regulation. While this is unclear, perhaps it is secondary to inadequate estrogen priming.

On the other hand, menses do not accurately predict the presence of functional and nonfunctional ovarian cysts. There is controversy as to whether preexisting ovarian cysts have an adverse effect on the outcome of IVF-ET (8). Small nonfunctional cysts (<25 mm) may be confused with developing follicles and larger functional cysts may adversely effect the local hormonal environment (8).

In summary, our report demonstrates that the presence of menses after the administration of GnRH-a is a valid predictor of pituitary down-regulation. On the other hand, the absence of menses only appears to be predictive of failure of down-regulation in younger women. Serum estradiol, which has long been the gold standard for documenting suppression, may not always be necessary. However, transvaginal ultrasonography still provides important and meaningful information in the monitoring of patients undergoing assisted reproduction, since menstrual history alone does not preclude the presence of pathological or functional ovarian cysts.

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Reduction of Human Menopausal Gonadotropin Dose Before Coasting Prevents Severe Ovarian Hyperstimulation Syndrome with Minimal Cycle Cancellation

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an important unintended effect of ovulation induction (1,2). Severe OHSS is potentially life threatening, with massive ovarian enlargement and increased capillary permeability resulting in fluid accumulation in peritoneal, pleural, and pericardial cavities. Complications include thromboembolism, acute renal failure, respiratory problems, and torsion of hyperstimulated ovaries. Management is symptomatic and aims to prevent complications (3). Cancellation of human chorionic gonadotropin (hCG) injection can prevent OHSS, but has financial and emotional implications (4). Sher *et al.* (5) suggested prolonged coasting to prevent OHSS in in vitro fertilization (IVF) patients. We adopted their coasting protocol, but several cycles were cancelled due to a sudden decrease in estradiol (E_2) level. The objective of our study was to evaluate the effect of reducing the human menopausal gonadotropin (hMG) dose before coasting on the incidence of OHSS and cancellation of the cycle in high-risk patients.

MATERIALS AND METHODS

The study group was 49 women at risk of developing OHSS during ovarian stimulation for IVF or intracytoplasmic sperm injection (ICSI). All patients received our long protocol using gonadotropin-releasing hormone analogue (GnRH-a) and hMG (6). The dose of hMG (Pergonal; E.I.P. Co. Industries, Cairo, Egypt) was 150 IU for patients below the age of 30 years, 225 IU for patients between 30 and 35 years, and 300 IU for patients above the age of 35 years. Patients were defined as at risk of OHSS if over 20 follicles developed and E_2 exceeded 3000 pg/ml when the leading follicle was 13 mm in diameter. They were allocated on an alternate basis into two groups.

In group A ($n = 25$) the dose of hMG was reduced to 75 IU daily if the patient was receiving 150 IU or 225 IU of hMG, or to 150 IU if she was receiving 300 IU. Daily E_2 assay and ultrasound were done. Menotropin injection ceased when the leading follicle was 16 mm in diameter. Coasting continued with daily monitoring until E_2 was 4000–5000 pg/ml, when 10,000 IU of hCG was given intramuscularly IM. Transvaginal ultrasound-guided oocyte retrieval was performed 36 hr later.

In group B ($n = 24$), the dose of hMG was unchanged. When the leading follicle reached 16 mm in diameter, complete coasting commenced. Other procedures were as group A. The coasting period was the number of days from final hMG injection to hCG administration. A historical group C ($n = 32$), in which E_2 was 3000 pg/ml with more than 20 follicles when the leading follicle was 13 mm in diameter, was used as a comparison group. These patients continued the same dose of hMG until the leading follicle reached 18–19 mm and hCG was given, unless the risk of OHSS was very high, when the cycle was cancelled.

Semen preparation, oocyte handling, IVF, ICSI, and embryo transfer were as previously described (7). Luteal-phase support was in the form of 100 mg progesterone IM (progesterone USP; STERIS, Phoenix, AZ). Clinical pregnancy was diagnosed by elevated serum β-hCG and ultrasound diagnosis of a gestational sac with fetal echoes. The definitions of severe and moderate OHSS were based on the classification of Golan *et al.* (8). Statistical analysis was done using a one-way analysis of variance.

RESULTS

Patient characteristics and results are shown in Table I. There was no significant difference in age or infertility period between the three patient groups. The E_2 level was significantly lower in group A compared to group B at the start of coasting. In group C the E_2 level (mean ± SD) on day of hCG was 9800 ± 3100 pg/ml, and 7200 ± 2150 pg/ml after excluding the five cancelled patients. Both levels were significantly higher than in groups A and B. The duration of coasting was significantly shorter in group A.

Injection of hCG was cancelled after a sudden decrease in E_2 level to below 1500 pg/ml in one patient in group A and in four patients in group B. In group C, hCG injection was cancelled in five patients at high risk of developing OHSS, and five patients developed severe OHSS, with no cases in groups A and B. Moderate OHSS developed in one patient in group A, four in group B and eight in group C.

DISCUSSION

The use of coasting as a means of preventing OHSS was first proposed by Rabinovici *et al.* (9), who in 1987 reported withholding hMG for several days before hCG administration in high-risk patients. Urman *et al.* (10) described 40 cycles in women with polycystic ovaries at risk for development of OHSS, using coasting until E_2 level fell. A reasonable pregnancy rate (PR) resulted with an OHSS rate of 2.5%. Sher *et al.* (5,11) also reported that coasting was effective in preventing OHSS.

