ORIGINAL ARTICLES

THE EFFECT OF COASTING AS A PREVENTIVE MEASURE FOR OVARIAN HYPERSTIMULATION SYNDROME (OHSS) ON INTRACYTOPLASMIC SPERM INJECTION (ICSI) OUTCOME

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ABSTRACT

Objective : To evaluate the effect of coasting in ovarian hyperstimulated (ICSI) cycles on the outcome.

Design : Retrospective study.

Material and Methods : The study includes cases at risk of Ovarian Hyperstimulation Syndrome (OHSS). Coasting was applied when the patient was considered at actual risk of developing OHSS as indicated by, large number of follicles > 20 in both ovaries and serum E_2 level ≥ 3000 pg/ml. Coasting did not begin till the leading follicles reached a diameter of at least 15 mm and continued until E_2 fell below 3000 pg/ml. Study group was divided into two groups based on the number of coasting days, group(I){duration of coasting ≤ 4 days} and group(II){duration of coasting >4 days} .

Result: Coasting was applied in twenty two patients out of one hundred seventy ICSI controlled ovarian hyperstimulated cycles, during the period between April 2005 and April 2006. E_2 level on day of initiating Coasting among group(I) and group(II) was 5162.9 ± 2891.9 pg/ml and 7198 ± 2313.3 pg/ml respectively (p value 0.26), E_2 level on day of HCG administration among group(I) and (II) was 2944.5 ± 12889 pg/ml and 2960 ± 2134.9 pg/ml respectively (p value 0.86), the mean number of oocytes and Metaphase II oocytes retrieved among group(I) were13 ± 4.9 and 10.4 ± 5.4 respectively and among group (II) were 5.6 ± 5.3 and 4.8 ± 3.9 respectively (p value 0.008); the mean fertilization rate among groups(I) & (II) was 69 % & 68% respectively, the mean number of embryos among groups(I) & (II) was 7.5 ± 3.1 & 4 ± 3.5 respectively, pregnancy rate per embryo transfer among groups (I) & (II) was 28.8 % & 0.0 % respectively and OHSS 0.58% (1/170) of stimulated cycles and 4.54 % (1/22) of patients at risk of developing OHSS

Conclusion: Coasting is effective in preventing OHSS and allow transfer of fresh embryos, without cycle cancellation. Prolonged Coasting (>4 days) may be detrimental to the quality of Oocytes , fertilization rate and pregnancy rate.

Key words : Coasting, ICSI, Outcome.

INTRODUCTION

The majority of IVF cycles result in some degree of hyperstimulation.[1] Iatrogenic hyperstimulation syndrome (OHSS) is the most important complication of ovulation induction. In it's severe form it is a potentially lethal disease.[2-4] The incidence of OHSS varies with the degree of OHSS. The incidence of severe forms of OHSS in patients undergoing ovarian hyperstimulation for IVF is 0.5-2%.[5] Risk factors for developing OHSS before gonadotrophin administration are : Young age, lean habitus, PCO (necklace sign), PCOD (hyperinsulinaemia) and allergy (immunoactivation). Risk factors presenting during or after gonadotrophin administration are: Development of > 20 follicles, a high serum oestradiol level (> 3000 pg/ml), supplementation of the luteal phase with HCG and occurrence of pregnancy in the treatment cycle. Different strategies for preventing OHSS have been proposed. HCG withholding, ovarian electrocautery, Coasting, follicular aspiration before or after HCG administration, intravenous albumin and cryopreservation of embryos. HCG withholding, is the most successful strategy; but this approach has significant financial and emotional costs to the patients. A widely used strategy is cryopreservation of all embryos. However, this does not prevent the early form of OHSS and generally yields inferior pregnancy rates compared with fresh embryo transfer.[6]

The technique of Coasting is appealing to both physician and patients because it allows transfer of fresh embryos, without additional treatment cycle. Coasting, involves withdrawing exogenous gonadotrophins and postponing HCG administration until the patients serum oestradiol (E_2) level decrease to safer levels. Coasting was first described by Rabinovici et al., (1987), and was first applied in IVF by Sher et al., (1993).[7] Removing the FSH stimulation of granulosa cells inhibits their proliferation causing down regulation of their receptors, reducing the number of granulosa cells available for luteinization. It has been suggested that a sharp decline in the FSH concentration may increase the rate of granulosa cells apoptosis.[8] Coasting leads to reduced number of retrieved Oocytes, which is in direct relationship to the duration of Coasting. However, there is no significant difference in Oocyte maturity, fertilizability and cleavage rate.[9,10]

