Agonist and antagonist coast

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The use of GnRH-a in ovarian stimulation permitted stronger stimulation resulting in an increased incidence of OHSS. The first Cochrane review comparing GnRH agonist and GnRH antagonist protocols for ovarian stimulation showed no significant difference in OHSS rate between the two protocols, however, a recent Cochrane review showed a highly significant decrease in the incidence in OHSS rate in the antagonist protocol. Coasting is a commonly used procedure for preventions of OHSS. The optimum time to start coasting is when the lead follicle reaches 16 mm in diameter and hCG should be given when E2 level drops below 3000 pg/ml. Coasting may act by diminishing the functioning granulosa cell cohort. Administration of daily GnRH antagonist in high risk patients for OHSS who were down-regulated by GnRH-a resulted in rapid drop of E2 and decrease in incidence of OHSS. A series of patients who developed early OHSS were treated by daily GnRH antagonist injections, all embryos were cryopreserved. No progression to severe OHSS was observed. (Fertil Steril® 2012;97:523–6. ©2012 by American Society for Reproductive Medicine.)
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Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of ovulation induction and it is a potentially life threatening iatrogenic complication (1). It is characterized by cystic enlargement of the ovaries and rapid fluid shifts from the vascular compartment to third spaces, leading to ascites and plural effusion. The triggering factor for development of OHSS is endogenous or exogenous hCG in patients with a large number of follicles (≥ 20) on both ovaries and E2 concentration ≥ 3000 pg/ml (2). The incidence of OHSS has been estimated at 3–6% for moderate and 0.1–2% for severe OHSS (2).

GONADOTROPIN RELEASING HORMONE AGONIST AND OHSS

It had been hoped that the use of GnRH-a in ovarian stimulation for IVF would decrease the incidence of OHSS. However, in practice, GnRH-a permitted a stronger stimulation of the ovaries, resulting in an increased incidence of OHSS (3). The French FIVNAT results from 1989 (4) showed that the use of GnRH-a led to significantly higher preovulatory oestradiol concentrations and to more frequent OHSS (4.5% compared with 0.6% for the non-GnRH-a/hMG cycles).

GnRH ANTAGONIST VERSUS AGONIST IN RELATION TO OHSS

The first Cochrane review comparing the IVF outcome between GnRH agonist and GnRH antagonist in 2002 showed that there was no statistically significant reduction in the incidence of severe OHSS (OR 0.51; 95% CI 0.22–1.18) using antagonist regimens as compared with the long GnRh-a protocol. There were significantly fewer clinical pregnancies in those treated with GnRH antagonists (OR 0.79; 95% CI 0.63–0.99) (5). In a later meta-analysis by Kolibianakis et al. (6) the authors showed that the incidence of OHSS associated with hospital admission was significantly lower for the antagonist arm (OR 0.46; 95% CI 0.26–0.8; $P \leq .01$). Al-Inany et al. (7) published an update to their Cochrane review (2006) and showed that there was a statistically significant reduction in the incidence of severe OHSS with the antagonist protocol (OR 0.61; 95% CI 0.42–0.89; $P = .01$). The ongoing pregnancy/live-birth rate showed the same significantly lower pregnancy in the antagonist group ($P = .03$; OR 0.82, 95% CI 0.69 to 0.98). In a further Cochrane review (8) the difference was even more prominent in demonstrating the lower incidence of OHSS with GnRH antagonist (29 trials: OR 0.43; 95% CI 0.33–0.57, $P < .00001$). There was no evidence of a statistically significant difference in rates of live-births (OR 0.86, 95% CI 0.69 to 1.08) or ongoing pregnancy (OR 0.87, 95% CI 0.7 to 1.00). However, in a systematic review of 1024 oocyte donor cycles in eight randomized studies, there was no significant difference in OHSS rate between agonist and antagonist cycles (RR 0.62, 95% CI 0.18–2.15) (9).

These recent data suggest that the optimum stimulation regimen to reduce the incidence of OHSS in high risk patients is the GnRH antagonist protocol. Use of a GnRH antagonist also allows triggering of ovulation using a bolus of GnRha (10), which is discussed in other reviews in this issue.

COASTING

Coasting is the complete discontinuation of exogenous gonadotropin while administration of GnRH agonist is continued (11), resulting in a drop of serum estradiol (E2) levels with administration of hCG after the serum E2 level reaches a safer level. Coasting has been employed in ovulation induction

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since the 1980s (12). Very soon it was introduced for prevention of OHSS in IVF (13) and it has been the most popular method to prevent OHSS for many years (2, 10, 14, 15).

The technique appeals to physicians and patients, and it also allows for the timely transfer of fresh embryos (16). The first report on coasting for IVF cycles (13) included 17 patients whose serum E2 levels exceeded 6000 pg/ml, with hCG withheld until serum E2 levels had fallen below 3000 pg/ml. The coasting period lasted between 4 and 9 days, after which six of the 17 cycles (35%) produced viable pregnancies. All 17 patients developed signs of grade 2 or 3 OHSS, but none developed severe OHSS.

