Prevention of Ovarian Hyperstimulation Syndrome by Early Aspiration of Small Follicles in Hyper-responsive Patients With Polycystic Ovaries During Assisted Reproductive Treatment Cycles

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Abstract and Introduction

Abstract

Objective: This study was designed to assess the efficacy of early aspiration of small follicles (EASF) in preventing moderate and severe ovarian hyperstimulation syndrome (OHSS) in women with polycystic ovaries who experienced excessive ovarian response during the early part of assisted reproductive treatment cycles (ART).

Study Design: EASF was undertaken transvaginally during 15 in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles in 14 women with polycystic ovaries who produced more than 20 small follicles during the early part of the cycle. A minimum of 10 small follicles (Outcomes: None of the patients developed moderate or severe OHSS. There were 9 intrauterine pregnancies (60 %) and 1 ectopic pregnancy.

Conclusions: EASF 4 to 7 days after starting gonadotropin injections prevented moderate and severe OHSS in susceptible patients with polycystic ovaries and resulted in a high pregnancy rate. Larger studies are needed to verify these promising results.

Introduction

Patients with polycystic ovaries who have been hyperstimulated during previous assisted reproduction cycles are at increased risk of developing moderate or severe ovarian hyperstimulation syndrome (OHSS). The total number of follicles and the level of serum estradiol are the 2 parameters used for risk assessment during treatment cycles. OHSS seldom occurs with serum estradiol levels below 1000 pg/mL (3700 pmol/L). Different threshold levels have been used to indicate increased risk,[1-3] but
most investigators have used a figure of 3000 pg/mL on the day of human chorionic gonadotropin (HCG) administration for that purpose.\cite{4} Similarly, the number of follicles used to indicate increased risk ranges from 20 to 30 follicles,\cite{5,6} but there is agreement that a high fraction of small and intermediate-size follicles at the time of HCG injection represent the main predisposing factor.\cite{7,8}

Since the early report by Gonen and colleagues\cite{9} contended that aspiration of follicles leads to significant reduction in serum estradiol and other hormones, different investigators have managed to reduce but not eliminate the risk of severe OHSS by bilateral\cite{6} or unilateral aspiration of follicles before\cite{10,11} or after\cite{12,13} HCG injection. It is notable that in all of these studies, the prognostic value of estradiol level and number of follicles, as well as the effort to avert the risk of OHSS, were focused around the time of HCG injection. Such late intervention most likely failed because of a more advanced stage of follicular development with more granulosa cell mass and a corresponding advanced stage in the chemical chain of events responsible for OHSS. Accordingly, we postulated that reducing the number of small follicles, and hence the granulosa cell mass earlier during the cycle, might prevent moderate and severe OHSS and improve the cycle outcome. We report here the results of a preliminary study of 15 treatment cycles conducted in 14 at-risk patients with polycystic ovaries.

**Subjects and Methods**

Fourteen patients with polycystic ovaries who had excessive ovarian response to gonadotropin injections during previous IVF or induction of ovulation cycles were included. The ovaries were designated as polycystic when they contained 10 or more follicles measuring 2 to 9 mm in diameter. The criteria used to select patients were previous moderate or severe OHSS and increased risk of similar response during the early part of FSH stimulation in the current study cycles (appearance of >/=20 follicles). Thus, each patient acted as her own control.

A long protocol was used for ovulation induction starting with subcutaneous daily injections of buserelin acetate (Hoechst UK Limited, Hounslow, Middlesex, UK), 300 micrograms, on Day 21 of the cycle. Recombinant FSH (Puregon, Organon Laboratories Ltd, UK) injections were administered after the third day of the subsequent cycle, at an initial dose of 150 IU; the doses were subsequently adjusted on the basis of responses, monitoring with transvaginal scan, and estradiol levels.

The duration of FSH stimulation ranged from 11 to 15 days, and serial estradiol estimations and ultrasound scans were performed on alternate days between Days 5 and 10 of the cycle and as necessary thereafter. The decision to proceed with EASF was made at the earliest sign of excessive ovarian response when 20 or more follicles were seen in both ovaries.