This procedure seems to be associated with quantitative but no qualitative changes of Oocyte /cumulus complex.[11] The selection criteria which determined the decision to use Coasting were variable. (Either a threshold value of E_2 varying between 2500 pg/ml and 6000 pg/ml or in other studies selection of 3000 pg/ml.). The number of follicles when deciding to Coast are usually 20-30 follicles in both ovaries. The coasting is initiated when at least half of the follicles have reached a diameter of 15-18mm.[12] The duration of Coasting is determined by the serum E_2 level and the diameter of the leading follicles when Coasting is initiated. If Coasting is initiated when the largest follicles are not more than 17-18mm and E_2 concentration is not more than 6000 pg/ml, a Coasting period of > 4 days can be avoided[13,14]. A recommended limit of 3000 pg/ml leads to effective prevention of OHSS and keeps the overall duration of Coasting <4 days, which is safe and does not reduce implantation or pregnancy rates.

PATIENTS & METHODS

This is a retrospective study which includes cases at risk of OHSS at The Assisted Reproductive Technique Unit (ART), International Islamic Center for Population Studies and Research (IICPSR).

Al-Azhar University. During the period from April 2005 to April 2006. 22 out of 170 ICSI controlled ovarian hyperstimulated cycles, Coasting was applied and the patients were devided into two groups according to duration of coasting (group (I) duration of coasting ≤ 4 days and group (II) duration of coasting ≥ 4 days). Controlled ovarian hyperstimulation (COH) was performed using Gn RH agonist long luteal protocol. Gn RH agonist (Lucrin 10 IU or Decapeptyl 0.1mg) was given Subcutaneously daily starting from day 21 of the preceding cycle. Two weeks later, serum E_2 was measured to confirm pituitary desensitization (E_2 50 pg/ml). The starting dose of gonadotrophins depended on, patient age, BMI, endocrinological status of the patient, number of antral follicles on cycle day 3, ovarian volume and previous ovarian response. The starting dose was fixed for the 1st 5 days, then the dose of gonadotrophins was adjusted according to individual ovarian response as indicated by transvaginal u/s every other day and serum E_2 level as indicated. Increased ovarian response was diagnosed by the number of follicles seen by u/s > 20 follicles in both ovaries & E_2 level > 3000 pg/ml. Coasting (withholding gonadotrophin injections & GnRH agonist continued) was applied for such cases. Coasting did not begin till the leading follicles reach a diameter of 15 mm. Serum E_2 was estimated every day and HCG (Choriomon 5000 IU) was given when serum E_2 fell below 3000 pg/ml. Ovum pick up was performed 34-36 hrs after HCG injection.

Retrieved Oocytes were subjected to ICSI. Embryos were transferred transcervically guided by u/s 2-3 days after retrieval. Number of transferred embryos varied with, age of the patient, embryo quality & previous cycle outcome. Luteal phase was supported by either Cyclogest 200mg suppository every 12 hrs or Prontogest 100mg ampoule intramuscularly every 24 hrs. Serum βHCG was estimated 2 weeks after embryo transfer. Clinical pregnancy was defined by the demonstration of a gestational sac on u/s.

Statistical analysis was performed with the aid of the analysis of variance (ANOVA) and student's t-test for different parameters. Fisher's was used to compare proportions; differences seen were considered to be statistically significant if $P<0.05$. Linear regression analysis was used to demonstrate the correlation between number of metaphase II oocyte, fertilization rate, number of embryos and duration of coasting.

