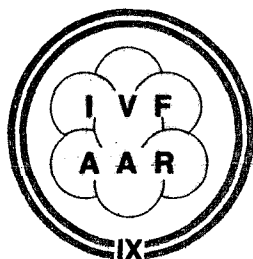


REPRINTED FROM:



WORLD CONGRESS ON IN VITRO FERTILIZATION AND ASSISTED REPRODUCTION

Vienna (Austria), April 3 - 7, 1995

Editors

A. ABURUMIEH, E. BERNAT, G. DOHR,
W. FEICHTINGER, F. FISCHL,
J. HUBER, E. MÜLLER, S. SZALAY,
W. URDL and H. ZECH

MONDUZZI EDITORE

INTERNATIONAL PROCEEDINGS DIVISION

IX

Improved pregnancy rates (PRs) in older patients or those with elevated baseline FSH levels with short flare or clomiphene-hMG hyperstimulation protocols (1)

B. SHANIS, J.H. CHECK, A. O'SHAUGHNESSY
and D. SUMMERS

UMDNJ, Robert Wood Johnson Med. School at Camden (USA)

SUMMARY

The present study compared the efficacy of two controlled ovarian hyperstimulation (COH) regimens: clomiphene citrate (CC)-human menopausal gonadotropin (hMG) vs flare-up in "poor responders" in an in vitro fertilization (IVF) program. The subjects had a day 2 or 3 serum follicle stimulating hormone (FSH) >18mIU/mL, were >38 years old, or previously demonstrated poor response to luteal phase hMG COH regimen or hMG alone. 99 women qualified as poor responders and were entered into the study; 72 received the flare-up stimulation protocol, 27 the CC/hMG protocol. Clinical and viable pregnancy rates (PRs)/retrieval were 23.6%, and 18.1% for flare vs 14.8% and 14.8% for CC/hMG (p=NS), respectively. No statistical differences were found in efficacy between the two COH regimens for poor responders in IVF.

INTRODUCTION

A poor response to controlled ovarian hyperstimulation (COH) in vitro fertilization (IVF) poses a therapeutic challenge. There are many reasons for poor responders, including problems with premature luteinization, polycystic ovaries, advanced age, or elevated baseline gonadotropins.

However, there is no consensus in the treatment of this condition. Conflicting reports in several publications have demonstrated, that in poor responders, there was an increased number of oocytes collected and increased fertilization and pregnancy rates (PRs) when using the follicular phase leuprolide acetate (LA)-human menopausal gonadotropin (hMG) (short flare-up) protocol, compared to stimulations with clomiphene citrate (CC)/hMG or hMG alone (2,3). However, other studies reported, in poor responders the luteal phase LA-hMG protocol induced a better ovarian response which resulted in higher PRs than CC/hMG stimulation (4,5). A good number of these cases were related to premature luteinization in patients who failed with CC-hMG or hMG alone.

In contrast, the study of Dor et al. (6) showed that GnRH agonist (GnRHa) in the long protocol does not seem to be superior to CC/hMG for the treatment of poor responders. However, Garcia et al. (7) reported that the short flare-up protocol gave a higher PR with a lower spontaneous abortion rate, as compared with the luteal phase leuprolide protocols.

Furthermore, in the specific instance of the older patient (age >38) or women with elevated serum FSH in the early follicular phase, the prolonged use of GnRHa may not solve the problem, but may even inhibit the response to gonadotropin stimulation (8).

At one time the Cooper Institute for IVF placed all patients undergoing their first cycle of IVF on the luteal phase LA-hMG regimen described by Meldrum et al. Several patients were found to respond poorly as far as forming mature follicles and after evaluating their characteristics we frequently found advanced age or high early follicular FSH levels in these patients.

The study presented herein compared two hyperstimulation regimens in "poor responders", which we define as patients whom 1) failed previously to stimulate with luteal phase LA-hMG or 2) have advanced age (>38 years), or, 3) have elevated FSH levels (>18 mIU/mL) in the early follicular phase.

MATERIALS AND METHODS

A total of 99 women presenting at our center for IVF-ET during the eight month period from 1/92 to 8/92, who were classified as poor responders, were prospectively randomized between two treatment groups, flare-up versus CC/hMG protocol.

The criteria for poor responders were elevated baseline FSH levels (>18 mIU/mL), advanced age (>38 yrs), or, a history of poor response to a long GnRHa suppression followed by gonadotropin stimulation protocol and/or hMG stimulation alone (<3 mature follicles). The choice of flare-up or CC/hMG was randomized by social security number - last digit even - flare-up; last two digits odd-CC/hMG; last two digits even-odd - flare-up. A total of 72 received flare-up vs 27 CC/hMG COH protocols.

