Journal of Assisted Reproduction and Genetics, Vol. 10, No. 2, 1993

CONTROVERSIES IN ASSISTED REPRODUCTION

Treatment of Low Responders

The treatment of low responders with in vitro fertilization (IVF) remains a challenge. It is extremely important to identify these patients prior to initiation of hormonal treatment for ovarian stimulation for IVF for two main reasons. First, these patients should be counseled regarding the reduced chances of achieving a pregnancy, so that they can have realistic expectations and consider alternative therapies, such as the use of donor oocytes or adoption. Second, stimulation protocols for these patients should have an acceptable rate of cancellation (<20%), yield the maximum number possible of healthy mature oocytes at a reasonable cost and duration of therapy, and provide a suitable endometrium for implantation and an adequate luteal phase for support and continuation of pregnancy. Despite the evolution and development of stimulation regimens for IVF, the ideal stimulation protocol for the low responder remains an unachieved goal.

Low responders can be prospectively identified by one or more different variables. Advanced maternal age (≥40) is usually associated with a suboptimal ovarian response to stimulation. Recent data from a large IVF program suggest that pregnancy rates are significantly reduced after the age of 35, so that potential IVF patients are best served if they are referred and treated at a younger age (1). Basal follicle stimulating hormone (FSH) levels on cycle day 3 have proved to be sensitive indicators of ovarian age and better predictors of ovarian response than chronological age (2). Patients with only one ovary and compromised ovarian status, based on elevated basal FSH levels, have a reduced potential of oocyte recruitment (3). Finally, a history of obtaining fewer than four mature oocytes in response to a standard stimulation protocol should categorize the patient as a low responder. In all of the above, it is extremely important for an obese potentially low-responder patient to lose weight in order to optimize ovarian response to hormonal stimulation.

The use of gonadotropin-releasing hormone agonist (GnRH-a) suppression followed by gonadotropin stimulation has proven to be beneficial in minimizing cancellation rates (mostly by preventing a premature luteinizing hormone surge) and improving follicular recruitment and yield of mature oocytes in intermediate and high responders (4,5). The benefit is more significantly apparent by cryopreserving excess preembryos for future thaw and transfer, thus enhancing the cumulative pregnancy rates per a single stimulated cycle (6). Unfortunately, prior suppression with GnRH-a in low responders results in excessive dampening of the ovarian response to hormonal stimulation, so that cancellation rates, due to lack of ovarian response, are unacceptably high or hormonal stimulation is excessively prolonged with increased cost and duration of treatment without a significant improvement on the yield of mature oocytes (clinical experience accumulated at The Jones Institute). In the United States, the cost of administered gonadotropins (Pergonal, Metrodin) is higher than in the rest of the world, and a significantly greater number of ampoules of gonadotropins used usually means a significantly higher cost of treatment to the patient, due to general lack of insurance coverage. As such, GnRH-a suppression should be avoided prior to ovarian stimulation in low responders.

The opinions presented in this column are those of its author(s) and do not necessarily reflect those of the journal and its editors, publisher, and advertisers.

1058-0468/93/0200-0112$07.00/0 © 1993 Plenum Publishing Corporation

The use of a high-dose FSH regimen (6–8 ampoules of Metrodin i.m. daily), starting on cycle days 1–3, can be employed for low responders. The strategy is to increase the circulating levels of FSH early in the cycle, so that a maximum possible number of oocytes can be rescued and recruited for IVF (7,8). Unfortunately, endogenous LH levels will not be suppressed, and premature luteinization and ovulation continue to be a risk with this stimulation, so that frequent monitoring of LH is required, possibly resulting in the cycle being canceled or the time of retrieval adjusted according to a premature LH surge (9).