Benadivia *et al.* (4) compared coasting and delaying hCG injection in high-risk patients with a control group treated by cryopreservation of all embryos. There was no significant difference in the fertilization rate (FR), miscarriage rate, delivery rate, and the incidence of OHSS between the two groups. The authors suggested that risk of cancellation cannot be completely eliminated with coasting, but a high PR resulted without the need for repeated frozen–thawed cycles. Tortoriello *et al.* (12) reported that coasting did not adversely affect outcomes in a subset of highly responsive IVF patients.

We adopted the protocol of Sher *et al.* (11) for 1 year, but although it was effective in the prevention of severe OHSS, in many patients the E_2 level fell suddenly to very low levels. This led to increased cycle cancellation, poor oocyte quality, and low FR and PR (unpublished data). We therefore planned a new coasting protocol in high-risk patients, starting when the leading follicle was 16 mm in diameter, irrespective of the E_2 level, to minimize cycle cancellation. To test the hypothesis that a decrease in hMG dose would be beneficial, in group A the dose of hMG was reduced

Table I. Patient Characteristics and Results in Groups A, B, and C[a]

	A	B	C	*P* value
No. of patients	25	24	32	
Age (yr)	28 ± 4.2	28.9 ± 4.6	27.2 ± 5.3	NS
Period of infertility (yr)	6.2 ± 2	7 ± 1.8	7.2 ± 2.1	NS
E_2 (pg/ml)				
lead follicle 13 mm	4200 ± 1300	4300 ± 1250	4420 ± 1330	NS
at start of coasting	5800 ± 1200	7150 ± 1050		$p < 0.001$
on day of hCG	4450 ± 1200**	4640 ± 1100**	7200 ± 2150*	$p < 0.001$[b]
Reduced hMG (days)	1.9			
Duration coasting (days)	1.8 ± 0.65	2.92 ± 0.92		$p < 0.001$
No. of oocytes	15.5 ± 4**	16 ± 3.5**	21 ± 5.5*	$p < 0.001$[b]
Fertilization rate	61%	59%	58%	NS
Pregnancy rate[c]	8 (33.3%)	7 (35%)	9 (33.3%)	NS
No. cancelled cycles	1	4	5	
No. severe OHSS	0	0	5	
No. moderate OHSS	1	4	8	

[a] Results are given as mean ± standard deviation or *n* (%); NS, not significant.
[b] Versus **.
[c] Per oocyte retrieval.

when the lead follicle diameter was 13 mm. In group B, the dose was maintained until coasting. We gave hCG when E_2 was 4000–5000 pg/ml, rather than at 3000 pg/ml as reported previously. Our study confirms that the decline in E_2 levels occurs 2 to 3 days after stopping hMG. The drop is unpredictable with levels as low as 560 pg/ml (11).

With this modified coasting protocol, no cases of severe OHSS occurred. Coasting duration was significantly shorter in group A. The periods of coasting are shorter than those reported by Rabinovici *et al.* (9) (range, 2–10 days), Sher *et al.* (5) (range, 4–8 days; mean, 4.8 days), and Sher *et al.* (11) (range, 3–11 days; mean, 6.1 days). Lowering the dose of hMG resulted in a significantly lower E_2 level in group A on starting coasting compared to group B. This may account for the shorter coasting period in group A, which reduced the cancellation rate after a marked drop of the E_2 level from four cancellations in group B to only one cancellation in group A.

Based on outcomes in group C, giving hCG at an E_2 level of 4000–5000 pg/ml in a cycle without coasting is associated with a risk of OHSS. However, giving hCG at the same E_2 level after coasting may not be associated with the same risk. The size of granulosa cell population available for luteinization following hCG administration determines the incidence and severity of OHSS (5). Without coasting, the granulosa cell mass is actively proliferating and will continue to produce higher levels of E_2 for a few days even in the absence of FSH. With coasting, the granulosa cell mass is on the decline and is about to lose, if it has not already lost, its capacity for producing high E_2 levels.

These results support Sher's work (11) which states that not only the E_2 level but also the size of the leading follicle are important when coasting starts. If prolonged coasting was initiated prior to 30% of the follicles having attained a mean diameter of 15 mm, rapid decline in plasma E_2 concentration often followed and oocyte, follicular, and embryo quality were usually compromised. Our study suggests that reducing hMG in high responders avoids early and prolonged coasting with its possible detrimental effect on oocyte quality and PR and increased cycle cancellation.

In group C five patients developed severe OHSS, six patients developed moderate OHSS, and hCG administration was cancelled in five patients. None of the patients in groups A and B developed severe OHSS. These numbers were too small for statistical analysis, although the trend was for lower cancellation rates in group A, less moderate OHSS with coasting, especially in group A, and the elimination of severe OHSS in groups A and B.

In conclusion, this study illustrates the value of coasting in the prevention of severe OHSS. When our coasting protocol was preceded by a decreased hMG dose, the duration of coasting and E_2 level before coasting were significantly reduced. Our results also have financial implications, with a decrease in the amount of hMG used and lower monitoring costs due to a shorter period of coasting. A prospective randomized

controlled trial to confirm these findings in a larger group of patients is needed.

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