RESULTS

The characteristics of the patients in the study groups are shown in table (I). The mean age of groups (I) & (II), were 28.9 ± 5.5 years & 31.2 ± 3.8 years respectively(p value 0.31). Six cycles (27.27%) were studied in patients with tubal factor, seven cycles (31.82%) were in patients with PCOS and nine cycles (40.91%) were in patients with impaired semen parameters. The mean BMI among groups (I) & (II), were 27.5 ± 2.1 & 29.9 ± 1.1 respectively (p value 1.01). The mean day 3 FSH in groups (I) & (II) were 5.3 ± 1.7 miu/ml & 6.9 ± 2.2 miu/ml repectively (p value 0.10) & LH in groups (I) & (II) were 6.7 ± 2.9 miu/ml & 5.9 ± 2.6 miu/ml respectively (p value 0.57).

Outcome of ICSI in women who underwent Coasting by duration of coasting is shown in table (II), E_2 level on day of initiating Coasting in group(I) {duration of coasting ≤ 4 days} and group(II) {duration of coasting > 4 days} was 5162.9±2891.9 pg/ml and 7199± 2313.3 pg/ml respectively (p value 0.26). E_2 level on the day of HCG administration in groups (I) and (II) was 2944.5± 12889 pg/ml and 2960 ± 2134.9 pg/ml respectively (p value 0.86). The mean number of oocytes and Metaphase II oocytes retrieved in group(I) were13 ± 4.9 and 10.4 ± 5.4 respectively and in group (II) were 5.6 ± 5.3 and

Table I : Characteristics of study groups (n 22) .

	Group I n = 17 Mean ± SD / %	Group II n = 5 Mean ± SD / %	P value
Age (years)	28.9 ± 5.5	31.2 ± 3.8	0.31
B.M.I (kg / m2)	27.5 ± 2.1	29.9 ± 1.1	1.01
FSH (miu / ml)	5.3 ± 1.7	6.9 ± 2.2	0.10
LH (miu / ml)	6.7 ± 2.9	5.9 ± 2.6	0.57
Aetiology			
Tubal	4 (67%)	2 (33%)	
Ovulatory	5 (71%)	2 (29%)	0.55
Male factor	8 (89%)	1 (11%)	

Table II : Outcome of ICSI in women who underwent coasting by duration of coasting (n 22) .

	Group I (coasting duration ≤ 4 days) n = 17 Mean ± SD / %	Group I (coasting duration > 4 days) n = 5 Mean ± SD / %	P value
E_2 level on day of starting coasting (pg / Ml)	5162.9 ± 2891.9	7198 ± 2313.3	0.26
E_2 level on day of hCG administration (pg / Ml)	2944.5 ± 12889	2960 ± 2134.9	0.86
Mean time of coasting	13.5 ± 2.3	12.8 ± 1.3	0.42
Mean duration of coasting	2.4 ± 1.1	5.6 ± 0.9	< 0.0001
No. of oocyte	13 ± 4.9	5.6 ± 5.3	0.008
No. of MII	10.4 ± 4.7	4.8 ± 3.9	0.03
Fertilization rate	69.6 %	68 %	0.90
No. of embryos	7.5 ± 3.1	4 ± 3.5	0.03
No. of embryos per transfer	3.1 ± 0.6	3.2 ± 0.8	0.66
Pregnancy rate per embryo transfer	28.8 %	0.0 %	

