Follicular aspiration versus coasting for ovarian hyper-stimulation syndrome prevention

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ABSTRACT

الأهداف: مقارنة سحب حويصلات المبيض مقابل حجب أدوية تحفيز المبيض للحد من متلازمة تهيج المبايض، فرص الحمل، ومعدل إلغاء الدورة العلاجية في دورات أطفال الأنابيب العلاجية

الطريقة: تم تصميم هذه الدراسة كدراسة استباقية في قسم أطفال الأنابيب في مدينة الملك عبدالعزيز الطبية، الرياض، المملكة العربية السعودية. مجموع 39 مريضة يتم علاجهن في قسم أطفال الأنابيب ولديهن خطورة الإصابة بمتلازمة فرط المبايض. المجموعة الأولى تتكون من 20 مريضة تم علاجهن بتوقيف أدوية تحفيز المبايض، و المجموعة الثانية من 19 مريضة تم سحب حويصلات مبيض واحد لديهن من الفترة أكتوبر 2010 إلى يناير 2011. حيث ان النتيجة الرئيسية هي انخفاض معدل متلازمة فرط المبيض

النتائج: 6 نساء (30%) تم إصابتهن بمتلازمة فرط المبايض من المجموعة الأولى و2 من النساء (10.5%) من المجموعة الثانية. معدل الحمل كان متشابه في المجموعتين، 4 نساء (20%) من المجموعة الأولى و 3 نساء (15.8%) من المجموعة الثانية. معدل الإلغاء كان متشابه في المجموعتين، ٦ نساء (30%) من المجموعة الأولى ومريضة واحدة (5.3%) من المجموعة الثانية. الوسيط لعدد الحويصلات المثقوبة كان أقل في المجموعة الثانية فقد كان 16 حويصله مقابل 29 حويصله في المجموعة الأولى. النتائج كانت متشابهة في المجموعتين من ناحية عدد البويضات المسحوبة والمتخصبة و المنقسمة وكذلك عدد الأجنة المنقولة في المجموعتين.

الخاتمة: لم يكن هناك فرق بين سحب حويصلات مبيض أو إيقاف أدوية تحفيز المبايض لتقليل نسبة الإصابة بمتلازمة فرط المبايض، معدل الحمل، أو معدل الإلغاء في دورات أطفال الأنابيب العلاجية.

Objectives: To compare follicular reduction prior to human chorionic gonadotropin (HCG) trigger and coasting in terms of ovarian hyper-stimulation syndrome (OHSS) reduction, pregnancy, and cancellation rates in in vitro fertilization/ intracytoplasmic sperm injection (IVF/ICSI) cycles.

Methods: This study was designed as a prospective study. The setting was the IVF unit at King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia. A total of 39 patients undergoing IVF/ICSI cycles, who were at risk of OHSS, 20 were put into a coasting group and 19 had follicular reduction instead. This occurred between October 2010 and January 2011. Our main outcome was OHSS reduction.

Results: Six (30%) women developed OHSS in the coasting group and 2 (10.5%) women developed OHSS in the follicular group (p-value=0.235). The pregnancy rates in the cycles were similar for both groups: 4/20 (20%) in the coasting group and 3/19 (15.8%) in the follicular group (p-value=1.000). The cancellation rate of the cycles was similar for both groups, 6/20 (30%) in the coasting group and 1/19 (5.3%) in the follicular group (p-value=0.09). The median number of punctured follicles was significantly lower in the follicular group (16 follicles, interquartile range (IQR)=21-12) compared to the coasting group (29 follicles, IQR=37.8-19.8, p-value=0.001). The retrieved, fertilized, and cleaved oocytes, as well as the number of embryos transferred, were similar amongst both groups.

Conclusion: There was no difference between follicular reduction prior to HCG and coasting, in terms of OHSS reduction, pregnancy, and cancellation rates in both the IVF and ICSI cycles.

