospermic (NOA) couples stimulated for ICSI with fresh testicular sperm but with failure to find sperm by the TESE. Aim of this study is to evaluate the place of follicular aspiration in prevention of severe OHSS.

Materials and Methods

This is a retrospective case-control analysis of 60 women planned to have controlled ovarian hyperstimulation (COH) and ICSI with fresh testicular sperm due to non-obstructive azoospermia (NOA) but without successful finding of sperm in the TESE or ending with total fertilization failure, in the infertility unit of our clinic between January 1999 and March 2004. Thirty-two patients who didn't undergo follicular aspiration because no sperm had been found in the TESE and 28 patients who underwent follicular aspiration but ended with fertilization failure were evaluated as the study and the control groups, respectively.

Two groups were compared for the severe early OHSS rates. The data were gathered from the patient files. We didn't administer any drugs or perform any invasive procedure except performing the routine protocol. For these reasons, institutional review board approval of the research was not taken. Control group was formed from women with fertilization failure to exclude the effect of pregnancy on severe OHSS incidence. Long gonadotrophin releasing hormone (GnRH) agonist protocol was used for COH, starting the GnRH agonist, subcutaneous leuprolide acetate 500 μg/day (Lucrin®, Abbot, Turkey), on the preceding cycle day 21 for pituitary down regulation in all patients. Gonadotropins were administered in the form of recombinant FSH (Gonal-F®, Serono, Turkey; Puregon®, Organon, Turkey) or human menopausal gonadotrophin (hMG), (Menogon®, Er-Kim, Turkey; Pergonal®, Serono, Turkey), starting from the cycle day 2; and, follicular maturation was monitored by serial determination of estradiol (E_2) levels and transvaginal ultrasonographic measurement of follicular diameters. The gonadotrophin dose was increased step-wise if necessary, depending on the follicular growth, until the leading follicle was ≥18 mm in diameter. Oocyte retrieval was planned on the thirty-sixth hours of 10 000 IU HCG administration and TESE was planned on the same day with oocyte retrieval. The OHSS risk was evaluated by the age, ultrasonographic appearance of ovaries, the induction period, total gonadotrophin dose, estradiol level on the day of hCG and follicle number greater than 15 mm in diameter on the day of hCG. The diagnosis of severe OHSS was made according to the Golan (13) criteria (presence of ascites and/or hydrothorax on ultrasonography, presence of dyspnea, increased blood viscosity due to hemoconcentration, presence of coagulation abnormalities, decreased renal perfusion and abnormal renal function test). No patient received coasting or intravenous albumin. For the statistical analysis Fisher's exact test was used to compare the incidence of OHSS and PCOS between the two groups. The odds ratio with a 95% confidence interval (CI) was calculated for the severe OHSS. The other variables were compared by independent samples t test. The p values less than 0.05 were accepted as statistically significant.

Results

The patient data of the study and control groups for the risk of OHSS are given in the Table 1. In the study group 15.6% of patients and in the control group 7.1% of patients had polycystic ovarian appearance (p=0.432). None of the patients was considered to have a high risk of OHSS.

There was no significant difference between the study group and the control group with respect to age, polycystic ovarian appearance, induction period, estradiol level on the day of HCG, number of follicles with >15 mm diameter and the gonadotrophin dose. Two groups were similar for the OHSS risk.

Table 1. The patient data for the risk of OHSS in study and control groups

	Age (years) *p*=0.862	Gonadotropin dose (IU) *p*=0.135	Induction period (days) *p*=0.202	E_2 level (pg/ml) *p*=0.163	Follicle number >15 mm *p*=0.569
Study group					
n	32	32	32	32	32
Mean	29.3437	2365.6250	11.4063	2414.3929	6.9062
Std. deviation	5.75079	709.66115	2.04560	1135.14621	2.51908
Median	28.5000	2287.5000	11.5000	2261.5000	7.0000
Minimum	19.00	900.00	7.00	252.00	2.00
Maximum	43.00	3675.00	16.00	3813.00	12.00
Control group					
n	28	28	28	28	28
Mean	29.6071	2724.1071	10.7143	2014.0000	6.5357
Std. deviation	5.8626	1101.01977	2.10567	975.83882	2.47180
Median	28.5000	2612.5000	10.5000	1978.5000	7.0000
Minimum	20.00	200.00	6.00	252.00	2.00
Maximum	43.00	5400.00	16.00	3813.00	11.00

E_2: estradiol.

In the study group 3 of 32 patients (9.4%) had severe OHSS. In the control group none of the patients had severe OHSS. The data of the patients who developed severe OHSS are presented in Table 2. Although, severe OHSS rate was not statistically different between the two groups (p=0.241), follicular aspiration decreased the severe OHSS rate (OR: 0.509; 95% CI: 0.394-0.657).

Discussion

OHSS is an iatrogenic condition resulting from supraphysiological stimulation of the ovary. The pathogenesis of OHSS is still unknown, so, there is no single method that allows OHSS to be reliably predicted and prevented. There is evidence that ovarian renin-angiotensin (14) and vascular endothelial growth factor (15) systems play a role in the pathogenesis of OHSS. Aspiration of follicular fluid and granulosa cells has a negative impact on the corpus luteum function (16). To modify the intraovarian mechanisms thought to be responsible for OHSS, surgical follicular aspiration is tried to decrease the OHSS risk. Various studies have demonstrated the protective value of follicular aspiration against OHSS at the time of oocyte retrieval (17), however, others couldn't confirm this (18,19).

