Serum oestradiol and progesterone concentrations during prolonged coating in 15 women at risk of ovarian hyperstimulation syndrome following ovarian stimulation for assisted reproduction treatment

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Serum oestradiol and progesterone concentrations were examined for up to 7 days after withholding gonadotrophins whilst continuing pituitary down-regulation in 15 women at serious risk of severe ovarian hyperstimulation syndrome (OHSS) (serum oestradiol >6000 pg/ml and >15 follicles per ovary). Serum oestradiol concentrations rose on day 1 of coating in all but two of the 15 women before falling, the decrement being in the order of 40% on each day. This observation permits a rational basis for the estimation of frequency of serum oestradiol measurements and duration of coating. The trends and rates of fall of serum oestradiol do not seem to predict the occurrence of moderate and severe OHSS, being similar in the six women who developed OHSS compared with nine women without OHSS. The trends in progesterone concentrations were unrelated to any aspects of the clinical outcome.

Key words: coating/OHSS/serum oestradiol

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a condition occurring in a severe life-threatening form in 0.5–2% of assisted reproduction treatment cycles (Forman et al., 1990; Navot et al., 1992), with at least 50 000 assisted reproduction treatment cycles being recorded in 1995 (World Collaborative Report on IVF, 1997). The diagnosis and treatment of OHSS is reviewed elsewhere (Rabau et al., 1967; Schenker and Weinstein, 1978; Brinsden et al., 1995) as well as the poorly understood pathogenesis (Uriel and Schenker, 1997). Medical and surgical strategies have been devised to reduce the incidence of OHSS (Shalev et al., 1995; Sher et al., 1995; Lewit et al., 1996; Tomazevic et al., 1996; Benadiva et al., 1997; Egbase et al., 1997, 1998; Rimington et al., 1997; Grudzinskas and Egbase, 1998; Tortoriello et al., 1998; Ferraretti et al., 1999) and several centres are currently evaluating the novel approach proposed initially by Sher and colleagues (1995) of withholding gonadotrophin stimulation during ovarian stimulation for assisted reproduction treatment whilst continuing pituitary desensitization with gonadotrophin-releasing hormone agonist (GnRHa) for a variable number of days (coasting). Whereas initial reports have described optimistic outcomes with respect to live births and a reduction in severe OHSS (Sher et al., 1995; Benadiva et al., 1997), recent findings have not uniformly confirmed the value of coating in the prevention of severe OHSS (Lee et al., 1998; Tortoriello et al., 1998). In addition, there is little information about the frequency of observations which are useful during coating, the optimal duration of coating or the effects of coating on trends of serum oestradiol and progesterone concentrations. In this study the trends in serum oestradiol and progesterone concentrations were examined from the day of commencing coating to the day of administration of human chorionic gonadotrophin (HCG) trigger to determine the usefulness of daily oestradiol and progesterone measurements in 15 women undergoing prolonged coating for up to 7 days in an ovarian stimulation programme for IVF or intracytoplasmic sperm injection (ICSI) and embryo transfer in a routine artificial reproduction technology setting.

Materials and methods

Serum oestradiol and progesterone were measured daily in 15 out of 30 patients who consented and were randomized to prolonged coating in a prospective study that compared prolonged coating to early follicular aspiration for the prevention of severe OHSS (Egbase et al., 1999). The study was approved by the Institution Clinical Practice review committee and the patients counselled in detail on the risk of OHSS and the novelty of the preventative strategy based on the available evidence in the medical literature. The risk factors for severe OHSS for the purpose of this study were defined as serum oestradiol >6000 pg/ml (Sher et al., 1995; Waldenstrom et al., 1999) and >15 follicles in each ovary with at least two leading follicles >18 mm in diameter. The details of the ovarian stimulation have been previously described (Egbase et al., 1996). Briefly, long protocol luteal phase pituitary down-regulation was carried out in all patients using gonadotrophin releasing hormone analogue (GnRHa) (Buserelin; Hoechst, Germany). Human menopausal gonadotrophin (HMG) injections (75 IU per ampoule) were administered initially at two ampoules per day. Transvaginal ultrasound was used to monitor follicular growth, the first being performed on day 8 of HMG injections and subsequent ultrasound scans performed at 2–3 day intervals. The dose of HMG was increased in a step up manner by one or two ampoules when necessary as indicated by the follicular growth on the ultrasound scans. When at least two follicles were >18 mm in diameter and the serum oestradiol was >6000 pg/ml, the HMG injections were stopped and coating commenced while the GnRHa was continued until the day of administration of HCG trigger (10 000 IU Profasi; Serono, Welwyn Garden City, Herts, UK). Serum oestradiol and progesterone concentrations were measured...
were subjected to conventional IVF or ICSI according to the cause of decrement in serum oestradiol is of the order of 40%, daily.