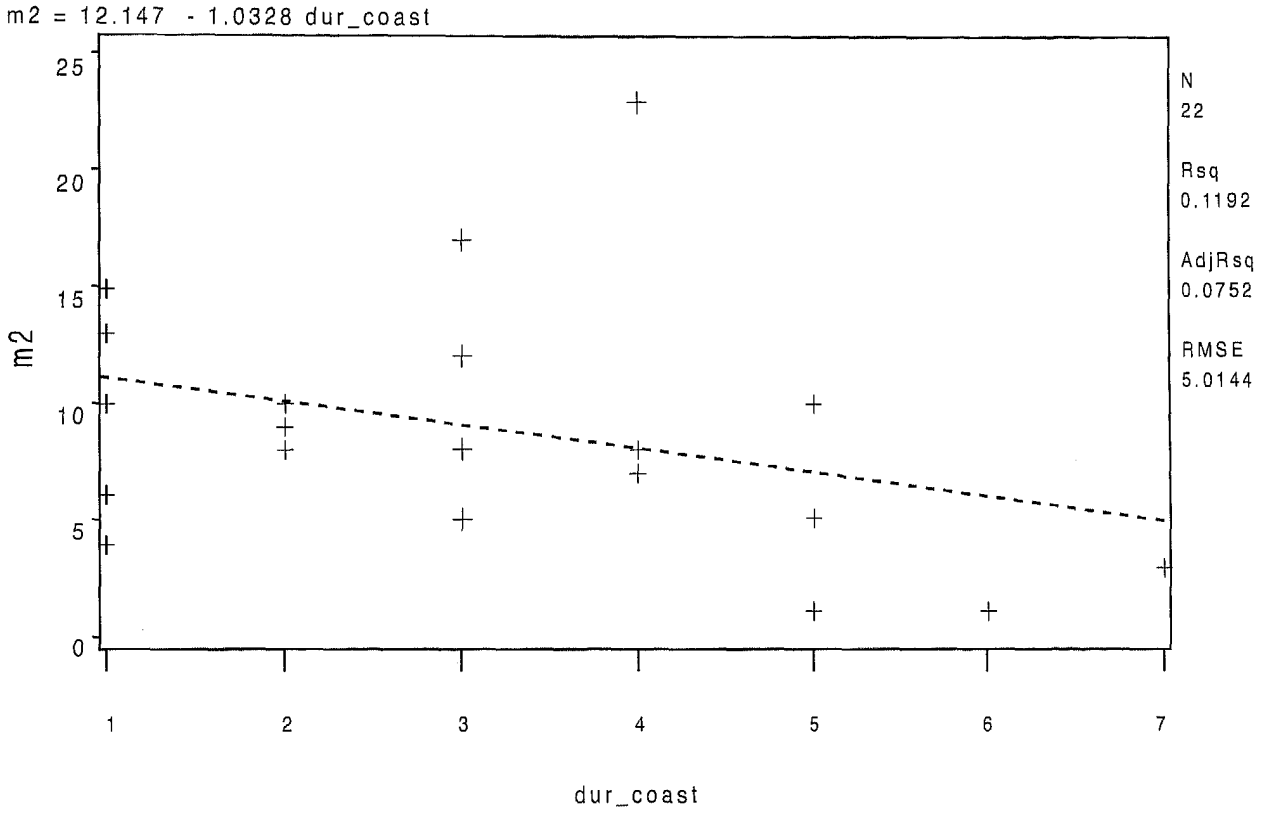

Fig. 1. Association between metaphasell and duration of coasting

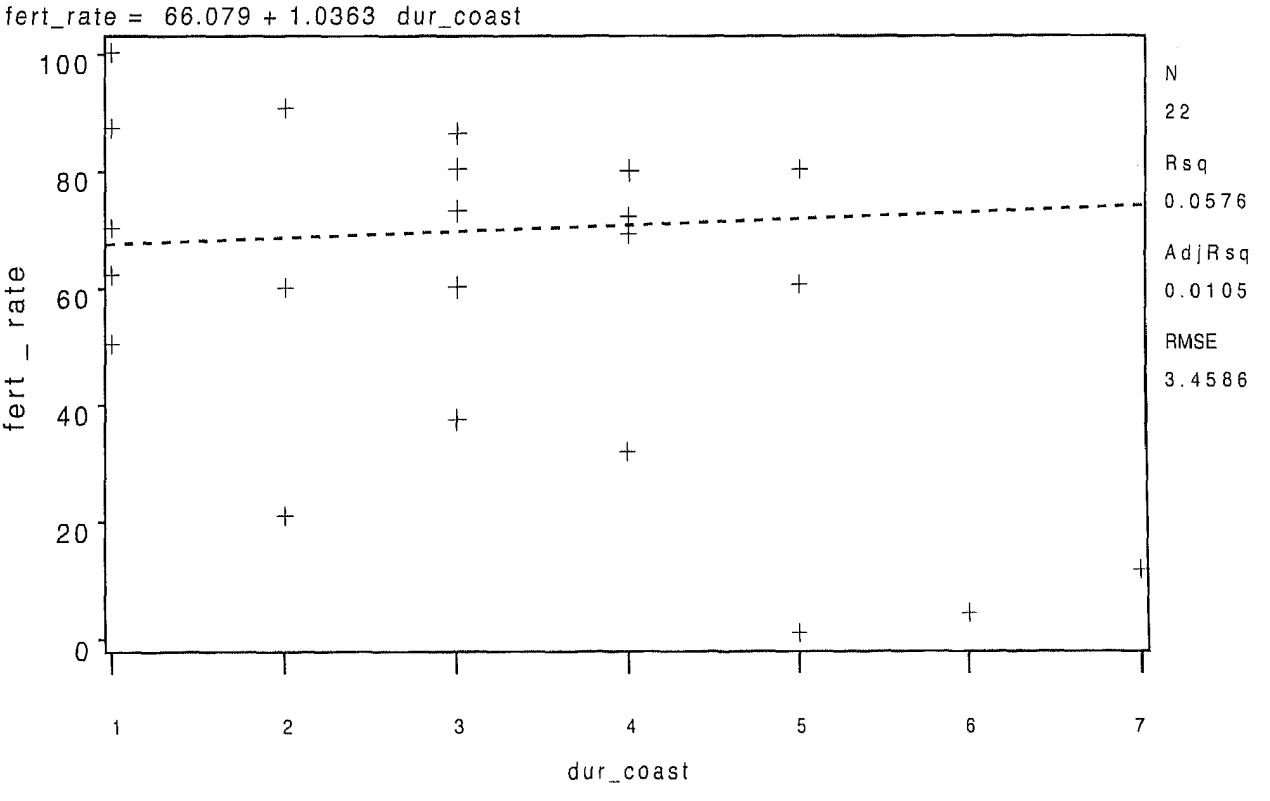

Fig. 2. Association between fertilization rate and duration of coasting

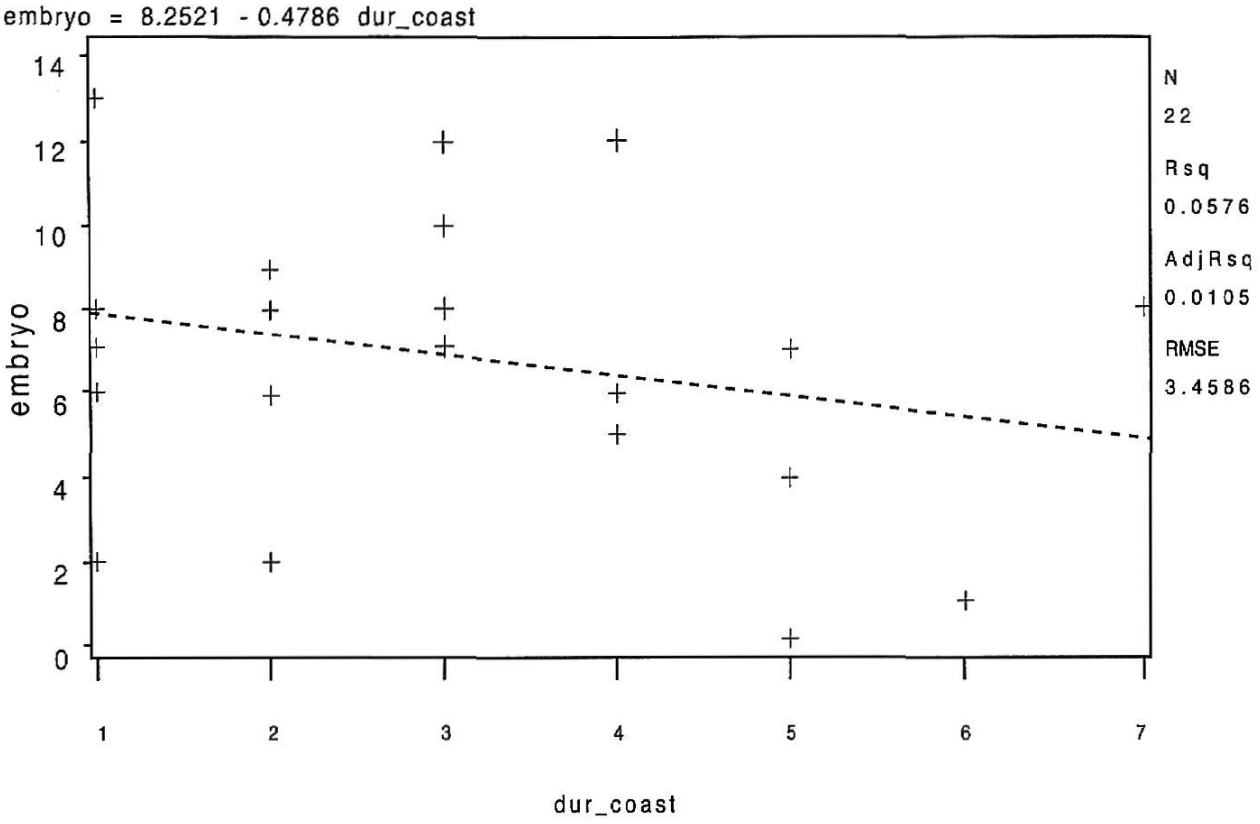

Fig. 3. Association between embryo number and duration of coasing

4.8±3.9 respectively (p value 0.008). The mean fertilization rate in groups (I) & (II) was 69% & 68% respectively (p value 0.90), the mean number of embryos in group (I) & (II) was 7.5 ± 3.1 & 4 ± 3.5 (0.03), pregnancy rate per embryo transfer in groups (I) & (II) was 28.8% & 0.0% respectively and OHSS 0.58% (1/170) of stimulated cycles and 4.54% (1/22) of patients at risk of developing OHSS .

DISCUSSION

The present study showed that, severe OHSS was developed in one patient (0.58%) (1/170) of stimulated cycles and in 4.55% (1/22) of patients at risk of developing OHSS. These findings are in agreement with the incidence of severe OHSS (0.5-2%) that has been reported[15] The pathophysiology of OHSS is only understood in part. Therefore, the treatment regimes are aimed at ameliorating symptoms.[16] Ascites or pulmonary edema due to increased vascular permeability followed by third space fluid accumulation.