Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome

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Objective: To evaluate the effect of low-dose aspirin therapy on ovarian hyperstimulation syndrome (OHSS) in an unselected group of patients undergoing in vitro fertilization (IVF).
Design: Randomized clinical trial.
Setting: Division of Reproductive Medicine at the Department of Obstetrics and Gynecology, University of Pécs, Faculty of Medicine, Pécs, Hungary.
Patient(s): Patients who underwent IVF between 2000 and 2006.
Intervention(s): Initiation of 3154 IVF cycles, for which gonadotropin-releasing hormone agonist was used in 2425 cycles; 1503 cycles randomly selected for low-dose aspirin treatment starting from the first day of controlled ovarian hyperstimulation compared with no treatment in the remaining 922 cycles.
Main Outcome Measure(s): The incidence of severe or critical OHSS and the rate of clinical pregnancy.
Result(s): During this time period, 45 cases of severe OHSS were detected. Only two of the OHSS patients had received aspirin previously.
Conclusion(s): Based on our preliminary results, introduction of low-dose aspirin therapy during ovulation induction for the prevention of OHSS in high-risk patients should be considered. (Fertil Steril® 2010;93:2281–4. ©2010 by American Society for Reproductive Medicine.)

Key Words: IVF, low-dose aspirin, ovarian hyperstimulation syndrome

With the widespread use of assisted reproductive techniques, especially in vitro fertilization (IVF), there are more and more pregnancies conceived by these methods (1). However, we have to consider the frequent incidence of potential side effects of IVF. One of them is the severe, occasionally lethal iatrogenic condition ovarian hyperstimulation syndrome (OHSS).

Ovarian hyperstimulation syndrome is a systemic disease triggered by vasoactive products released from hyperstimulated ovaries. According to previous studies, mild form of OHSS is common, affecting up to 33% of IVF cycles. Approximately 3% to 8% of IVF cycles are complicated by moderate to severe OHSS (2). The majority of severe OHSS cases are seen after IVF treatment, but the syndrome can occur after any form of supraphysiologic ovarian stimulation, including clomiphene and gonadotropin ovulation induction.

The incidence of OHSS is increased in young women, in patients with polycystic ovaries, and in cycles where conception occurs, particularly in cases of multiple pregnancies. Leading symptoms and signs of this severe condition include free fluid collection in serous cavities, skin edema, hemoconcentration, stimulation of the renin-angiotensin and sympathetic nervous systems, and antidiuretic hormone production. Increased heart rate and cardiac output are also observed. It is characterized by increased capillary permeability, leading to leakage of fluid from the vascular compartment, causing free fluid accumulation and intravascular dehydration.

The exact etiology of the syndrome is still unknown, but vasoactive substances such as factors belonging to the renin-angiotensin system and cytokines, including the interleukins (IL-8 and IL-6), tumor necrosis factor α, endothelin-1, and vascular endothelial growth factor (VEGF), are thought to trigger increased vascular permeability. A growing body of evidence suggests, that increased platelet activation strongly correlates with VEGF levels (3). Moreover, activated platelets in OHSS can release histamine, serotonin, platelet-derived growth factor, or lysophosphatidic acid (LPA), substances that might further potentiate the pathophysiologic cascade leading to OHSS (4, 5). Among them, LPA, a biologically active phospholipid, has recently been found to mediate excessive IL-8 and IL-6 secretions from multiple corpora lutea of superovulated ovaries (6).

On the basis of this theory, aspirin (acetyl-salicylic acid) administration may be an effective prophylaxis for patients at high-risk for ovarian hyperstimulation.

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Diverse clinical manifestations of the syndrome include a tendency to develop phlebothrombosis, renal and liver dysfunction, and adult respiratory distress syndrome (ARDS), all responsible for serious morbidity associated with OHSS.

The diagnosis is usually straightforward: it is based on a previous history of ovarian stimulation followed by the typical symptoms of abdominal distension, abdominal pain, nausea, and vomiting. This is then further confirmed by laboratory parameters and ultrasound imaging (7).

