Coasting

A viable option for patients at risk of ovarian hyperstimulation syndrome

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ABSTRACT

Objectives: To present our experience in 48 coasted patients and how they performed in terms of the number of eggs collected, numbers of embryos available for embryo transfer after in vitro fertilization, pregnant and on going pregnancy rate.

Methods: The study was conducted at Lister Hospital, London, United Kingdom, during the period October 1998 through to May 2001. For the purpose of the study, we selected coasted cycles in patients who were less than 38 years of age (n=48 patients). A control group of cycles consisted of all cycles during the same period in patients less than 38 years of age, who were not coasted because they did not fulfil the at risk criteria, but yet we collected 20 oocytes or more (n=115 cycles, 113 patients).

Results: The study showed that there is no significant difference in outcome between the 2 groups (52.1% pregnancy rate in the coasted group versus 51.3% in the control group). The incidence of severe ovarian hyperstimulation syndrome was 4.3% in the study group versus 12.2% in the control but this did not reach statistical difference.

Conclusion: We therefore conclude that coasting is a safe and viable option for patients at risk of ovarian hyperstimulation syndrome in an assisted conception cycle that allows the transfer of fresh embryos.

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Ovarian hyperstimulation syndrome (OHSS) is a well-recognized life threatening complication of ovarian stimulation in assisted reproductive technologies (ART). It occurs in 4% of all ART cycles but in its severe form, is estimated to have an incidence of 0.3-0.9%.[1] The various risk factors include young age (<35 years), lean patients, pregnancy, polycystic ovarian disease (PCOD), raised serum estradiol (E2) just prior to oocyte retrieval, raised number of follicles (>30) and the use of human chorionic gonadotrophin (hCG) for luteal support.[1] However, it may occur in any patient undergoing ovarian stimulation and is sometimes unpredictable. The pathophysiology is unclear and thus treatment is very often symptomatic. The mainstay of management is prevention. Coasting (discontinuing exogenous gonadotrophin and deferring hCG administration until the E2 levels drops below 3000 pg/mL) was suggested as a viable and effective way of reducing the risk of severe OHSS and permitting the transfer of fresh embryos.[2] In our unit it was the policy to cancel the treatment cycle of women who were at risk of OHSS (many follicles and E2>10000 pmol/L on the planned day of hCG administration) but this was associated with a significant emotional and financial toll. We thus

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decided to embark on a policy of coasting and to reassess our performance after a reasonable time. This is a report of coasting in 48 ART cycles; the results of which are compared with a group of control cycles during the same time period in patients who were also at risk of OHSS (n=115) but were not coasted.

Methods. Patients at risk of OHSS were defined as those having more than 15 follicles greater than 12 mm diameter on the last transvaginal scan before hCG injection and also having a serum estradiol level on the same day above 10000 pmol/L. During the period 1 October 1998 through to 28 May 2001 we coasted 48 cycles patients in which the patients fulfilled the above criteria. Coasting meant continuing gonadotrophin releasing hormone analogue, withholding exogenous gonadotrophin and performing daily estradiol measurement until the level was below a certain level. This level was 10,000 pmol/L from the beginning of 1998. In one case that will be described in detail later on, a clinical decision was made to take the patient for oocyte retrieval despite a very high estradiol level. For the purpose of this study, we selected coasted cycles in patients that were less than 38 years of age (n=48 cycle, 48 patients). A control group of cycles consisted of all cycles during the same period in patients less than 38 years of age, who were not coasted as they did not fulfil the at-risk criteria but yet we collected 20 oocytes or more (n=115 cycles, 113 patients). The study and control groups were tested for homogeneity for age and for other possible confounding factors such as nulligravidity, cause of infertility, ultrasonic PCOD appearance and type of ART treatment. No statistical difference was found in any of the above factors (**Table 1**). Women were down regulated with a gonadotrophin releasing hormone analogue (Naffarlin puffs, 200 mg 2 puffs twice daily) from the mid-luteal phase of their cycle. A baseline scan was then organized on the 3rd or 4th day after the onset of the next menses. If the lining of the endometrium was less than 5 mm thick and there were no ovarian cysts greater than 10 mm as assessed by vaginal ultrasonography, exogenous gonadotrophin injections were commenced. A follow-up scan was performed 7 days after commencement of gonadotrophin injections and the dose was adjusted accordingly to achieve a satisfactory follicular response. When at least 2 follicles were above 18 mm in diameter and the endometrial thickness was above 7 mm on transvaginal ultrasound, the patients were deemed to be ready for egg collection. If the number of follicles above 12 mm was more than 15, a serum estradiol level was performed and if it was above 10,000 pmol/L, the patient was coasted. Otherwise, 15,000 units of hCG (Profasi; Serono, Welwyn Gardens, United Kingdom) was given intramuscularly at midnight. Vaginal oocyte collection was performed 34-38 hours after the hCG injection. Trans-cervical embryo transfer was carried out 2-3 days after oocyte collection. Luteal support was provided by Cyclogest pessaries (400 mg/day: Hoechst) for 2 weeks after embryo transfer. A serum qualitative beta-hCG was carried out 2 weeks after embryo transfer and if this was positive, a transvaginal ultrasound was performed a further 2 weeks after the blood test to confirm an intra-uterine pregnancy. A positive clinical pregnancy outcome was taken as one in which the ultrasound confirmed an intrauterine pregnancy. An ongoing pregnancy was defined as one in which the viable pregnancy has progressed past 8 weeks gestation. We compared both groups to see if there was any difference in the main outcome parameter for example pregnancy and secondary outcome parameters: number of oocytes collected, number of embryos available for transfer, number of embryos transferred and ongoing pregnancy rate.