Aspiration was carried out using a 16-gauge double lumen ovum pickup needle (Cook Ireland Ltd, National Technological Park, Limerick, Ireland) and a regulated vacuum pump model KMAR-5000 (Cook Medical Technology) at -230 mm Hg. A minimum of 10 follicles

Treatment with gonadotropin injections was continued until at least 3 follicles reached >/=18 mm in diameter; the final stages of oocyte maturation were induced with the administration of 5000 IU of HCG (Profasi, Serono UK Limited). Transvaginal oocyte retrieval was done 36 hours after HCG administration. Fertilization was checked 18 hours after insemination, and embryo transfer was done 2 or 3 days after oocyte retrieval. Two or 3 embryos were replaced in the uterine cavity depending upon the patient's age, quality of embryos, number of previous attempts, and the couple's wishes.

Luteal phase support was achieved with 400 mg Cyclogest (Cox Pharmaceuticals, Whiddon Valley, UK) twice daily per rectum for 16 days when a pregnancy test was performed. All patients were observed regularly for symptoms and signs of OHSS using the criteria described by Golan and colleagues,\cite{14} and a blood test for beta HCG was done 14 days after embryo transfer in those who had not menstruated.

**Results**
The Table shows the attributes of the patients and a summary of the results. None of the patients developed moderate or severe OHSS during the subsequent period of close follow-up, even during conception cycles. Many of the follicles aspirated on the day of oocyte retrieval contained blood-stained fluid, yielded no oocytes, and had few or no granulosa cells in the aspirate. This was especially evident in cycle numbers 1, 2, 4, 10, and 12. Nine cycles ended in intrauterine pregnancies with successful childbirth, and there were no miscarriages in this group. One cycle ended in right tubal pregnancy, which was treated with laparoscopic salpingectomy. This same patient had a successful twin pregnancy and another patient had a successful singleton pregnancy following a replacement of embryos frozen during the reported study cycle.

Comment

Reduced morbidity and mortality associated with severe OHSS requires effective preventive strategies, including the correct identification of women at risk, using the minimum effective dose of gonadotropins, and strict monitoring during treatment cycles with ultrasound scan and serum estradiol assessments. These measures are effective in reducing but not eliminating risk. Early cancellation of the treatment cycle before giving the HCG injection is the most effective way to prevent OHSS risk.

Unfortunately, there are no guarantees that a similar excessive response would not occur in subsequent induction cycles despite reducing the gonadotropin dose. This was the pattern seen in the patients in our study. Several strategies have been described to prevent cycle cancellations and to reduce the consequent financial losses. Elective cryopreservation of all embryos and embryo transfer in future cycles is a widely used technique. Gonadotropin-releasing hormone agonist (rather than HCG) to trigger ovulation in women at risk has been used to prevent severe OHSS without compromising pregnancy rate, but it is not appropriate for downregulated cycles.

Reducing or withholding gonadotropin injections for a few days before HCG administration (coasting) has been described by various groups. However, many questions still remain unanswered about how coasting should be managed without compromising the final outcome of the cycle. Bilateral and unilateral aspiration of follicles before or after HCG administration have been described previously. It is evident that the ideal strategy to prevent OHSS is yet to be found, stressing the need for further research in this area.

Since moderate and severe OHSS usually followed cycles with an excessive number of small follicles in susceptible patients, we targeted these small follicles as soon as excessive ovarian response was diagnosed by ultrasound scanning – usually 4 to 7 days after starting gonadotropin injections – which may be a critical time frame for such a procedure. Reducing the granulosa cell mass at such an early stage would reduce the capacity of these follicles to produce vasoactive and other factors responsible for the development of OHSS after HCG administration. We stress the point that all empty follicles in this study showed only a few or no granulosa cells on the day of egg collection.