The use of a flare effect from the initial stimulatory phase of GnRH-a action on pituitary hormone levels (FSH, LH) can be employed to improve the stimulatory response of low responders. The timing of initiation of gonadotropin stimulation relative to the administration of GnRH-a has been varied by different investigators. For example, Garcia *et al.* have reported on the successful use of GnRH-a initiated on the second day of the cycle, followed by gonadotropin (FSH/hMG) stimulation starting on the fifth day of the cycle (10). The protocol was used for all IVF patients and not selectively for low responders. Winslow *et al.*, in a group of low responders, reported on GnRH-a initiation on cycle day 2, followed by gonadotropin stimulation on cycle day 4 (11). Unfortunately, the flare effect is much reduced after 2 days of GnRH-a administration, as evident from a significant number of patients who demonstrated an estradiol plateau or decrease after an initial increase, due to the flare-up effect of GnRH-a, on cycle day 3. Brzyski *et al.*, in a small group of low responders, had reported earlier that there was an increase in the yield of atretic oocytes with concurrent initiation of GnRH-a and FSH on cycle day 3 (12).

More recently, we have had an extensive experience with the use of a modified GnRH-a flare protocol in low responders. Leuprolide acetate (Lupron, TAP Pharmaceuticals, Abbott Park, IL) was started on cycle day 2, 1 mg subcutaneously (s.c.) daily, decreased to 0.5 mg, s.c. daily on cycle day 5, and continued until human chorionic gonadotropin administration. High-dosage FSH (Metrodin, Serono Laboratories, Inc., Randolph, MA) therapy, 6–8 ampoules i.m. daily, was started on day 3 and adjusted, usually in a step-down manner, after cycle day 6, based on response parameters to stimulation. With 150 stimulated cycles in 127 patients, the cancellation rate was 5%, the mean peak estradiol was 793 ± 472 pg/ml, the mean number of ampules of Metrodin used was 26.2 ± 7.6, and a mean of 4.9 ± 4.0 mature oocytes was retrieved. The clinical pregnancy rate was 21.3 and 24.6% per stimulated attempt and transfer, respectively (13). A progesterone increase in serum levels, in the early follicular phase (cycle days 3–6), was demonstrated in 85% of the patients in whom the flare protocol was used. Although there were no significant differences in serum progesterone levels between pregnant and nonpregnant patients, the number of mature oocytes was significantly less in the group that demonstrated a progesterone rise. Furthermore, the pregnancy rate per stimulated cycle (but not per embryo transfer), was significantly lower (19.7 vs 30.4%) in the group with a demonstrable rise in serum progesterone. This increase in serum progesterone levels results from activation of a less than completely demised corpus luteum from the preceding cycle. Furthermore, elevations of se-

Table I. Stimulation Characteristics and Pregnancy Rates at the Jones Institute During 1991–1992

	Mean ± SD		
	GnRH-a suppression protocols	GnRH-a flare protocols	FSH only protocol
Attempts	488	331	201
Age (years)	33.7 ± 3.7	37.6 ± 4.0	36.0 ± 4.3
Basal FSH (mIU/ml)	8.7 ± 2.8	15.5 ± 6.4	14.5 ± 4.7
Cancellation rate (%)	5	10	17
Ampoules FSH/hMG	23 ± 6	27 ± 5	30 ± 6
Preovulatory eggs aspirated	10.4 ± 2.2	4.9 ± 2.3	5.0 ± 2.8
Cycles with cryopreserved embryos (%)	61	17	19
Clinical pregnancies/retrieval (%)	38	22	19
Cumulative (fresh + cryopreserved to date/retrieval; %)	50	24	21

rum testosterone and androstenedione have been noted in the follicular phase in patients on flare-up stimulations (14). Although we have demonstrated a negative correlation between an increase in serum progesterone levels in the early follicular phase and oocyte yield, the effect on implantation is currently unknown and deserves investigation before widespread use of GnRH-a flare-up regimens in IVF.

Table I illustrates stimulation characteristics and pregnancy rates with different stimulation protocols used at The Jones Institute during 1991–1992. It is to be emphasized that GnRH-a suppression protocols were used exclusively for adequate responders, while GnRH-a flare protocols and high-dosage FSH therapy were used exclusively for low responders. The results illustrate the inherently reduced pregnancy potential of low responders.