Statistical analyses was performed on a computer programme, statistical program for social science using Chi-square for categorical data and Student t-test for continuous data to test for any statistical difference between the coasted and control group. A p value of 0.05 was taken as the level of significance.

Results. We did not cancel any of the 48 cycles that were coasted and thus they all reached the oocyte retrieval stage and had at least one oocyte retrieved (mean 18, range 1-38). As it was a prerequisite in the control group, all patients reached egg collection with at least 20 oocytes retrieved (mean 23, range 20-39). There was failure of fertilization in one coasted cycle and in one control cycle. The pregnancy rate per cycle started in the coasted group was 52.1%, compared with a pregnancy rate per cycle started of 51.3% in the control group. The difference was not statistically significant (p=0.93, odds ratio 1.0, 95% confidence interval 0.5, 2.0). The ongoing pregnancy rates were also similar in the 2 groups (**Table 1**). The mean number of oocytes collected, the mean number of embryos available for transfer and the mean number of embryos transferred were all significantly more in the control group (all $p<0.01$) (**Table 1**). The incidence of severe OHSS that required hospitalization was higher in the control group (12.2% versus 2.1%) but this difference did not reach statistical difference.

Discussion. Ovarian hyperstimulation syndrome remains one of the most serious complications of ovulation induction. The mainstay of management is prevention. Strategies proposed to prevent OHSS in at risk patients include cancellation of treatment cycle, cryopreservation of all embryos and subsequent replacement in a non-stimulated cycle, and giving intravenous albumin at the time of oocyte retrieval. However, all the above methods are not

Table 1 - Comparison of coasted and control groups.

Variables	Coasted group n (%)	Control group n (%)	P
n of cycles	48 (100)	115 (100)	-
Mean age (SD)	31.4 (3.5)	32.2 (3.6)	NS
Ultrasonic polycystic ovarian appearance	30 (62.5)	53 (46.1)	P=0.06
Pregnancy rate	25 (52.1)	59 (51.3)	NS
Mean number of oocytes collected (SD)	17.9 (7.5)	24.2 (4.2)	<0.01
Mean number of embryos available for transfer (SD)	8.8 (6.1)	11.5 (5.2)	<0.01
Mean number of embryos transferred (SD)	2.5 (0.8)	2.8 (0.5)	<0.01
Ongoing pregnancy rate	23 (47.9)	55 (47.8)	NS
OHSS rate	2 (4.2)	14 (14.2)	NS

n - number, P - p value, NS - not significant at the 0.05 level
SD - standard deviation, OHSS - ovarian hyperstimulation syndrome

Table 2 - Ovarian hyperstimulation syndrome in the 2 groups.