The reduction in estradiol level reported by Gonen and colleagues after follicular aspiration was mostly associated with a similar trend for the precursor molecules (androgens), although the authors did not consider these hormones in their analysis. In this respect, these changes could simulate in part the effects reported after ovarian diathermy. Lower follicular fluid androgens have been reported during IVF cycles preceded by ovarian diathermy. This was associated with significant improvement in the ongoing pregnancy rate, probably as a result of the improvement in the intraovarian endocrine milieu, as androgens have a deleterious effect on the quality and final maturation of oocytes, embryo quality, and the estrogen-induced endometrial growth and development. A detrimental effect of high luteal phase serum testosterone on pregnancy outcome has already been documented.

The improved pregnancy rate reported after IVF cycles preceded by transvaginal aspiration of all visible small follicles in women with polycystic ovarian syndrome was expected as it reduced the number of small follicles and atretic cysts. Aspiration of the latter group reduced the intraovarian androgenic environment, which could improve the quality and implantation capacity of embryos generated from the remaining oocytes as well as improve endometrial receptivity through a similar effect. A similar pattern could be seen after EASF, which would explain the high pregnancy rate in this study and the lack of any miscarriages following 9 intrauterine conceptions.

Polycystic ovaries contain multiple partially stimulated antral follicles, and increased local estrogen concentration would increase the sensitivity of these follicles to over-
respond to exogenous gonadotropins. Accordingly, the decision to proceed with EASF should be based primarily on the total number of follicles before the exponential rise in serum estradiol level. This decision can be made very early during the cycle — as soon as ultrasound scan shows excessive ovarian response irrespective of serum estradiol levels on the day (Figure). By the time the exponential rise in serum estradiol begins, or the reported high levels associated with OHSS are reached, the corresponding vasoactive and other chemical cascades would be too advanced to halt by any means other than halting the HCG dose. Thus, we could conclude that the timing of EASF during this study is the important factor in preventing OHSS, as similar attempts in previous studies concentrated around the time of HCG injection.
(A) Bilateral polycystic ovaries stuck together before starting IVF treatment in cycle number 12. (B) Excessive response occurs as early as the 5th day after starting gonadotropin injections. Serum estradiol was only 933 pmol/L (252 pg/mL) and shot up to 4573 pmol/L (1575 pg/mL) on Day 8 of the cycle when 14 small follicles were aspirated. Estradiol on the day of oocyte retrieval was 3645 pmol/L (985 pg/mL). This patient hyperstimulated during 2 previous IVF attempts.

Although a larger study is needed to verify these results, there would be an ethical difficulty in selecting the study strategy. During controlled cohort studies, each patient at the time of selection must have an equal chance of being assigned to either the study or control groups. However, matching patients on a single variable (the presence of polycystic ovaries only) that is not strongly correlated with the outcome (moderate or severe OHSS) would not be effective and would lead to loss of statistical power. This
is especially so since women with polycystic ovaries have different physical and biochemical attributes and show variable response to gonadotropin therapy. Indeed, the same patient might show a different response to gonadotropins during different cycles. A stronger matching variable would be the combined presence of polycystic ovaries and excessive ovarian response during a previous assisted reproduction attempt and during the early part of the study cycle itself as represented by our patients in this study. However, it would be inconceivable to assign any of these patients to the non-treatment arm of a comparative study because of the perceived high risk of hyperstimulation. Accordingly, a similar but larger study would be required to confirm these results.

Table. Patient Characteristics and Relevant Results

<table>
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<th>Age (yrs)</th>
<th>BMI</th>
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<th>Infertility (yrs)</th>
<th>Other Infertility Factors</th>
<th>EASF (N)</th>
<th>Follicles on Day of VEC</th>
<th>Oocytes Collected</th>
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<th>Fertilized Oocytes</th>
<th>Embryos Replaced</th>
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*Outcomes include not pregnant (NP), intrauterine pregnancy (IUP), or right tubal pregnancy (ectopic). ART = assisted reproduction technology; BMI = body mass index; EASF = early aspiration of small follicles; ICSI = intracytoplasmic sperm injections; IUP =
References

21. Gadir AA, Alnaser HM, Mowafi RS, Shaw RW. The response of patients with polycystic ovarian disease to human menopausal gonadotrophin therapy after


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