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In assisted reproductive technology (ART), controlled ovarian stimulation (COS) can lead to short-term complications including ovarian hyper-stimulation syndrome (OHSS), thromboembolism (TE), adnexeal torsion, infection, and bleeding.[1-3] Ovarian hyper-stimulation syndrome is one of the most serious and potentially life-threatening complications.[4] The reported incidence of moderate to severe forms is 3-10% and can reach up to 20% in high-risk women.[5,6] The clinical manifestations of OHSS result from depleted intravascular space and excessive protein-rich fluid in the body cavity and interstitial space due to vasoactive substances produced from the ovary mainly vascular endothelial growth factor (VEGF) and angiotensin.[4,7,8] Many trials have been conducted to evaluate different interventions that reduce the risk of OHSS. Follicular aspiration at the time of oocyte retrieval may offer some protection by causing intra-follicular hemorrhage, thus decreasing the ovarian production of vasoactive substances responsible for OHSS. Different timings of follicualar aspiration have been shown to induce similar effects (for instance, reduction of follicles before human chorionic gonadotropin (HCG) trigger). Follicular reduction performed 6-8 hours prior to or 10-12 hours after HCG trigger is one of the secondary preventive methods, though data on outcome is limited.[9-11] In contrast, coasting is one of the most well-studied interventions. This process involves postponing the HCG trigger until estradiol (E2) levels decrease to a safer level. Since larger follicles are resistant to atresia and continue to grow even when follicle stimulating hormone (FSH) level declines and smaller follicles undergo selective regression, this approach reduces the granulosa cell mass and vasoactive substances produced by the ovary responsible for OHSS mentioned earlier.[12,13] However, empirical evidence in support of coasting for OHSS prevention is lacking and more data is required.[14,15] Ovarian hyper-stimulation syndrome remains a challenging hurdle in ART in need of effective preventive methods. The aim of this study is to compare follicular reduction prior to HCG trigger with coasting in terms of OHSS prevention, pregnancy and cancelation rates in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment.

Methods. Ethical approval was obtained from King Abdullah International Medical Research Center (KAIMRC) on the 3rd of March 2013. A prospective cohort study was conducted according to the Helsinki Declaration. Inclusion criteria was patients who were at high risk for OHSS (E2 levels of 20,000 pmol/l on the day of HCG injection) according to the departmental policy. These patients were identified in the period from October 2010 to January 2011 and enrolled in this study. All patients provided written informed consent prior to study initiation.

The 39 patients were randomly alternatively divided into 2 groups: unilateral follicular aspiration prior to HCG injection (19 patients) or coasting on the day of HCG injection (20 patients). Follicular reduction after COS was achieved using the short GnRH agonist protocol that is the standard of care in our IVF unit. An injection of GnRH agonist (Decapeptyl 0.1 mg/day, IPSEN, Paris, France) was delivered subcutaneously (SC) on day 3 or 4 of the cycle if baseline endometrial thickness was less than 6 mm. Controlled ovarian stimulation was initiated on the same day with either recombinant FSH (rFSH) (Gonal-f, Merck, NJ, USA) or human menopausal gonadotrophins (HMG) (Menogon, Ferring, Saint-Prex, Switzerland or Merional, IBSA, Lugano, Switzerland) for 7 days. Estradiol E2 levels and vaginal ultrasonography were assessed on day 8 to inform gonadotrophins dosage decisions going forward. Dosage will be decreased if higher E2 level and number of follicles than required were found, and vice versa.

On HCG injection day, patients with E2 levels over 20,000 pmol/l and at least 2 follicles measuring ≥18 mm were randomized into 2 groups. The first group underwent a procedure for follicular reduction of most of the follicles that could be aspirated in one ovary under moderate sedation. Patients were discharged with an HCG 10,000 IU injection (Choriomon, IBSA, Lugano, Switzerland) given on the same day 35 hours before their scheduled ovum pick up procedure for the contralateral ovary. Embryo transfer (ET) was performed after 2-3 days at the 4-8 cells stage. Supplementary progesterone (Cyclogest, L.D.COLLINS & CO., London, UK) was prescribed at ET and continued for 12 weeks in the case of successful pregnancies.

The second group was treated with coasting in which gonadotrophins were withheld. Patients had their E2 level checked daily until it dropped to <20,000 pmol/l. Then HCG injection was performed and patients were scheduled for ovum pick-up after 35 hours, followed by ET as described above.

Patients were called after 16 days of ET for a pregnancy test. Those who developed symptoms of OHSS were referred to the emergency department or

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to the IVF clinic and results were documented in their files.

The pregnancy rate was defined as the number of patients with positive pregnancy tests after 16 days of ET over the total number of patients in each group. The cancellation rate represents the number of patients who had cycle cancellation over the total number of patients started in each group. Ovarian hyper-stimulation rates represent the patients who developed severe OHSS (according to the Royal College of Obstetricians and Gynaecologists' classification of OHSS severity) over the total number of patients in each group.

Patient demographics and clinical characteristics including age, body mass index (BMI), type of infertility, treatment, HMG duration and dose of treatment, and E2 level were analysed. Patients with polycystic ovaries and a history of OHSS were identified as high risk for OHSS.

Statistics revealed that our data were not normally distributed. Therefore, the Mann–Whitney U test was used to compare the median of age, BMI, and amount of HMG used between the 2 groups (coasting and follicular). Chi-squared test was used to compare percentage of infertility causes between the 2 study groups. Fisher-Freeman-Halton exact in crosstabs was used when any cells have expectation of less than 5. All statistical analyses were performed using statsDirect statistical package (version 2.8.0 Cheshire UK 2013). A *p*-value <0.05 was considered statistically significant.