n of patients	No OHSS n (%)	Mild OHSS n (%)	Moderate OHSS n (%)	Severe OHSS n (%)
Coasted n=48	40 (83.3)	4 (8.3)	3 (6.3)	1 (2.1)
Control n=115	95 (82.6)	2 (1.7)	4 (3.5)	14 (12.2)

n - number, OHSS - ovarian hyperstimulation syndrome

entirely satisfactory and do not completely eliminate the risk of OHSS. Cancellation of a treatment cycle is always a difficult decision as the patient has often had all their gonadotrophin injections at that stage in the cycle and would thus have physically and financially gone through most of the treatment cycle. Besides, there is no guarantee that the patients will not hyperstimulate again in the next cycle. (Also, with repeated use of ovulation induction drugs, the question of cancer especially ovarian cancer cannot be ignored). Cryopreservation of all embryos and subsequent transfer in an unstimulated cycle requires multiple freeze-thaw cycles and is associated with a lower pregnancy rate.[3] Intravenous albumin given to patients at high risk of OHSS at the time of oocyte retrieval was initially proposed as a possible solution,[4] however, recently it has lost much of its support. Chen et al[5] reported that intravenous albumin prevented OHSS in some high-risk patients who did not conceive, but did not do so in patients with multiple pregnancy.[5] Shaker et al[6] found that although it was no worse than cryopreservation of all embryos and subsequent transfer in an unstimulated cycle, the pregnancy rate was much lower in the intravenous albumin. In view of these limitations, Sher et al[2] proposed coasting as a viable, effective alternative in preventing OHSS and allowing replacement of fresh embryos without necessitating cycle cancellation. Subsequent reports by the same group[7] and others[8,9] have been encouraging with respectable pregnancy rates. In the former report, there were no incidence of OHSS in 51 cases of coasting, whilst in the latter report, the OHSS rate in 22 coasted patients did not differ from 26 patients that had their embryo transfer cancelled with subsequent transfer in a unstimulated cycle.

This study was undertaken to assess the coasting policy instituted in our in vitro fertilization programme since October 1998 through to May 2001. In particular, we were interested to examine if coasting compromised the pregnancy rate and what the OHSS rate in this group was. Ideally a control group would consist of all groups that were equally at risk of OHSS but were not coasted. Such a group was not available and probably not ethically possible to arrange even in a prospective study. We thus selected a group of patients that did not fulfil our, at risk criteria prior to oocyte retrieval but, according to 2 previous studies, they were also at risk of OHSS as we collected 20 or more eggs from them.[10,11]

The most interesting finding in our study is that despite more eggs, more available embryos for transfer, more embryos actually transferred, the pregnancy rate in the control group was not higher than the coasting group (**Table 1**). By depriving the granulosa cells of gonadotrophins, one might cause a culling of the granulosa cells, which might lead to atresia of the poorer quality pre-ovulatory follicle, and hence a diminution in the number of oocytes retrieved. Although fewer in numbers, these represent the best quality oocytes and hence perhaps that is why one does not find a decrease in the pregnancy rate. In both the high risk populations of the coasted and control group, the severe OHSS rate was 2.1% and 12.2%. In the 2 cases where the patients in the coasted group had severe OHSS, one was totally unpredictable whilst the other could have probably been prevented. In the former case, she had 17 follicles before oocyte retrieval where we collected 14 eggs, 11 of which fertilized by conventional in vitro fertilization and 2 embryos were electively transferred back into the uterus without success. Her pre-egg collection estradiol level was 6004 pmol/L. The other case was carried out very early on in our coasting programme when a decision was made to take a patient to theatre for oocyte retrieval despite a very high estradiol level of 56,000 pmol/L. This was

due to the estradiol level falling very quickly from 140,000 pmol/L the day before. In that case, we collected 38 eggs, of which 23 fertilized and 3 were transferred back into the uterus but she did not fall pregnant. Since that case, we have adhered strictly to a set limit for the estradiol level to fall below before embarking on oocyte retrieval. This level has been gradually reduced to 10,000 pmol/L as it did not appear to make any difference to our pregnancy rate and may have an impact on the incidence of OHSS.

This study strongly suggests that in women undergoing ART cycles at risk of OHSS, coasting does not appear to compromise the outcome. We feel that if a strict limit is set and the estradiol level is allowed to fall below this level, the incidence of severe OHSS will be reduced. We are proposing that this level be set at 10,000 pmol/L.

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