[17] Prominent features of OHSS are an elevated risk of thromboembolism due to enhanced production of von willebrand factor by endothelial cells.[18] Both of these sequelae can be evoked by vascular endotherial growth factor (VEGF), also known as vascular permeability factor.[19]

The present study aimed to evaluate the effect of coasting on CS outcome. In our study, the cut-off level of E_2 at starting coasting was >3000 pg/ml; this agrees with the majority of previous studies, the reported E_2 level at initiating coasting ranged from 2500-3000 pg/ml. (Sher et al., 1995; Benavida et al., 1997; Dhont et al., 1998; Lee et al., 1998; Tortoriello et al., 1998; Fluker et al., 1999; Al-Shawaf et al., 2001 and Ragaa et al., 2005) [20,21,9,22,8,24,25,26] while in other studies, the reported cut-off level of E_2

at initiating coasting was > 6000 pg/ml (Egbase et al., 1999) [27] and > 4000 pg/ml (Ulgu et al., 2002). [28] The cut-off level of E_2 at starting coasting, (> 3000 pg/ml) is effective in preventing of OHSS and Keep the overall duration of coasting <4 days, as the longer the duration of coasting (>4 dys), the lower implantation rates and pregnancy rates.

But the coasting is initiated when at least half of follicles have reached a diameter of 15-18mm. Oocytes in smaller follicles may undergo atresia following coasting. If too many follicles are larger than the thresholds size, cystic follicles and poor quality oocytes could result (Sher et al., 1995).[20] In the present study, the mean E_2 level on day of HCG administration in groups (I) & (II) was 2944.5 ± 12889 pg/ml & 2960± 2134.9 pg/ml respectively (P value 0.86). As in most previous studies, E_2 must fall below 3000 pg/ml before HCG administration (Sher et al., 1995; Benavida et al., 1997; Tortoriello et al., 1998; Dhont et al., 1998; Lee et al., 1998; Egbase et al., 1999; Waldenstrom et al., 1999; Fluker et al., 1999 and Ragaa et al., 2005). [20,21,8,9,22,27,13,24,26]

The reported E_2 level on the day of hCG administration was < 4000 pg/ml (Ulgue et al., 2002).[27] E_2 level on the day of hCG administration, <3000 pg/ml is effective in preventing OHSS (Sher et al., 1995; Benavida et al., 1997; Dhont et al., 1998; Tortoriello et al., 1998; Al-Shawaf et al., 2001 and Ragaa et al., 2005),[20,21,9,8,25,26] but if the E_2 level fell too low below 3000 pg/ml; this leads to vaginal bleeding and cycle cancellation, and also to retrieval of very low number of oocytes with poor quality (Waldenstrom et al., 1999).[13]