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| Table I. Clinical characteristics, details of ovarian stimulation, embryology events and clinical outcome in 15 women at risk of severe ovarian hyperstimulation syndrome (OHSS) who underwent prolonged coasting. |
|-----------------|-----------------|-----------------|
| Mean age (years) | 33.5 ± 2.8      |                 |
| Body mass index | 34.8 ± 5.2 (26–49) |                 |
| Indication for assisted reproduction (n) | PCOS | 2 |
| | Tubal disease | 2 |
| | Male factor | 5 |
| | Tubal + PCOS | 2 |
| | Male + PCOS | 4 |
| No. of HMG ampoules | 50.2 ± 16.5 (15–87) | |
| Duration of HMG administration (days) | 14.1 ± 3.2 (11–19) | |
| Duration of coasting (days)* | 4.9 ± 1.6 (3–7) |
| Serum oestradiol concentrations (pg/ml) on day of commencement of coasting/day of HCG administration* (range) | 10.055 (6050–15 026)/1410 ± 246 (640–2190) |
| Mean ± SD percentage oocytes retrieved of all follicles punctured | 28.3 ± 3.7 |
| Mean ± SD percentage fertilization | 58.4 ± 2.1 |
| Mean ± SD percentage cleavage | 76.3 ± 5.8 |
| No. of embryos transferred | 2.7 ± 0.1 |
| Incidence of OHSS | Moderate (%) | 3 (20) |
| | Severe (%) | 3 (20) |
| Clinical pregnancy rate per initiated cycle (%) | 5/15 (33.3) |

*Day 1 of coasting = the day after the last HMG injection
PCOS = polycystic ovarian syndrome; HMG = human menopausal gonadotrophin; HCG = human chorionic gonadotrophin; OHSS = ovarian hyperstimulation syndrome.

Values are mean ± SD with range in parentheses unless otherwise indicated.

In this analysis, trends in serum oestradiol and progesterone concentrations were examined for up to 7 days of withholding gonadotrophins whilst continuing pituitary down-regulation, the clinical outcome of IVF/ICSI having been reported in detail previously (Egbase et al., 1999). As serum oestradiol concentrations rose in all but two of the 15 women reported here before falling, given the high initial serum oestradiol concentrations, it is possible to recommend the frequency for clinical follow-up and serum oestradiol measurements. As the decrement in serum oestradiol is of the order of 40%, daily sampling is not mandatory in all women.

Firstly, if serious risk of OHSS is evident after ovarian stimulation using the criteria described above, i.e. serum oestradiol >6000 pg/ml and >15 follicles per ovary with two leading follicles each >18 mm in diameter, it is possible to conclude that daily serum oestradiol measurements are not indicated until the third day of coasting as the oestradiol concentrations in all but one woman were >3000 pg/ml, the arbitrary concentration of oestradiol at which the risk of OHSS is considered to be minimal. When the serum concentrations are lower, it may be wise to perform the serum oestradiol measurements daily to observe the trend before deciding on the frequency of sampling.

Secondly, the subsequent frequency of sampling can be determined by the serum oestradiol concentration on day 3 of coasting, the second sample being indicated on the following day if the serum oestradiol concentration was ≤6000 pg/ml as was the case in five women (Figure 1), otherwise further serum oestradiol measurements could be delayed until day 5.

