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Selective Follicular Reduction: What to Do with the Oocytes?

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ABSTRACT: **Objective**—To investigate the possible benefits of in vitro fertilization (IVF) of oocytes retrieved during selective follicular reduction of supernumerary follicles in non-IVF cycles. **Methods**—Selective follicular reduction of supernumerary follicles was used to prevent ovarian hyperstimulation syndrome and multiple pregnancies in gonadotropin-stimulated cycles. We analyzed the data of 13 cycles (13 women) retrospectively. **Results**—Three pregnancies occurred in these 13 cycles (23%), one after intra-uterine insemination and two after timed coitus. In all cycles, oocytes were retrieved, and in 10 cycles fertilization was achieved (77%); in 6 cycles cryo-preservation was successful (46%) and in 3 cycles embryo transfer (ET) was performed (23%). All embryos were of poor quality and no pregnancies occurred after ET of frozen–thawed embryos. The diagnostic value of fertilization failure seems to be low, since one of the patients who failed to show fertilization became spontaneously pregnant afterward. **Conclusion**—Based on our observations, the beneficial effect of IVF/cryopreservation during selective follicular reduction appears questionable. *Int J Fertil* 41(6):506–508, 1996

KEY WORDS: aspiration, follicle, ovarian hyperstimulation syndrome, oocytes, IVF

INTRODUCTION

THE USE OF GONADOTROPINS FOR THE induction of ovulation may be complicated by multiple pregnancies and the ovarian hyperstimulation syndrome (OHSS) [1–5]. The risk of these complications may be reduced by intensive monitoring of follicular development by ultrasound and serum estradiol measurements. If too many follicles are developing or the estradiol level is too high, the cycle can be canceled or the gonadotropins can be withdrawn for several days ("drifting" or "coasting") [6,7].

Alternative approaches are conversion of the cycle into in vitro fertilization (escape-IVF [8–9]) and ultrasound-guided selective follicular reduction [10,11]. During selective follicular reduction the two or three largest follicles remain intact and may result in pregnancy, and the retrieved oocytes are discarded.

However, the oocytes retrieved during selective follicular reduction can be fertilized in the IVF laboratory and, after cryopreservation, embryo transfer (ET) of frozen-thawed embryos can be performed. Only one case report in the literature describes this combination of selective follicular reduction and IVF/cryopreservation [12]. There are two possible benefits of this procedure: fertilization can be tested and the pregnancy rate can be increased by ET of the frozen-thawed embryos. The present study was conducted to evaluate the possible benefits of IVF/cryopreservation during selective follicular reduction in non-IVF cycles.

MATERIALS AND METHODS

In our outpatient clinic controlled ovarian hyperstimulation is performed with human menopausal gonadotropin (hMG) (Humegon, Organon, Oss, the

Netherlands) and human chorionic gonadotropin (hCG) (Pregnyl, Organon). Before starting gonadotropin treatment transvaginal ultrasonography is done to ensure the absence of ovarian cysts. The initial dosage of gonadotropin preparation usually consists of 1 or 2 ampules daily (75 or 150 IU). Treatment is started on day 3 of the menstrual cycle. The next visit is planned on day 8. Follicular development is monitored with repeated vaginal ultrasonography and by frequent measurement of the estradiol concentration in serum with time-resolved fluoroimmunoassay (DELFIA, Wallac Oy, Turku, Finland) or enzyme-linked fluoroimmunoassay (ELFA, Biomerieux, Den Bosch, the Netherlands). Subsequently, the dose of gonadotropins may be increased, depending on the follicular response and estradiol level. If the largest follicle reaches a diameter of 18 mm, ovulation is induced with 10,000 IU hCG. Injection of hCG is followed by insemination (34 hours after hCG injection) or intercourse (30 hours after hCG injection).

The luteal phase is supported by progesterone, 200 mg intravaginally for 12 days. If more than three follicles larger than 15 mm in diameter have developed, or the estradiol level exceeds 1,000 pmol/L per mature follicle, the couple is informed about the risk of a high-grade multiple pregnancy and the ovarian hyperstimulation syndrome. Puncturing and aspirating supernumerary follicles under ultrasound guidance will then be considered.

We studied the results of 13 cycles in which selective follicular reduction was combined with IVF of the retrieved oocytes and cryopreservation of the embryos. The transvaginal aspiration of the supernumerary follicles took place 32–36 hours after hCG injection, leaving the two or three largest follicles in situ. Aspiration was performed after the administration of analgesic or sedative medication. The number of oocytes was counted under a stereomicroscope. Each oocyte was inseminated in a tissue culture disk with approximately 100,000 motile spermatozoa. If fertilization was achieved, an attempt was made to cryopreserve the embryos. OHSS was classified according to Golan et al [13]. Results are expressed as mean ± standard deviation.