In our study, the mean duration of coasting in groups (I) & (II) was 2.4 ±1.1 days & 5.6 ± 0.9 days (P value <0.001); this agrees with most previous studies (Benavida et al., 1997; Tortoriello et al., 1998; Dhont et al., 1998; Lee et al., 1998; Dechauched et al., 2000; Ohata et al., 2000; Aboulghar et al., 2000 and Al-Shawaf et al., 2001), [21,8,9,22,29,30,31,25] other studies, the reported mean duration of coasting 4.9-6.1 days, ranging up to 11 days (Sher et al., 1995; Egbase et al., 1999). [20,27] In the present study, the mean number of Oocytes and metaphase II Oocyes in group (I) 13±4.9 and 10.4± 4.7 respectively, and in group (II) 5.6± 5.31 and 4.8± 3.9 respectively (P value 0.008). This agrees the majority of previous studies (Benavida et al., 1997; Tortoriello et al., 1998; Fluker et al., 1999; Waldenstrom et al., 1999; Egbase et al.1999, Dechauched et al., 2000; Ohata et al., 2000; Aboulghar et al., 2000; Al-Shawaf et al., 2001; Ragaa et al., 2005), [21,8,24,13,27,29,30,31,25,26] other studies the reported mean number of Oocytes was 21 and 19.7 (Sher et al., 1995 and Dhont et al., 1998). [20,9] The association between number of metaphase II oocytes and duration of coasting is demonstrated in figure(1).

In our study, the mean fertilization rate among groups (I) &(II) was 69.6% and 68% respectively (P value 0.90), this agrees with most previous studies (Sher et al., 1995; Benavida et al., 1997; Tortoriello et al., 1998; Lee et al., 1998; Fluker et al., 1999; Waldenstrom et al., 1999; Egbase et al., 1999; Ohata et al., 2000; Aboulghar et al., 2000; Al-Shawaf et al., 2001; Ulgu et al., 2002; Ragaa et al., 2005). [20,21,8,22,24,13,26,29,30,24,27,25] The association between fertilization rate and duration of coasting is demonstrated in figure (2). In our study, the mean number of embryos among groups(I) & (II) was 7.5 ± 3.1 & 4± 3.5 respectively (P value 0.03). The association between number of embryos and duration of coasting is demonstrated in figure (3). pregnancy rate per embryo transfer among groups (I) & (II) was 28.8% & 0.0% respectively, and this value comparable with non coasted patients in our unit. The reported pregnancy rate per embryo transfer in other studies was 40% and 51% (Lee et al., 1998; Ulgu et al., 2002). [22,28]

In other studies, if the duration of coasting was >3 days, the mean number of oocytes retrieved, implantation and clinical pregnancy rates were significantly reduced (Ulgu et al., 2002; Ragaa et al., 2005).[28,26] Coasting of < 4 days does not compromise cycle outcome, and coasting of > 4 days reduces number of oocytes retrieved, with lower implantation and pregnancy rates but does not alter fertilization rates. The lower pregnancy rate in patients coasted for > 4 days, is due to the detrimental effect of prolonged coasting on receptivity of endometrium. Although the exact timing of the endometrial implantation window has not been clearly identified, it is likely that in order to obtain a successful outcome, the synchronization of the endometrial phase to the embryonic developmental phase should be achieved (Ulgu et al., 2002).[28]

In our study, the incidence of severe OHSS was 0.58% (1/170) of stimulated cycles and 4.54% (1/22) of patients at risk of developing OHSS. In most previous studies, the reported incidence of severe OHSS in coasted patients was <2%. (Sher et al., 1995; Benavida et al., 1997; Dhont et al., 1998; Tortoriello et al., 1998; Fluker et al., 1999; Waldenstrom et al., 1999; Al-Shawaf et al., 2001; Egbase et al., 2002; Ulgu et al., 2002; Ragaa et al., 2005). [20,21,9,8,24,13,25,27,28,26]

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