In conclusion, the treatment of low responders in IVF remains a challenge and requires constant scrutiny and modification of currently used stimulation protocols. It is highly doubtful whether we can raise the success rates for these patients to even approach those achieved for the intermediate and high responders. However, we can definitely improve on the yield of fertilizable oocytes. The challenge is to be able to do that at a minimum increase in cost and duration of treatment, and without adversely affecting endometrial receptivity for implantation. We need constantly to reevaluate our current methods and employ newer technologies so that we can help IVF patients, especially the low responders, achieve their miracle babies.

REFERENCES

1. Tan SL, Royston P, Campbell S, Jacobs HS, Betts J, Mason B, Edwards RG: Cumulative conception and live birth rates after in vitro fertilization. Lancet 1992;339(8806):1390–1394
2. Toner JP, Philput C, Jones GS, Muasher SJ: Basal follicle stimulating hormone level is a better predictor of in vitro fertilization performance than age. Fertil Steril 1991;55(4): 784–791
3. Khalifa E, Toner JP, Muasher SJ, Acosta AA: Significance of basal (day 3) follicle stimulating hormone levels in women with one ovary in a program of in vitro fertilization. Fertil Steril 1992;57(4):835–839
4. Muasher SJ: Use of gonadotropin-releasing hormone agonists in controlled ovarian hyperstimulation for in vitro fertilization. Clin Ther 1992;(Suppl A)14:74–86
5. Brzyski RG, Jones GS, Muasher SJ: Impact of leuprolide acetate on the response to follicular stimulation for in vitro fertilization in patients with normal basal gonadotropin level. J Vitro Fert Embryo Transfer 1989;6:290–293
6. Toner JP, Brzyski RG, Oehninger S, Veeck LL, Simonetti S, Muasher SJ: Combined impact of the number of preovulatory oocytes and cryopreservation on IVF outcome. Hum Reprod 1991;6(2):284–289
7. Hofmann GE, Toner JP, Muasher SJ, Jones GS: High-dose follicle stimulating hormone (FSH) ovarian stimulation in low-responder patients for in vitro fertilization. J Vitro Fert Embryo Transfer 1989;6:285–289
8. Karande VC, Jones GS, Veeck LL, Muasher SJ: High dose follicle-stimulating hormone stimulation at the onset of the menstrual cycle does not improve the in vitro fertilization outcome in low-responder patients. Fertil Steril 1990;53: 486–489
9. Droesch K, Muasher SJ, Kreiner D, Jones GS, Acosta AA, Rosenwaks Z: Timing of oocyte retrieval in cycles with a spontaneous luteinizing hormone surge in a large in vitro fertilization program. Fertil Steril 1988;50:451–456
10. Garcia JE, Padilla SL, Bayati J, Baranki TA: Follicular phase gonadotropin-releasing hormone agonist and human gonadotropins: A better alternative for ovulation induction in in vitro fertilization. Fertil Steril 1990;53:302–305
11. Winslow KL, Toner JP, Brzyski RG, Oehninger S, Acosta AA, Muasher SJ: The gonadotropin-releasing hormone agonist stimulation test—a sensitive predictor of performance in the flare-up in vitro fertilization cycle. Fertil Steril 1991;56:711–717
12. Brzyski RG, Muasher SJ, Droesch K, Simonetti S, Jones GS, Rosenwaks Z: Follicular atresia associated with concurrent initiation of gonadotropin-releasing hormone agonist and follicle-stimulating hormone for oocyte recruitment. Fertil Steril 1988;50:917–921
13. Sims JA, Seltman HJ, Muasher SJ: The impact of early follicular serum progesterone levels on in vitro fertilization outcome utilizing a flare-up protocol with gonadotropin-releasing hormone agonist. Fertil Steril 1993 (in press)
14. San Roman GA, Surrey ES, Judd EL, Kerin JF: A prospective randomized comparison of luteal phase versus concurrent follicular phase initiation of gonadotropin-releasing hormone agonist for in vitro fertilization. Fertil Steril 1992;58:744–749

Suheil J. Muasher
The Jones Institute for Reproductive Medicine
and
Eastern Virginia Medical School
Norfolk, Virginia