CLINICAL ASSISTED REPRODUCTION

Pregnancy Rate in IVF Rescue in High Responders to Human Menopausal Gonadotropin

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Purpose: *In vitro* fertilization had been previously suggested by us as a means of "rescue" for patients with imminent ovarian hyperstimulation syndrome (OHSS) during treatment with human menopausal gonadotropin (hMG). We evaluated the pregnancy rate of rescued IVF cycles.

Methods: During the years 1994–1995, women treated with hMG and at risk of developing OHSS were referred to our IVF unit. Their estradiol level was above 1500 pg/ml, and eight or more follicles were observed by ultrasonography in all the patients. These high responders were offered the option to undergo ovum aspiration. We report the pregnancy rate in this group of patients.

Results: Thirty-nine women were referred to our unit for rescue IVF. Two were ineligible due to high progesterone concentrations. Thirty-seven women underwent ovum pickup and 32 had embryo transfer. The clinical pregnancy rate was 40% (13/32). Only two women had clinical OHSS.

Conclusions: We suggest that rescue IVF may be considered in hMG cycles of high responders with imminent OHSS. Rescue IVF offers a high rate of conception, avoids high-order multiple pregnancy, and appears not to increase the risk of OHSS in these women.

KEY WORDS: ovarian hyperstimulation syndrome; rescue in vitro fertilizations; human menopausal gonadotropin.

INTRODUCTION

Human menopausal gonadotropins (hMG) have been used in ovulation induction for the last 30 years. hMG induction of ovulation is used extensively in both anovulatory and ovulatory women. The most serious complication related to gonadotropins treatment is ovarian hyperstimulation syndrome (OHSS).

Women presenting with a high response to hMG treatment are at high risk for developing OHSS. Several therapeutic regimens emerged during the past few years to prevent or reduce the susceptibility to OHSS in these high responders. Cancellation of treatment cycle by withholding human chorionic gonadotropin (hCG) usually reduces the risk of—but does not entirely prevent—the development of OHSS. This whole process involves considerable frustration and disappointment as well as financial waste. Itskovitz *et al.* (1) used a bolus gonadotropin releasing hormone (GnRH) analogue instead of hCG to trigger an adequate midcycle luteinizing hormone (LH) surge. They suggested that this regimen might reduce the incidence of OHSS. In 1991, we proposed an additional approach in the treatment of these women (2): we avoided cancellation of potential hyperstimulation hMG cycles by converting them to in vitro fertilization (IVF), i.e., IVF–embryo transfer (ET) during the same cycle. By doing so, we achieved pregnancies with no observable increase in the incidence of OHSS.

In this study, we evaluated the pregnancy rate achieved in high responders treated by conversion to IVF ("rescue IVF") during ovulation induction by hMG.

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MATERIALS AND METHODS

Ovulation induction at Lis Maternity Hospital infertility clinics included 2 ampoules of hMG, initiated 5 days after spontaneous or progestin-induced menstruation. The treatment was monitored with serum estradiol (E_2) concentrations obtained 14 hr after hMG administration and with transvaginal ultrasonography assessment of follicular growth carried out every other day. At that time, we did not use treatment protocols of prolonged administration of low dose hMG in women with polycystic ovarian disease (PCOD).

Between January 1, 1994, and December 31, 1995, all women treated with hMG at the Lis Maternity Hospital infertility clinics who were found to be at high risk for the development OHSS during the treatment cycle were referred to our IVF unit. They all had more than seven ovarian follicles (>16 -mm diameter) as detected by transvaginal ultrasound, and their E_2 levels exceeded 1500 pg/ml. These women were offered the opportunity to continue treatment during the same cycle by conversion to IVF. The study group included all the women who agreed to undergo this "rescue IVF."

The clinical pregnancy reported for the group was documented by gestational sac demonstrated on ultrasound.

RESULTS

Thirty-nine women who were referred to our IVF-ET unit due to potential development of OHSS met the inclusion criteria and agreed to undergo "rescue IVF" during the study period. Twenty-seven of them (70%) were in their first hMG cycle treatment. In 2 of the 39, a progesterone concentration in peripheral blood above 3 ng/ml mandated cancellation of treatment due to early luteinization. Thirty-seven women underwent ovum pickup and ova were collected in them all. The average number of ova per pickup was 16.6. There was no evidence of fertilization in two women and ET was not done in another three women, due to early development of OHSS in one of them and because of fever in the other two. In the latter three women, embryos were cryopreserved. The fertilization rate in this group was 57%. No more than three embryos were transferred in each cycle. Overall, 32 ETs were carried during the patients' cycle treatment.

