Metabolic characteristics of women who developed ovarian hyperstimulation syndrome

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BACKGROUND: The aim of this study was to investigate whether a higher incidence of hyperinsulinism is found in women who have suffered from ovarian hyperstimulation syndrome (OHSS) as compared with other IVF patients. Additionally, we also assessed whether any abnormalities in the haemostatic system were more frequent in women with a past history of OHSS. METHODS: A pilot study was carried out involving OHSS patients and matched IVF patients. Homeostasis model assessment (HOMA) of insulin sensitivity was calculated. The main outcome measures were: insulin sensitivity, coagulation anomalies, factor V Leiden mutations, methylene tetrahydrofolate reductase (MTHFR) polymorphism and prothrombin gene mutation, protein C and protein S deficiency. RESULTS: No increased incidence in hyperinsulism nor in abnormalities of the haemostatic system were observed. CONCLUSIONS: This pilot study does not provide evidence for an increased prevalence of hyperinsulinism among women who have developed OHSS in the past.

Key words: insulin resistance/IVF/ovarian hyperstimulation syndrome (OHSS)

Introduction

The ovarian hyperstimulation syndrome (OHSS) is a dramatic iatrogenic complication of gonadotrophin treatment that can sometimes be fatal (Mozes et al., 1965; Risk and Smitz, 1992). Although many papers have been published about the physiopathology of this syndrome, its exact mechanism is still not fully elucidated (Schenker, 1999). A higher incidence of ovarian hyperstimulation has been reported in polycystic ovarian syndrome (PCOS)-affected patients who have hyperinsulinism than in those who have normo-insulinism (Fulghesu et al., 1997). Therefore, the first aim of this study was to evaluate whether women who have suffered from OHSS in the past, with or without PCOS, have an increased incidence of insulin resistance, suggesting a physiopathological role of hyperinsulinaemia in the development of OHSS. Since hyperinsulinism has been associated with an increased risk in cardiovascular diseases, we also evaluated their family and personal history in relation to cardiovascular risk (Lobo and Carmina, 2000).

The second aim of the study was to assess whether abnormalities in the haemostatic system were more frequent in women with a past history of OHSS since the latter is known to predispose to thromboembolism (Hollemaert et al., 1996).

Materials and methods

Population characteristics

Using the IVF data bank of the CHU St Pierre and of The Institut Médical E Cavell, we selected 256 women who had presented with at least one OHSS episode (mild, moderate or severe) in 1990–2000, during their IVF trial (summarized in brief). These women were receiving a GnRH agonist (generally in a short protocol). Ovarian stimulation occurred using HMG (n = 24) or recombinant FSH (n = 1) (150 IU). The induction of the ovulation occurred with 10 000 IU HCG, 34 h before the oocyte retrieval. These women were matched to women of similar age (±2 years) who had undergone an IVF trial at approximately the same time, but had not developed OHSS. There were no differences in stimulation protocol between OHSS patients and control patients. Only one patient in the OHSS group and none in the control group suffered from demonstrable PCOS disease.

Patients were defined as those who presented with complicated OHSS identified when they specifically consulted a few days after embryo transfer because of disabling abdominal pain (after exclusion of other aetiologies, such as infection). This symptom characterizes the first stage of hyperstimulation in IVF cases (Golan et al., 1989). In the present study, all the OHSS patients presented with an early form of OHSS.

These women were invited to participate in a matched controlled study. After exclusion of women who might be pregnant or with an IVF cycle in progress, 32 women consented to participate in the trial,
which had been approved by the review board of the institution. Using the computer database, these women were matched to women of similar age (± 2 years) who had undergone an IVF attempt at approximately the same time, but had not developed OHSS. We, therefore, invited 279 control patients to participate in the study and were able to evaluate 28 selected matched controls. Finally, 25 pairs of patients could be matched.

Anamnestic information concerning cardiovascular diseases and their risk factors were collected. Waist and hip circumferences were measured and a score for hirsutism was established (Ferriman and Gallway, 1961).

