Article

Clinical and laboratory evaluation of hospitalized patients with severe ovarian hyperstimulation syndrome

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is an important complication of ovarian stimulation and IVF that enhances patients' morbidity. To evaluate any increased incidence of hospitalization from severe OHSS during 2000, this study analysed certain clinical, ultrasound and laboratory characteristics of hospitalized patients with severe OHSS. These studies were carried out on women undergoing IVF who were hospitalized because of severe OHSS between 1996 and 2000 at the Hôpital Antoine Béclère. Patients' ages and serum hormone concentrations were collected on day 3 of ovarian stimulation for various assays, and laboratory and ultrasound measurements taken during ovarian stimulation for IVF were compared. An increase was noted during last year in the frequency of the severe form of OHSS requiring hospitalization (0.9 versus 1.8%, $P < 0.05$). Patients' ages and hormonal characteristics on day 3 of menstrual cycle, and laboratory and ultrasound variables were similar between the two groups. In addition, the increased incidence of OHSS during 2000 was not associated with any special laboratory or ultrasound parameter, and the policy of ovarian induction had not changed. It is essential to introduce a simple ovarian stimulation protocol providing acceptable IVF results with a minimum of risk.

Keywords: *oestradiol, ovarian induction, severe OHSS, ultrasound*

Introduction

The main objective of ovarian stimulation for IVF is to obtain a higher number of oocytes,, a larger number of embryos and an increase in pregnancy rate. However, as IVF has developed, an increase has occurred in the incidence of ovarian hyperstimulation syndrome (OHSS) from 0.2 to 1.0% of all assisted conception cycles (Abramov *et al.*, 1999). The exact causes of this increase in this complication are not well understood. The principal physiopathological mechanism of this syndrome is increased capillary permeability with a shift of the intravascular fluid to the third space (Whelan and Vlahos, 2000).

However, if the aetiology is not well understood, some associated factors are well demonstrated. These include age, body weight, use of gonadotrophin-releasing hormone (GnRH) analogues and gonadotrophins, oestradiol concentrations, number of follicles and oocytes, and OPK-like profile, which are risk factors for the development of OHSS (Whelan and Vlahos, 2000).

Special attention should be given to the severe form of this syndrome which has increased in frequency during recent years, even though the same forms of ovarian induction protocols are still in use. The severe form is associated with a higher morbidity and increased treatment costs (Abramov *et al.*, 1999; Whelan and Vlahos, 2000).

Several studies reported different results of clinical and laboratory parameters in patients suffering from OHSS (Blankstein *et al.*, 1987; Delvigne *et al.*, 1993; Morris *et al.*, 1995; Tsirigotis *et al.*, 1995; Bódis *et al.*, 1997; Enskog *et al.*, 1999; Egbase *et al.*, 2000; Al-Shawaf *et al.*, 2001). However, this particular group of patients (severe OHSS which required hospitalization) has not been well explored or studied. To prevent the occurrence of OHSS and design better treatments, the clinical and laboratory characteristics linked with the pathophysiology of the severe form of this disease must be clarified (Enskog *et al.*, 1999).

In 2000, an important and significant increase was observed in the number of patients hospitalized with OHSS as compared with previous years (1996–1999). The aim of this study is to determine if particular clinical and laboratory variables could explain the difference of OHSS incidence between the two periods.

Materials and methods

Design

A retrospective analysis was performed of all IVF cycles between January 1996 and December 2000. A total of 3668 cases were studied. Of these, only cases resulting in hospitalization due to the severe form of OHSS were selected for analysis, according to the Golan classification (Golan *et al.*, 1989). Thirty-nine cases were included in this analysis.

In order to compare a probable increase in the incidence of severe OHSS, patients hospitalized during the year 2000 were compared with patients hospitalized during the 4 previous years.

Patients

A total of 39 patients were studied in terms of particular clinical and laboratory parameters. These patients were divided into two groups. Group I included 26 patients hospitalized between January 1996 and December 1999 and group II comprised 13 patients hospitalized for severe OHSS in the year 2000.

Measurements

The groups were compared in terms of age, baseline (LH, FSH and oestradiol) serum concentrations, polycystic ovary (PCO)-like profile and LH/FSH ratio. To evaluate baseline hormonal serum concentrations, samples were collected on the third day of the treatment cycle.

