Comparing mild/minimal stimulation protocol with GnRH antagonist to stimulation with GnRH agonist “long protocol” for IVF in patients at high risk of Ovarian Hyperstimulation Syndrome.

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OBJECTIVES

Ovarian Hyperstimulation Syndrome (OHSS) is a dangerous complication of controlled ovarian hyperstimulation (COH); its frequency estimated as 0.2-1% in all assisted reproduction cycles, but higher after IVF and in polycystic ovarian syndrome (PCOS) or PCOS-like patients. Recently protocols using gonadotrophins and GnRH antagonists have been extensively used with some evidence of reduced risk for OHSS in unselected population, when compared to ovulation induction protocols for IVF who provides GnRH agonist down regulation followed by gonadotrophins. We undertook a prospective investigation of a group of patients at high risk of OHSS by using COH with either GnRH antagonists or GnRH agonist to determine which protocol optimizes the procedure and present the results below.

METHODS

We undertook a prospective randomized study in a group of 433 patients who had previously undergone a COH for IVF with ‘long protocol’: the ART cycle had been cancelled either for high risk of OHSS (>25 follicles seen at ultrasound and/or 3000 pg/ml of E2 on the day of HCG) or completed and followed by a clinical moderate/severe OHSS without pregnancy.

The patients were divided randomly into two groups: Group A had minimal/mild COH with either clomiphene citrate + rFSH + GnRH antagonist or GSFS + GnRH antagonists (Group A = 231 cycles); Group B had COH with a “cautious” long protocol: pituitary down regulation was induced with subcutaneous daily administration of GnRH from the mid-luteal phase of the previous cycle for a minimum of 14 days, followed by the lowest possible dose of FSH as a starting point, decided on the basis of the experience from the previous stimulation (Group B = 202 cycles).

In all patients the length of stimulation (days), the total amount of gonadotrophins (UI), E2 on the day of HCG, the number of eggs collected, the number of mature oocyte, the number of embryos obtained, the number of embryos transferred into the uterus and pregnancy rate were evaluated.

Furthermore the risk of OHSS was evaluated on the basis of oestradiol levels on the day of HCG and number of oocytes retrieved. The threshold of E2 level above which there is a considerable risk of OHSS, varies widely among different investigators. Most of the studies selected an E2 of 3000 pg/ml as a safe value for hCG administration, so patients with oestradiol levels higher than 3000 pg/ml were considered at risk for OHSS. Similarly the number of oocytes retrieved above which the risk of OHSS appears to increase varies among the different Authors, ranking from 10 to 30 oocytes collected: we choosed a cut off value of 20 oocytes. Incidence and severity of clinical OHSS were also evaluated.

RESULTS

rFSH Ul used was significantly less ( Group A 1834 ± 792 UI vs Group B 2318 ± 1091 UI; p<0.05) and the terminal E2 was significantly higher (Group A 1807 ± 701 pg/ml vs Group B 1677 ± 749 pg/ml; p<0.05) in antagonists group than in agonist group, whereas no statistical differences were noted in the length of stimulation among the groups (Group A 13.7 ± 2.2 days vs Group B 14 ± 3.2 days).

The number of eggs retrieved (Group A 7.5 ± 3.7 oocytes vs Group B 6.8 ± 3.4 oocytes; p<0.05), number of embryo obtained (Group A 3.4 ± 2.3 embryos vs Group B 2.8 ± 2.1 embryos; p<0.05) and transferred (Group A 2.2 ± 0.8 embryos transferred vs Group B 1.9 ± 1.0 embryos transferred; p<0.05) were significantly higher in the antagonist group. Pregnancy rate was statistically significantly higher in group A patients (antagonist group) than Group B patients (agonist group) (32.0% vs 22.7% - p<0.05).

The rate of patients with oestradiol levels higher than 3000 pg/ml or with more than 20 oocytes retrieved (considered at risk of OHSS) did not differed among the two groups. No differences were also noted in incidence and severity of clinical OHSS.

CONCLUSIONS

Prevention or elimination of OHSS would remove the most serious and potentially life-threatening side effect of ART treatment. However, patients at risk for OHSS after a stimulation for an ART programme are a heterogeneous population, including not only predictive categories such as the classical PCOS patients, but also patients that can be identified as at risk patients only retrospectively; i.e. because they suffered OHSS after previous stimulation. Multiple strategies have been reported in the literature to decrease the incidence of OHSS in patients at high risk, but none of these strategies prevent OHSS completely. Mild/minimal stimulation offers an attractive option for patients who have experienced this complication in a previous treatment cycle as it can reduce the incidence of OHSS in patients at high risk. Our data show that in patients at high risk of OHSS a minimal/mild stimulation using GnRH antagonist provides a statistically significant higher pregnancy rate without increasing the risk of OHSS when compared to COH long protocols who induce down regulation with GnRH agonists followed by rFSH administration.

References