**Biochemical analyses**

Serum samples were obtained under fasting conditions for all measurements. Insulin was assayed with a commercially available radio-immunoassay (RIA) kit (Pharmacia, Uppsala, Sweden). Intra and inter-assay coefficients of variation were both lower than 11%. Estimations of pancreatic β-cell function (% B) and insulin sensitivity (% S) were calculated from fasting plasma glucose and serum insulin levels according to the homeostasis model assessment (HOMA)/CIGMA software (Matthews et al., 1985; Hermans et al., 1999). HOMA is a mathematical model of insulin/glucose interactions that estimates the insulin sensitivity and β-cell function. Results are expressed as a percentage of the values found in young, fit subjects, with ideal body weight, who were taken as an absolute reference population for constructing the model (Matthews et al., 1985; Hermans et al., 1999). HOMA estimations correlate with measurements of β-cell function and insulin sensitivity by glucose clamps but are less sensitive and reproducible.

General coagulation was assessed by the prothrombin time (PT), the activated partial thromboplastin time (aPTT), the fibrinogen level. Furthermore, the following thrombophilia parameters were also measured: antithrombin III, APC resistance, lupus anticoagulant and anticardiolipids. All women were tested for factor V Leiden mutations (R506Q), methylene tetrahydrofolate reductase (MTHFR), C677T polymorphism and G20210A prothrombin gene mutation, and protein C, or protein S deficiency (Bertina et al., 1994; Frost et al., 1995; Poort et al., 1996).

**Statistical analyses**

We calculated that using a paired Student’s t-test with a significance level \( P \leq 0.05 \) and a power of 80%, a sample of 14 patients per arm would be necessary in order to observe an estimated difference in mean distribution of 25% between the OHSS group and the matched control group for the HOMA test.

Paired Student’s t-test and non-parametric analyses (Wilcoxon test) were performed when appropriate with a significance level of \( P < 0.05 \).

**Results**

**Clinical characteristics**

Twelve out of the 25 OHSS patients had developed a severe form of OHSS (grade IV, \( n = 11 \); grade V, \( n = 1 \)), whereas seven had developed a moderate OHSS (grade III) and six a mild form (grade II, \( n = 4 \); grade I, \( n = 2 \)). None of the patients had suffered from a thrombosis.

There was no difference in age distribution between the OHSS group and the control group (respective mean ± SD: 36.4 ± 5.9 versus 35.9 years ± 5.9 years respectively), nor in the aetiology of their sterility. Neither was there a difference in weight, height or BMI (23.2 ± 4.3 versus 21.7 ± 2.3), between the two groups. The waist/hip ratio was not different (0.78 ± 0.07 versus 0.77 ± 0.07) nor was the mean index of Ferriman and Gallway. The number of women who used to smoke was identical in the two groups (36%).

**Hyperinsulinaemia**

There were no differences in distribution of percentage of insulin resistance (% B) (108.5 ± 35.5 versus 106.6% ± 27.1%) or of percentage of insulin sensitivity (% S) (104.8 ± 34.3 versus 115.6% ± 44.06) between the OHSS group and the control group. An insulin resistance was found in six women (three women in each group). There were no differences or tendencies to differences between the OHSS group and the control group, when mild OHSS patients were excluded or when only patients affected by a severe form of OHSS were considered.

**Thrombosis risk**

There were no differences in coagulation tests between the OHSS and the control group with the exception of fibrinogen which was slightly higher in the OHSS patients (272.9 ± 71.2 versus 243.1 ± 33, \( P = 0.04 \)). Neither was there a difference in the proportion of carriers of mutations: four women among the OHSS group and four among the control group were found to be homozygous carriers of the MTHFR mutation, while 14 and 9 respectively were found to be heterozygous carriers. Two out of the OHSS group and one out of the control group were found to be heterozygous carriers of the prothrombin mutation. There were three heterozygous carriers for the Leiden factor in the OHSS group and one among the control patient. They also had an activated protein C (APC) resistance. There were no homozygous carriers for the last two mutations. Only one OHSS patient had an abnormally prolonged thrombin time and another one a decreased antithrombin III. Two OHSS patients had a deficit in protein C. There were no abnormalities of the lupus anticoagulants among the investigated women.