In more recent studies, surgical follicular aspiration is tried before or early after hCG administration to decrease the OHSS risk. In 1995, early follicular aspiration was first applied to 17 patients at risk of OHSS (excessive E_2 values, multiple follicles) 12 hours after hCG administration, followed by regular oocyte retrieval 36 hours later (11). Post hCG aspiration in one ovary has led to the withdrawal of all signs of OHSS within 6 days.

In 1997, Egbase et al. evaluated the effect of unilateral follicular aspiration 6-8 hours prior to hCG administration (12). Thirty-one women with a high risk of OHSS (E_2 >12 000 pmol/ml, >12 follicles each >12 mm in diameter per ovary) were randomized to two groups. Unilateral follicular aspiration was performed in 16 women, while 15 women didn't undergo aspiration. The incidence of severe OHSS was not different between the two groups.

Same research group evaluated in another study the effect of early unilateral follicular aspiration 10-12 hours after hCG administration (20). Thirty patients with high risk of OHSS (E_2 >6000 pg/ml and more than 15 follicles, each with ≥18 mm diameter per ovary) were allocated to have early unilateral follicular aspiration or coasting. The incidence of severe OHSS was not different between groups.

Table 2. The data of the patients developed severe OHSS

	Age (years)	Gonadotropin dose (IU)	Induction period	E_2 level (pg/ml)	Follicle number	PCO apperance
Patient 1	26	2325	15	927	5	–
Patient 2	31	1855	10	3813	12	–
Patient 3	22	2850	12	3813	7	–

PCO: polycystic ovary.
E_2: estradiol.

In 2003, Schröder et al. have performed unilateral follicular aspiration 12-84 hours before hCG administration to 5 patients with a high risk of OHSS (≥15 follicles each of 12-15 mm per ovary and an estradiol level of ≥2500 pg/ml) (21). Severe OHSS has occurred in 4 of the 5 patients.

Follicular aspiration seems not to be protective against OHSS. As the result of these studies, follicular aspiration can not be recommended for the prevention of OHSS. In our clinic between 1999-2004, we didn't perform follicular aspiration in patients who were given controlled ovarian hyperstimulation ICSI and TESE due to non-obstructive azoospermia but with failure to find motile sperms. Our study is a retrospective study designed to evaluate the effect of follicular aspiration during oocyte retrieval on the incidence of severe OHSS in couples with nonobstructive azoospermia treated between January 1999 and March 2004. ICSI with freshly prepared testicular sperm was planned for these couples and TESE was performed on the day of oocyte retrieval. For the NOA patients the probability of finding sperm is only ~50% in the TESE of a nonselected population (22-24). Cryopreservation of the testicular sperm for ICSI may overcome this problem (25), however the impaired quality of the testicular tissue of NOA patients doesn't allow for cryopreservation and the later use for ICSI in all cases. A significant decrease in sperm motility and viability by freezing and thawing of testicular sperm has been demonstrated (26). This implies that cases with extremely low numbers of sperm retrieved can hardly be considered candidates for cryopreservation. Use of freshly prepared testicular sperm for ICSI is our first-line approach but diagnostic surgery combined with cryopreservation is also offered to couples. The control group was formed from patients who underwent COH, oocyte retrieval for ICSI without successful fertilization, to exclude the effect of pregnancy on OHSS. Forming the control group from patients in whom follicular aspiration was done, although, sperm was not found in TESE could be more correct methodologically. But in respect of the literature, we preferred not to perform an invasive procedure such as follicular aspiration to patients if no sperm was found in the TESE. Instead we formed the control group from demographically similar patients with the study group, but underwent follicular aspiration without successful fertilization to exclude the effect of pregnancy on severe OHSS development. Same treatment protocol with similar dosages was used for both the study and control groups. Early OHSS rates were compared between the groups since the effect of pregnancy had been avoided. Between January 1999 and March 2004, among the infertile couples with NOA, there were 32 patients in whom no sperm was found in TESE so follicular aspiration was not performed and 28 patients with fertilization failure. Study group and control group were similar for the risk of OHSS. In the study group 3 of 32 patients (9.4%) had severe OHSS; where as none of patients had severe OHSS in the control group. Severe OHSS rate decreased by performing follicular aspiration (OR: 0.509; 95% CI: O.394-0.657), but the difference was not statistically significant (p=0.241).

The potential weakness of this study is in being retrospective and in being based on 60 women who did not have a high risk of OHSS. In a larger cohort with high OHSS risk the increased OHSS by not performing follicular aspiration can be significant.

According to our results confirming those of others, follicular aspiration is not recommended as a preventive measure against OHSS for the patients who are planned to have ICSI with fresh sperm obtained by TESE on account of non-obstructive azoospermia but resulting with no sperm extraction if the OHSS risk is not high. For the patients with high risk, however, follicular aspiration may be preventive for severe OHSS. Additional randomized prospective studies in larger cohorts including patients with high OHSS risk are needed to investigate the role of follicular aspiration to prevent OHSS.

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