Results. Thirty-nine (N=39) women at risk for OHSS were enrolled in this study. They were divided randomly into a coasting group (n=20, 51.3%) and a follicular group (n=19, 48.7%).

The median age was similar in both groups: 31.5 years (interquartile range (IQR)=35-26.3) in the coasting group and 31 years (34-25.0) in the follicular group; the Mann–Whitney U test revealed a *p*-value of 0.517. Their BMIs were also similar (coasting group=30.5, IQR=36.3-24.0 kg/m^2; follicular group=29, IQR=32-25 kg/m^2). The median number of follicles punctured was significantly lower in the follicular group (16 follicles, IQR=21-12) compared to the coasting group 29 (IQR=37.8-19.8) (*p*-value=0.001, **Table 1**). The numbers of retrieved, fertilized, cleaved, and implanted embryos were similar between the 2 groups (**Table 2**).

Six (30%) women developed OHSS in the coasting group compared to 2 (10.5%) women in the follicular group (*p*-value=0.235). The pregnancy rates were similar for both groups: 4/20 (20%) in the coasting group and 3/19 (15.8%) in the follicular group (*p*-value=1.000).

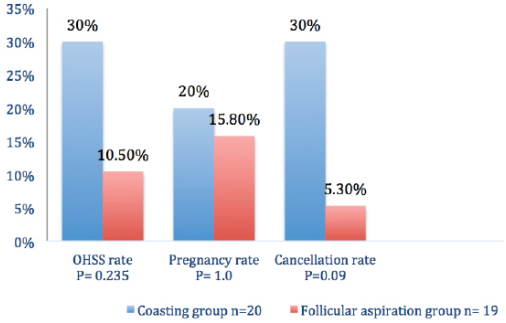

Figure 1 - Intervention outcomes among 39 patients undergoing IVF/ICSI cycles, 20 were put into a coasting group and 19 had follicular reduction instead between October 2010 and January 2011.

Table 1 - Basic patients' characteristics among 39 patients undergoing IVF/ICSI cycles, 20 were put into a coasting group and 19 had follicular reduction instead between October 2010 and January 2011.

Characteristic	Coasting group (n=20)	Follicular aspiration group (n=19)	Total	*P*-value
Age median (IQR) years	31.5 (35-26.3)	31 (34-25)	31 (35-26)	0.517*
BMI median (IQR) kg/m^2	30.5 (36.3-24)	29 (32-25)	30 (33-25)	0.545*
HMG ampoules number	21 (38-14)	16 (28-14)	21 (28-14)	0.222*
HMG treatment duration days	7 (9-7)	8 (9-7)	7 (9-7)	0.544*
Number of follicles	21 (30-14)	24 (27-18)	21 (27.3-15)	0.951*
E2 level Pmol/ml	29009 (36525-23557)	35440 (36700-27444)	31552 (36700-23950)	0.117*
Secondary infertility n (%)	10 (50)	12 (63.2)	22 (56.4)	0.523**
Risk factor for OHSS n (%)	17 (85)	16 (84.2)	33 (84.6)	1.000***
Hormonal infertility n (%)	12 (60)	10 (52.6)	22 (56.4)	0.751**
Male factor infertility n (%)	10 (50)	10 (52.6)	20 (51.3)	1.000**
Male/female infertility n (%)	2 (10)	3 (15.8)	5 (12.8)	0.661***
Unexplained infertility n (%)	1 (5)	1 (5.3)	2 (5.1)	1.000***

Mann-Whitney U test*, Chi-square**, Fisher-Freeman-Halton exact***, BMI - body mass index, HMG - human menopausal gonadotrophins OHSS - ovarian hyper-stimulation syndrome

Table 2 - Treatment cycles characteristics among 39 patients undergoing IVF/ICSI cycles, 20 were put into a coasting group and 19 had follicular reduction instead between October 2010 and January 2011.

Characteristic	Coasting group (n=20)	Follicular aspiration group (n=19)	Total	*P*-value
Follicles aspirated median	29 (37.8-19.8)	16 (21-12)	20 (29-14.5)	0.001*
Oocytes retrieved median	14.5(23-9.5)	12 (18-8)	12 (18-9)	0.339*
Oocytes fertilized median	8 (10.5-7)	6 (10-4)	8 (10-5.3)	0.126*
Cleaved embryos median	8 (10.5-7)	6 (10-3)	7 (10-5)	0.077*
Embryos transferred median	3 (3-2)	3 (3-2)	3 (3-2)	0.857*
Rate of ICSI technique n (%)	17 (85)	17 (89.5)	34 (87.2)	1.000***

Mann-Whitney U test*, Fisher-Freeman-Halton exact***, ICSI - intracytoplasmic sperm injection

The cancelation rates were also similar for both groups: 6/20 (30%) in the coasting group and 1/19 (5.3%) in the follicular group (*p*-value=0.09) (**Figure 1**).