**Discussion**

Fulghesu et al. had observed during ovulation induction that PCOS-affected patients who have hyperinsulinaemia had a higher incidence of ovarian hyperstimulation than PCOS patients with normoinsulinism (Fulghesu et al., 1997). Complex interferences of insulin with follicular maturation have been suggested. Granulosa cells may play a crucial role in the development of OHSS and insulin seems to increase the aromatase activity of these cells resulting in a higher estradiol/androstenedione ratio (Fulghesu et al., 1997). Higher insulin levels may alter the ovarian response to FSH and enhance the production of antral follicles, resulting in an increased number of small non-atreic follicles, which are associated with a higher rate of ovarian growth as observed during OHSS. One may hypothesize, therefore, that hyperinsulinaemia plays an aetiologial role in the development of OHSS among PCOS patients. In this respect we wanted to assess whether hyperinsulinaemia occurs frequently in women who have developed OHSS, whether or not in relation to PCOS. In this study, we were unable to find a difference in insulin sensitivity or in insulin resistance prevalence between the group of women who had
suffered from OHSS and the control group. Thus our results are in agreement with those of Fedorcšák et al. who found no relation between insulinemia and IVF outcomes or OHSS rates (Fedorcsäk et al., 2001). There are several limitations to the generalization of the results of our study. It is possible that the sample of OHSS patients which we investigated is not representative of OHSS patients in general. We selected patients using the classification of Golan et al. (Golan et al., 1989). Some of these patients presented with only mild or moderate OHSS according to that classification and we may have lacked power to detect a modification which may occur only in patients affected by a severe form of OHSS. This study was powered to detect a difference of about 25% in insulin resistance between both groups of patients, but it is possible that a more modest difference may still have a clinical impact that has not been detected. Therefore, this study should be viewed as a pilot study. Furthermore, the HOMA model is a simplified and therefore more acceptable method to detect hyperinsulinaemia which correlates well with the euglycaemic clamp, but it may have a lower detection capacity (Matthews et al., 1985; Bonora et al., 2000).

Finally, our patients were not investigated during OHSS, but after rather a short period of time, on completion of IVF treatment. It is therefore still possible that some of these patients have developed hyperinsulinaemia during their IVF cycle, or will develop it after a more prolonged period of time. This is similar to the case in women who develop gestational diabetes during their pregnancy, recover after delivery, but are at risk of diabetes during later life.

The second aim of this study was to detect whether abnormalities in the haemostatic system were more frequent in women with a past history of OHSS since OHSS predisposes to thromboembolism, for which the exact physiopathological mechanism still needs to be elucidated (Hollemaert et al., 1996; Glück et al., 2000). In the present study, we found no difference in coagulation tests between the two groups of women, with the exception of fibrinogen levels for which a slight, statistically significant effect was observed. This isolated finding may be because of chance and multiple measurements and has probably little clinical significance.

In this study, similar high rates of prevalence of thrombophilia were found in both groups of patients. For instance, the global rate of heterozygosity of the C677T MTHFR polymorphism, the factor V and the prothrombin mutation were 46, 8, and 6% respectively. These rates are high compared with others that have been published earlier (Froost et al., 1995; Laffan and Tuddenham, 1998).

Nevertheless, Alfirevic et al. also reported recently high rates of abnormal thrombophilia screening in women with and without pregnancy complications (53 versus 39%) (Alfirevic et al., 2001). Furthermore, we were unable to observe a higher prevalence of thrombophilia in IVF patients who developed OHSS versus those who did not. For this purpose, our study is underpowered; however, with the current observed prevalence, a sample of 80 individuals per arm would be necessary.

In summary, this pilot study does not provide any evidence for an increased prevalence in hyperinsulinism among women who have developed an OHSS in the past and who do not suffer from PCOS. Similarly, no increased incidence in abnormalities of the haemostatic system could be found after the resolution of their problem, but we may have lacked statistical power to detect such anomalies.

References


Submitted on September 20, 2001; resubmitted on November 23, 2001; accepted on April 3, 2002.