To determine the prognosis, depending on the time of onset, classification of OHSS into early and late types may be useful. After the ovulatory dose of human chorionic gonadotropin (hCG), OHSS that presents within 9 days is likely to reflect an excessive ovarian response along with the precipitating effect of exogenous hCG administered for final follicular maturation. When OHSS presents after this period, it reflects endogenous hCG stimulation from an early pregnancy. Late OHSS is more likely to be severe and last longer than early OHSS (8). Although therapy with dopamine is usually effective, the main goal remains to prevent OHSS.

Earlier studies have shown a beneficial effect of low-dose aspirin therapy during IVF (9). In IVF centers the main goal of aspirin therapy was to improve pregnancy rates. Based on the theory, that superovulation treatment may induce platelet hyperstimulation, which is associated with OHSS, and that aspirin therapy may inhibit this effect, we started the administration of aspirin as a preventive measure. We describe our results with the administration of aspirin in controlled ovarian hyperstimulation cycles at our IVF-center with regard to the development of OHSS.

MATERIALS AND METHODS

Patient Groups

Between January 1, 2000, and December 31, 2006, we started 3154 IVF cycles. In 2425 cases, we administered gonadotropin-releasing hormone (GnRH) agonist, and in 729 cases GnRH antagonist. In 62% (n = 1503) of the 2425 GnRH agonist cycles, we administered low-dose (100 mg/day) aspirin therapy; in 38% of the cycles (n = 922), no aspirin treatment was given. Aspirin was randomly given to patients based on the paired or unpaired status of their social security number and was started on the first day of the menstrual cycle when IVF was performed. It was continued until menstruation, a negative pregnancy test, or the ultrasonographic detection of embryonic cardiac activity.

Patients were divided into two groups according to their risk of developing OHSS: group 1, high-risk, and group 2, low-risk patients. The criteria for risk assessment included the presence of a prior history of OHSS, polycystic ovaries, and age under 30 years.

Aspirin was administered at a dose of 100 mg per day in 1503 cases of the 2425 induced cycles. Among those who received aspirin, 52% (n = 780) were in the high-risk group, and 48% (n = 723) in the low-risk group. Among the 922 receiving no aspirin, 45% (n = 412) and 55% (n = 510) of patients were in the high-risk and low-risk groups, respectively.

Study Protocol

Superovulation treatment was started after the necessary examinations, including cervical smear, serum hormone measurement (follicular-stimulating hormone and luteinizing hormone, prolactin, estradiol, progesterone, testosterone, and thyroid-stimulating hormone) on days 3 and 21 of the unstimulated cycle, human immunodeficiency virus, and hepatitis-B surface antigen screening, andrologic examination, and hysteroscopy. Patient enrollment in the IVF procedure was approved by two independent physicians.

In 77% of the cycles, the GnRH-agonist triptorelin (Decapeptyl; Ferring, St. Prex, Switzerland) was used in a long or short protocol, and the stimulation was performed with individual dosages of follicle-stimulating hormone (Gonal-F; Serono S.A., Geneva, Switzerland; or Puregon; Organon, Oss, the Netherlands), varying from 100 to 200 IU per day depending on the follicular maturation. The latter was determined by ultrasound examination from day 6 of the cycle every other day, and by measuring serum luteinizing hormone and estradiol levels. Serum hormone levels were measured by radioimmunoassay. We changed the amount of the administered gonadotropins individually according to the size of the follicles. Ovulation was induced by injection of 250 μg of hCG (Ovitrelle; Serono), and aspiration of follicular fluid was performed 36 hours later by ultrasonography-guided transvaginal puncture. Embryo transfers were done 3 to 5 days after the oocyte retrieval. Progestogen supplementation was provided using 300 mg of progesterone three times a day (Utrogestan; Laboratoire Besins International S.A., Paris, France).

To evaluate the success of the treatment, we performed the transvaginal ultrasound examination 21 days after the embryo transfer. Diagnosis of OHSS was based on the presence of abdominal pain, the ultrasound finding, and the blood test result for hemoglobin, hematocrit, and white blood cell count.

Statistical Analysis

To determine whether the observed data were statistically significantly different from the frequencies we would expect by chance, the chi-square test was applied. The Yates-correction for continuity was used to complete the chi-square test, when the treated and nontreated subgroups of group 1 were compared.

RESULTS

Out of 2425 cycles, severe or critical OHSS was observed in 1.8% (n = 45). These patients were admitted to the hospital for intensive care and correction of dehydration and hemoconcentration and for transvaginal aspiration of free fluid