Discussion. Ovarian hyper-stimulation syndrome is characterized by ovarian enlargement and increased vascular permeability provoked by a number of inflammatory mediators derived from the ovary; the most important is VEGF which is increased by HCG.[5,7] The cause of OHSS has not yet been thoroughly identified. However, regardless of the cause, gynaecologists and physicians should be aware of OHSS because of its high morbidity and potential mortality.[1,2] While it is impossible to avoid OHSS completely, patients who are at risk should be identified early since preventive measures taken during the early stages of COS can improve outcome.[15,16]

In this study, we compared 2 modalities used for OHSS prevention. Although 30% of the coasting group developed OHSS compared to only 11% of the follicular group, this difference did not reach statistical significance. In addition, both groups experienced similar pregnancy and cancelation rates. The Egbase group explained the effectiveness of follicular aspiration using variable timing in the cycle by causing intra-follicular haemorrhage, granulosa cells aspiration, and corpora lutea functional alterations in the follicles.[11] According to these findings, follicular aspiration prior to HCG injection should be more protective against OHSS occurrence than 35-36 hours after HCG.[11]

A similar comparative study was performed to address follicular reduction at different times in coasting using early unilateral follicular aspiration (EUFA), which involves aspiration of follicles in one ovary at 10-12 hours after HCG. They found no difference between both methods in OHSS prevention, oocyte fertilization, embryo cleavage, and clinical pregnancy. However, the mean number of oocytes retrieved and percentage of oocytes retrieved per follicle ruptured were significantly higher in patients with EUFA.[10] This finding is unusual given that one ovarian yield was lost before the oocyte recovery procedure. Our analysis revealed higher follicles punctured, oocytes recovered, and oocytes fertilized in the coasting group but these findings were not significant, likely due to our small sample size.

In a prospective study, unilateral ovarian follicular aspiration (UOFA) was performed 6-8 hours prior to HCG.[11] The study revealed no differences between patients undergoing UOFA and the control group who did not undergo UOFA in terms of severe OHSS occurrence, fertilization, or embryo cleavage; they also reported a lower mean number of oocytes from the UOFA group, as expected.[11]

Other studies have reported that follicular aspiration 12 hours after HCG trigger decreased OHSS occurrence.[17,18] The Tomaz group analysed follicular aspiration benefits on 109 patients and found decreased rates of OHSS.[17] The timing of aspiration just prior to ET was evaluated by the Amit group and concluded it was a safe and effective modality in reducing the incidence and severity of OHSS.[19] The Oyawove group however, reported benefits from aspiration on day 4-7 of stimulation with aspiration of at least 10 follicles ≤12mm.[20]

In this study, follicular aspiration was compared to coasting, which is effective for reducing the risk and severity of OHSS but cannot prevent it completely.[21] This technique is supported by many researchers and preferred by patients over other methods such as cycle cancellation or embryo freezing.

Initiating coasting depends on both E2 levels and follicle size and number. Different protocols and criteria for coasting are used in different clinical centres. It is usually initiated when E2 levels are >3000 pg/ml (11,000 pmol/L) with numerous immature follicles <16 mm with rapidly increasing E2 levels until reaching 3000 pg/ml, which is considered safe.[7,22] Many have reported that coasting for more than 3 days can adversely affect

IVF outcome, perhaps due to the deleterious effects on the endometrium with prolonged coasting.[7,15,22] Cycle cancellation should be considered if coasting is required for more than 4 days or if E2 levels decrease by more than 30% from the HCG trigger-day levels.[7]

A systematic review of randomized controlled trials addressing the use of coasting for OHSS prevention concluded that there was no evidence to support coasting for OHSS prevention over not coasting or any other intervention.[23] In 2015, a review of evidence available regarding OHSS detection and prevention, could not reach a conclusion regarding coasting as a modality of OHSS prevention.[24]

On the contrary, another systematic review concluded that coasting decreased the incidence of OHSS even though it did not prevent it completely.[25] In addition, some studies have reported that coasting decreases OHSS risk without compromising pregnancy outcome in IVF.[26]

Unfortunately, our findings are limited due to the small cohort of patients included in this analysis. Further studies are needed with more patients to reach significant conclusions. However, since no difference in OHSS prevention was observed between the 2 groups, we sense that coasting is likely superior in terms of convenience and safety. Follicular aspiration requires considerable time for operation from the physician and the patient. It also carries the risk of complications including pain, bleeding, and sedation exposure. Financial issues should be considered as well since the procedure adds extra cost to the treatment cycle.

We found no difference between follicular reduction prior to HCG and coasting in terms of OHSS reduction, pregnancy or cancelation rates in ART. Further researches are needed with a bigger number of patients recruited, putting into account the financial expenses and patients wish and acceptance of having an extra procedure which they can avoid with other modalities to prevent OHSS.

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