In a very large retrospective study (1223 patients), the criteria for a successful coasting protocol were described. The optimum time to start coasting was when the lead follicle was 16 mm in diameter and optimum hCG timing was when the E2 level had dropped below 3000 pg/ml. The incidence of severe OHSS was 0.13% of all stimulated cycles and 1.3% of patients at risk of developing OHSS. The implantation and pregnancy rates were significantly lower if coasting was continued for 4 days or more (11). In a recent retrospective study of 1068 coasted cycles, the authors reported 1.9% severe OHSS, the mean days of coasting was 4.7 days and no effect on the live birth rate was observed with up to 8 days of coasting (17).

A systematic review was conducted to analyze whether evidence is sufficient to justify the general acceptance of coasting. The 12 studies involved 493 patients. In most studies a threshold value of E2 (often 3000 pg/ml) and/or the number of follicles were considered when deciding whether to coast. The fertilization rates (36.7–71%) and the pregnancy rates (20–57%) were acceptable in comparison with those of other large IVF databanks. In 16% of the cycles, ascites was described and 2.5% of the patients required hospitalization. In conclusion, while coasting does not totally avoid the risk of OHSS, it decreases its incidence in high-risk patients (18).

LENGTH OF COASTING

In a retrospective study (19) the average length of coasting in GnRH agonist cycles was 2.2 days. A significant decrease in implantation rate was reported when coasting lasted for 4 or more days, together with a trend towards a higher cancellation rate (20). It is not recommended to coast for more than 3 days.

WHEN TO START AND WHEN TO STOP COASTING

Coasting is generally initiated when follicles are 15 to 16 mm in diameter and serum E2 levels are >3000 pg/ml. The large follicles have a low dependency on FSH and can tolerate a few days without gonadotropin administration. The immature follicles enter atresia as they are very dependent on FSH and the mature follicles will progress and be ready for oocyte retrieval (21). The majority of publications suggest that E2 of 3000 pg/mL (22, 23) is a limit below which coasting can be terminated and hCG can be safely administered, while still maintaining good oocyte function.

HOW DOES COASTING WORK?

It is well established that high E2 levels are associated with a high incidence of OHSS. However, it is very unlikely that high E2 levels are the direct cause of OHSS (24). Coasting may act by diminishing the functioning granulosa cell cohort, as many cells become apoptotic, resulting in a gradual decline of E2 levels, but more importantly, a reduction in the primary agent that augments capillary permeability, which is vascular endothelial growth factor (VEGF) (25). In a study of 160 women undergoing coasting and 116 controls, serum and follicular fluid VEGF concentrations were determined. Real-time PCR was performed to evaluate VEGF gene expression in granulosa cells and cell death was studied by flow cytometry. Follicular cells aspirated from coasted patients showed a ratio in favor of apoptosis, especially in smaller follicles (48% versus 26%, $P<.05$). Follicular fluid determinations confirmed that coasting reduces VEGF protein secretion (1413 versus 3538 pg/ml, $P<.001$) and gene expression (2-fold decrease) in granulosa cells (25).

A RECENT CONFLICTING COCHRANE REVIEW (2011)

A recent Cochrane review (26) reported no difference in the incidence of moderate or severe OHSS (OR 0.53, 95% CI 0.23–1.23) after coasting. There was no difference in clinical pregnancy rate and significantly fewer oocytes were retrieved with coasting. The Cochrane review included only four studies, three of which showed no significant difference in the incidence of OHSS with coasting compared to control groups. Two of these studies compared coasting with early unilateral follicular aspiration (27, 28), a procedure which never gained acceptance in clinical practice. The third study compared coasting versus giving GnRH antagonist and there were no severe OHSS cases in either arm (29). The fourth trial compared coasting versus no coasting (30). In the last study, there was evidence of significantly fewer cases of moderate and severe OHSS in the coasting group as compared to the no coasting group (OR 0.17, 95% CI 0.03–0.88, $P=.03$). They concluded that there is evidence to suggest a benefit in favor of coasting versus no coasting in the prevention of OHSS, but that clinicians should employ other strategies to reduce the incidence of severe OHSS rather than coasting. Their conclusions were based on heterogeneous studies, and may bias physicians against using a procedure which proved effective in several retrospective controlled studies and in the only randomized study the authors included in their review that compared coasting versus not coasting and it was shown that coasting is effective. The idea of waiting for a larger randomized study comparing coasting versus not coasting patients at high risk for OHSS may not be ethical because it will subject the no treatment arm to a high risk of development of OHSS.

COASTING FOR GnRH ANTAGONIST CYCLES

The use of coasting in GnRH antagonist protocols was first described in few case reports that showed no compromise of IVF outcome (31, 32). A recent study compared coasting for