RESULTS

Thirteen cycles in 13 women were analyzed. Mean duration of infertility was 2.4 ± 1.4 years, the average age of the patients was 31.2 ± 4.4 years. The cause of infertility was andrologic (3 couples) or anovulation (10 couples). The number of ampules at start was 1.2 ± 0.5 and the total number of ampules per cycle was 24.5 ± 7.5. The maximum serum estradiol level was 7,520 ± 3,920 (pmol/L), and the number of follicles >15 mm was 8.9 ± 3.3. In 3 cycles, intra-uterine insemination (IUI) was performed, and in 10 cycles timed coitus was advised. All 13 cycles were ovulatory, and none of the cycles had to be canceled on account of premature ovulation.

Three of the 13 treatment cycles (23%) resulted in ongoing singleton pregnancies (two after timed coitus and one after IUI). Oocytes were retrieved in all cycles and the mean number of oocytes per cycle was 10.5 ± 7.4 (range 2–26, n = 13). Fertilization was achieved in 10 of the 13 cycles (77%) and in 70 of the 136 oocytes (51%). The mean number of fertilized oocytes per cycle was 5.4 ± 4.6 (range 0–15, n = 13). One of the three couples that did not show fertilization achieved pregnancy spontaneously 2 years after the procedure.

In 4 of the 10 cycles with fertilization, cryopreservation was not successful because of bad morphological quality of the embryos. In 6 cycles (46%), cryopreservation was successful (46/70 embryos; 66%). The mean number of cryopreserved embryos per cycle was 3.5 ± 5.0 (range 0–15, n = 13). In three of those six couples ET was carried out. The number of transferred embryos was 2 (1 good and 1 bad quality), 3 (2 moderate and 1 bad quality), and 4 (2 moderate and 2 bad quality). No pregnancies occurred after ET of these thawed embryos. In two of the six couples, ET was not performed because pregnancy was achieved in the cycle during which the aspiration of supernumerary follicles was performed, and in one of the six couples, because of the very bad quality of the thawed embryos.

None of the treatment cycles were complicated by any moderate or severe forms of OHSS. In five women (38%) mild signs of OHSS were observed including abdominal distention and discomfort. Two of these patients were pregnant. Complications of follicle aspiration, such as pelvic infections or abdominal bleeding, did not occur.

DISCUSSION

The main goal of this study was to evaluate the possible benefits of IVF of the oocytes retrieved

during selective follicular reduction in non-IVF cycles. This procedure, resulting in cryopreservation of embryos, might increase the pregnancy rate of the whole treatment. Secondly, IVF of retrieved oocytes during aspiration of supernumerary follicles can be used as diagnostic test whether or not fertilization in a couple can be achieved.

The value of IVF aspiration of supernumerary follicles seems to be arguable. We found that in only 38% of the cycles could embryos be cryopreserved, and in only 23% of the cycles was ET deemed worth performing. The embryos were mostly of morphologically bad quality, and no pregnancies occurred after ET of thawed embryos. Although the numbers are small, this observation is in agreement with the literature, since no pregnancies have been described with frozen-thawed embryos after selective follicular reduction [12].

In addition, the predictive value of fertilization failure is not great: in this study, one of the three couples whose retrieved oocytes were not fertilizable achieved pregnancy spontaneously 2 years after the procedure.

A good explanation for the probably low additive value of IVF and cryo-ET after selective aspiration of supernumerary follicles remains difficult. Possibly, the maturity of the oocytes is not optimal, because of the relatively small diameter of the aspirated follicles. The two or three largest follicles are left in situ, and may contain the best oocytes. Our data support the concept that selective follicular reduction in non-IVF cycles is a good alternative or supplement to such previously described methods as cancellation, "drifting," "coasting" [6–7] or escape-IVF [8–9]. The pregnancy rate is good, and the risk of multiple pregnancies and OHSS is reduced [11].

In conclusion, our data and the data in the literature show that selective follicular reduction is an effective method for reducing the frequency of OHSS and multiple pregnancies after ovarian hyperstimulation, without compromising the pregnancy rate. Furthermore, our data show that the beneficial effect of IVF/cryopreservation during selective follicular reduction is questionable. We believe this procedure should not be practiced until the opposite has been proved in randomized studies.

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