The possibility of a PCO-like profile was assessed during vaginal ultrasound examination, and was defined when each ovary presented >10 follicles with a diameter of <4 mm. Follicular diameter was measured using transvaginal ultrasound (7.5 MHz transvaginal probe, Siemens Elegra®; Siemens SAS, Saint-Denis, France) and calculated as the mean of two perpendicular measures.

Endocrine and other parameters included the dose of gonadotrophin needed to induce ovulation, the length of induction (days), ultrasound characteristics and hormonal profiles on the day of human chorionic gonadotrophin (HCG) administration were measured. The oestradiol/follicular ratio was assessed as the ratio between serum oestradiol concentration and number of follicles >12 mm on the day of HCG administration. Plasma oestradiol, progesterone, LH and FSH concentrations were determined by automated and direct chemoluminescent methods (ACS:180; Chiron Diagnostics Corp., Emeryville, CA, USA). Sensitivity for oestradiol (minimum detectable concentration) was 10 pg/ml with a conversion factor to SI units of 3.671; 0.1 ng/ml for progesterone (conversion factor 3.180); 0.1 mIU/ml (1.00) for LH; and 0.3 mIU/ml (1.00) for FSH. Intra- and inter-assay coefficients of variation over the concentration range were <7% for oestradiol, <10% for progesterone and <5% for both LH and FSH.

All patients were stimulated with the long GnRH agonist protocol. Day 2 embryo transfer was performed and all patients received micronized progesterone for luteal phase support.

Statistical analysis

The variables were compared using the Mann–Whitney U-test, since the distribution was not parametric. The incidence of OHSS between 1996 and 2000 was compared using the χ^2 test. Fisher's exact test was also used for categorical data comparison.

Results are expressed as medians and ranges. Significance levels were 5%.

Results

The incidence of hospitalization from severe OHSS was 5/810 in 1996, 9/819 in 1997, 5/682 in 1998, 7/629 in 1999 and 13/723 in 2000. The incidence of severe OHSS requiring hospitalization during the period 1996–1999 was 0.9%. However, a significant increase to 1.8% occurred during the year 2000 ($P < 0.05$, χ^2 test) (**Table 1**).

Clinical and baseline hormonal measurements are shown in **Table 2**. No significant difference was found between the groups.

The incidence of a PCO-like profile in groups I and II was 23% ($P = 1.00$, χ^2 test). This tendency is confirmed in **Table 3**, showing ultrasound and hormonal measures to be similar between the two groups of patients on the day HCG was given.

Thirteen out of 25 patients (52%) were pregnant during the

Table 1. Statistical analysis of OHSS incidence during the period of 1996–2000 (adjusted chi-squared test; $P = 0.032$).

	Group I (controls)	*Group II (cases)*
Period	1996–1999	2000
Hospitalized patients from OHSS (*n*)	26	13
Total of patients (*n*)	2940	723
Proportion of exposed patients	0.009	0.018

Table 2. Clinical and baseline hormonal measurements (day 3 of the cycle), medians and range.

	Group I (n = *26*)	*Group II* (n = *13*)	P-*values*
Age (years)	29.0 (23–37)	31.50 (26–39)	0.161
Oestradiol (pg/ml)	32.60 (15–97)	37.00 (5–167)	0.719
LH (IU/l)	4.20 (1.60–18)	5.20 (1.60–10.90)	0.344
FSH (IU/l)	4.90 (3.40–7.20)	5.35 (3.70–9.90)	0.195
LH/FSH ratio	1.00 (0.27–4.62)	0.88 (0.30–2.27)	0.905

Table 3. Hormonal and ultrasound measurements on the day of HCG administration, medians and range.