There were 13 pregnancies (13/39;33%) in this group. The pregnancy rate per ET was 40%. Three women eventually developed OHSS but in only one

did this require hospitalization (for 4 days). In this group we had two cases of twin pregnancies. Four women (4/13) had a miscarriage. The overall "take-home baby" rate in this group was 9 of 39 (23%).

DISCUSSION

Since the early 1980s, gonadotropins have been widely used in the preparation of women undergoing IVF-ET or other assisted reproductive treatments. The most serious complication related to treatment of ovulation induction with hMG is OHSS. The development of OHSS is much more frequent in "high responders," i.e., individuals with multiple follicular cysts and very high concentration of E_2 in peripheral blood. In the past few years, several alternative regimens had been proposed in the effort to reduce or eliminate the risk of developing OHSS in women susceptible to develop this syndrome.

One of the main challenges in using these regimens is not to eliminate the possibility of conception. The most common practice was to prevent ovulation by avoiding the administration of hCG. This regimen did reduce the incidence of development of OHSS but did not prevent it, and conception was not achievable. Consequently, this approach involves frustration of the couple and wasted expenses for having canceled the cycle. In 1994, Balasch *et al.* (3) suggested the use of GnRH analogue as a trigger for the endogenous LH surge in cycles with a high response which would otherwise have been canceled. This group reported 4 pregnancies of 23 hMG cycles, a pregnancy rate of 17.4% per cycle. Itskovitz-Eldor *et al.* (4) proposed the use of GnRH agonist instead of hCG to induce oocyte maturation during induction of ovulation with hMG in the IVF-ET program. In their preliminary report (1), none of the eight patients considered to be "high responders" developed OHSS, and there were two successful pregnancies.

A different approach was described by Wada *et al.* (5). Women with high E_2 following induction of ovulation with hMG and buserelin in an IVF-ET program had all their embryos cryopreserved electively at the pronucleate stage. Forty-five percent of the group had features of polycystic ovary syndrome (PCO); 27% of their subjects suffered from OHSS, and a pregnancy rate of 19% was achieved.

In 1991, Lessing *et al.* (2) presented for the first time a novel approach for women undergoing ovulation induction with hMG and who were at high risk for the development of OHSS. Instead of canceling treatment

cycles in high responders in order to reduce the risk of OHSS, they offered them a regimen of "rescue IVF." This study included 12 women treated with hMG for anovulation. All of them were high responders and bore a high risk of developing OHSS. These patients were transferred for the continuation of treatment to IVF-ET unit. Of this group, two women developed mild OHSS and five (41%) conceived. The authors suggested that IVF-ET should be considered in cases in which OHSS is imminent. A very similar approach was described by Bergh *et al.* (6). In that report 50% pregnancy rate was achieved in 25 cycles which were converted to IVF.

In the present study on the use of rescue IVF, the incidence of OHSS was relatively low compared to the expected rate, considering the fact that all the study patients were judged as being high responders. More striking is the conception rate which was 40%. Thus, high-responsive patients might benefit from a higher pregnancy rate with rescue IVF than their pregnancy rate had they not been given the opportunity to be "rescued." This pregnancy rate achieved in rescue IVF is much higher than the one previously reported using GnRH instead of hCG (1, 3, 4, 6, 7). Furthermore, in the majority of the women, embryos were cryopreserved due to the high number of ovum. This should add to the cumulative pregnancy rate in this group. This approach of conversion to IVF also avoids high-order multiple pregnancies.

Women suffering from anovulation, most of which being due to PCO, tend more often to be high responders. Indeed, in our study group, 60% of the women had anovulation and PCOD.

Women undergoing rescue IVF are more likely to be in their first or second cycle of treatment. This itself might have theoretically improved their chances to conceive, but when we tried to control for this factor,

we observed no increased incidence of conception in women undergoing their first hMG cycle treatment.

In conclusion, in patients who are considered to be highly susceptible to develop OHSS during hMG treatment, transfer to IVF-ET offers the advantage of a high conception rate, and one which exceeds that achieved by the reported conception rate using GnRH analogue. It eliminates the risk of high-order multiple pregnancies and it may also offer reduction in the risk of developing OHSS in these women.

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