Thirdly, our observations permit a possible rational basis for an estimate of the duration of coasting according to the
Figure 1. Trends in serum oestriadiol concentrations in 15 women at risk of ovarian hyperstimulation syndrome (OHSS) in whom human menopausal gonadotrophin (HMG) injections were withheld for up to 7 days in relation to polycystic ovarian syndrome (PCOS) (○; n = 8) or not (●; n = 7). OHSS occurred in six women (- - -) and did not occur in nine women (-----). Pregnancy occurred in four women, complicated by OHSS (- - -) in one woman but not in the remaining three (-----).

Figure 2. Mean serum oestriadiol concentrations ± SD as a percentage of the pre-coasting serum oestriadiol concentration in women with ovarian hyperstimulation syndrome (OHSS) (- - -), n = 6 and no OHSS (-----), n = 9.

Serum oestriadiol on days 1 and 3 of coasting in women at serious risk of OHSS. When the initial serum oestriadiol concentration on day 1 of coasting is >8000 pg/ml, the duration of coasting will be at least 4 days; by contrast, if the value is 6000–8000 pg/ml, coasting is possible for 4 days in the majority of women as only one woman was triggered after 3 days of coasting.

The trend and rate of fall of serum oestriadiol concentration during coasting do not seem to predict the occurrence of moderate and severe OHSS, being similar in the six women who developed OHSS compared with the nine women without OHSS (Figures 1 and 2). This finding is in agreement with earlier reports that high serum oestriadiol concentrations on day of HCG administration, though a risk factor, are of poor predictive value in assessing the incidence of moderate or severe OHSS (Jaffe et al., 1993; Morris et al., 1995; Chen et al., 1998) in ovarian stimulation cycles without coasting. Although coasting allowed serum oestriadiol concentration to fall to a mean of 1410 ± 246 pg/ml on the day of HCG trigger in the 15 patients, the development of moderate and severe OHSS in six of the patients further shows the poor predictive value of serum oestriadiol. Likewise the occurrence of pregnancy was unrelated to the trends in oestriadiol concentrations (Figure 1).
Coasting oestradiol in relation to OHSS

Figure 3. Trends in serum progesterone concentrations in 15 women at risk of ovarian hyperstimulation syndrome (OHSS) in whom human menopausal gonadotrophin (HMG) injections were withheld for up to 7 days in relation to polycystic ovarian syndrome (PCOS) (○; n = 8) or not (●; n = 7). OHSS occurred in six women (- - - -) and did not occur in nine women (-----). Pregnancy occurred in four women, complicated by OHSS (- - -) in one woman but not in the remaining three (----).

The trends in serum progesterone concentrations were unrelated to any aspects of embryological or clinical outcome in this study. This is somewhat surprising but in agreement with previous reports (Sher et al., 1995; Benadiva et al., 1997). Thus, whilst continuing pituitary down-regulation during coasting, measurements of serum progesterone do not appear to be required. It is concluded that the measurements of serum oestradiol only on day 1 of coasting, and repeated on days 3 and 5 were adequate to monitor patients at risk of severe OHSS with the criteria defined in this study when prolonged coasting is being employed as a preventative strategy. It is acknowledged that the number of patients in this study was small, but the frequency of measurements of the serum oestradiol and progesterone concentrations for up to 7 days provided sufficient data to depict the trends and rate of fall of these steroid hormones during prolonged coasting.

The apparent large number of ampoules of gonadotrophins administered to achieve ovarian stimulation was related to the characteristics of the patients (polycystic ovarian syndrome and high body mass index) in the study (Egbase et al., 1999).

However, the full value of prolonged coasting in the prevention of severe OHSS in patients at risk identified at an advanced stage of ovarian stimulation (Sher et al., 1995; Benadiva et al., 1997) needs to be further ascertained by prospective randomized studies. It is possible that serum oestradiol, being a poor predictor of the development of severe OHSS (as confirmed in the study) and which is currently being employed to monitor the events of coasting, contributes to the difficulty in assessing the effectiveness of this strategy. The trends and rate of changes in the concentrations of a more specific biochemical marker could enhance the potential usefulness of prolonged coasting against the development of severe OHSS. We are currently studying vascular endothelial growth factor concentrations in prolonged coasting in a larger population of patients.

References


Received on March 21, 2000; accepted on June 15, 2000