	Group I (n = *26*)	*Group II* (n = *13*)	P-*values*
Induction duration (days)	11 (9–14)	11 (9–14)	0.986
Oestradiol (pg/ml)	2648.50 (679–6089)	3131.50 (950–5232)	0.294
Progesterone (ng/ml)	0.50 (0.17–2.90)	1.16 (0.21–2.66)	0.107
LH (IU/l)	1.60 (0.30–11)	1.75 (0.60–4.90)	0.705
IU FSH administered	2412 (500–3750)	1762 (950–2225)	0.263
Follicles (12–13.9 mm)	3.0 (0–8)	5.0 (2–12)	0.195
Follicles (14–15.9 mm)	3.5 (1–13)	5.0 (2–13)	0.327
Follicles (>16 mm)	7.5 (1–14)	6.0 (2–10)	0.208
Total number of follicles	12.5 (3–26)	16.0 (12–28)	0.644
Larger follicle diameter (mm)	19.0 (16–22)	18.5 (16–21)	0.195
Oestradiol:follicular ratio	154.42 (64.64–403.25)	195.01 (79.17–313.54)	0.381

period 1996–1999 and 7/12 (58%) in 2000 ($P = 0.741$, Fisher's exact test). Two patients in each group had their embryos cryopreserved because of evidence of OHSS.

Discussion

The increased incidence of hospitalization from the severe form of OHSS in 2000 did not appear to be related to particular hormonal or ultrasound characteristics. During this time, the ovarian induction protocol remained unchanged and all patients studied were submitted to IVF using the long GnRH agonist protocol.

Statistical analysis of the data showed an important and significant difference in terms of OHSS incidence, (0.9 versus 1.8%), during the studied period (1996–2000). Although the incidence of severe OHSS is quite low, the study of this form of OHSS is fundamental, since it can be associated with a significant increase in health care costs and, more importantly, with the patient's morbidity.

Several investigators have tried to identify a laboratory or clinical parameter for the early or more precise diagnosis of this syndrome (Morris *et al.*, 1995; Bódis *et al.*, 1997; Enskog *et al.*, 1999, 2000; Ludwig *et al.*, 1999; Egbase *et al.*, 2000). Results described in these papers agree with the present results in showing large variabilities in these parameters and in the heterogeneity of the studied population, based on the clinical diagnosis and classification of OHSS.

Recently, a prospective study showed how OHSS is associated with a better IVF prognosis and the presence of allergy, demonstrating an important role of the immune system in the pathophysiology of this syndrome (Enskog *et al.*, 1999). Moreover, other group of investigators identified an association between levels of free vascular endothelial growth factor on the day on which HCG was administered and the development of OHSS (Ludwig *et al.*, 1999), emphasizing a role for the immune system. The higher PCO-like profile in both groups confirms the associated risk of OHSS with this finding (Blankstein *et al.*, 1987), although it was not possible to define precisely which patient with a PCO-like profile would develop OHSS.

The pathophysiology of this syndrome is probably related to immunological, clinical and ovulatory factors. Patients with PCO-like profiles, higher numbers of follicles, allergy and those treated with the use of GnRH agonists are at risk (Ludwig *et al.*, 1999; Whelan and Vlahos, 2000). The principle of ovarian stimulation to obtain several oocytes and embryos is based on the concept of pregnancy rates per cycle (or transfer), but not on the concept of risks/benefits/costs.

Why is a simple and rational protocol not prescribed? It is known that the GnRH antagonists, recently available, are associated with a reduced incidence of OHSS (Albano *et al.*, 1997; Olivennes *et al.*, 1998; European Orgalutran Study Group, 2000). In addition, the use of GnRH antagonists to prevent premature LH surges can be associated with the administration of GnRH agonists to induce oocyte maturation (Olivennes *et al.*, 1996, 1998; Kol and Itskovitz-Eldor, 2000). The severity of OHSS is also related to implantation and pregnancy rates (Pattinson *et al.*, 1994; Morris *et al.*, 1995). Reducing the number of transferred embryos could also reduce the severity of this complication.

In conclusion, an increased incidence of severe OHSS requiring hospitalization has been demonstrated during the last year. This finding is not associated with a particular ultrasound or laboratory factor, nor is it related to ovulation induction

policy, since this was not modified over the period of study. It is imperative to find good predictors of the occurrence of this syndrome, and to introduce simple protocols for ovarian stimulation combined with achieving better risk:benefit:cost ratios.

Acknowledgement

Dr JS Sabino Cunha-Filho was supported by a CAPES post-doctoral grant.

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Received 4 November 2002; refereed 23 January 2003; accepted 31 January 2003.