In the group using the flare-up protocol (7), LA was started on the

second day of the menstrual cycle and continued until the day of hCG administration; the dosage of LA was 0.75 mg/day (weight <150 lbs) or 1.0 mg/day (weight >150 lbs).

In addition to LA, 150 IU of pure (p) FSH (Metrodin, Serono Laboratories, Randolph, MA) and 150 IU of hMG (Pergonal, Serono Laboratories, Randolph, MA) were administered daily and started on the fifth day of the patients' cycle. Thereafter, the FSH was decreased in a step-down fashion according to serum estradiol (E_2) levels and follicular development as determined by ultrasound (with an E_2 level of >300 pg/mL only 75 IU pFSH was given and it was completely eliminated and only hMG given with level of ≥ 600 pg/mL).

Clomiphene citrate/hMG protocol was started with CC 100 mg/day on day three to seven plus 75 IU of hMG on day three to six, then increased to 150 or 225 IU/day from day seven. Human menopausal gonadotropin was discontinued the day hCG was administered.

Patients were divided into groups based on the COH used (flare vs CC/hMG). The mean age, baseline sera levels, number of follicles observed, number of oocytes retrieved, fertilization rate (FR), embryos transferred, E_2 levels and endometrial thickness were compared in the two groups and tested for equality using a t-test for independent groups with a .05 level of significance.

The association between PRs and protocol used was tested using a chi-square test with a .05 level of significance. The analysis was performed initially for all retrievals completed and secondly for all transfers completed.

RESULTS AND CONCLUSIONS

There were a total of 99 retrievals performed; 72 following the flare COH, 27 following the CC/hMG protocol. There was no difference in the mean age per group (36.2 ± 4.5 years for flare, 37.2 ± 4.2 for CC/hMG). In the flare group, 43.7% of the women were ≥ 38 years of age, compared to 46.1% in the CC/hMG group.

The mean baseline sera levels were the same in both groups, as were the E_2 levels on day of hCG, endometrial thickness and day of cycle hCG was administered.

Comparison of the IVF parameters relating to oocytes and embryos yielded some differences. Per retrieval, the mean number of follicles observed, and mean number of oocytes retrieved were higher in the flare group (11.3 ± 7.9 and 9.3 ± 6.7) than the CC/hMG group (6.4 ± 4.7 and 4.3 ± 3.5). Since the FRs in both groups were the same, the mean number of embryos transferred/retrieval was higher in the flare group than in the CC/hMG group (3.3 ± 1.8 vs 2.4 ± 1.7).

The overall PRs/retrieval were 23.6% (17/72) in the flare group and 25.9% (7/27) in the CC/hMG group. Clinical PRs were 23.6% (17/72) for flare, 14.8% (4/27) for CC/hMG. Ongoing PRs were 18.1% (13/72) for flare, 14.8% (4/27) for CC/hMG. Results of the chi-square analysis showed no statistically significant difference by protocol.

The overall PRs/transfer were 27.9% (17/61) in the flare group and 30.4% (7/23) in the CC/hMG group. Ongoing PRs/transfer were 21.3% (13/61) for flare, 17.4% (4/23) for CC/hMG. Results of the chi-square analysis showed no difference in the PRs/transfer by protocol.

In the flare group, seven patients had thin endometrium (<10mm)

(9.7%) as compared to five (18.5%) of the CC/hMG group. In the flare group there were three pregnancies in which the endometrium was <10mm, 14 when the endometrium was greater \geq 10mm. In the CC/hMG group there was one pregnancy when the endometrium was <10, six when the endometrium was >10mm. There were not enough cases in which endometrial thickness was <10mm to make valid inferences.

There were 40 patients with baseline FSH levels >18 mIU/mL; 6 (15.0%) achieved viable pregnancies. The baseline FSH levels of these poor responders were 21, 23, 28, 37, 41, and 62.8 mIU/mL. The viable PR for patients with elevated FSH levels was the same for each protocol: 14.2% (1/7) for CC/hMG, 15.1% (5/33) for flare.

The 99 cycles evaluated prospectively in the present study occurred in 337 IVF cycles (29.4%) during the eight month time period of this study; only 32/99 cycles (32.3%) were actually used because of previous poor response to luteal phase LA-hMG, whereas, 67.7% were used because of advanced age and/or high FSH levels (which previously had been found to have a higher rate of poor response using luteal phase LA-hMG protocol).

Many of the early reports of "poor responders" were based on failure to respond to standard CC-hMG or hMG protocols, because of premature luteinization. The cases evaluated in the study presented herein - actual or potential poor responders to luteal phase LA-hMG stimulation carefully excluded premature luteinization as the reason for poor response. The data found that either the flare-up or CC-hMG regimen may be effective for this subset population.

REFERENCES

1. Check JH, Choe JK, Lurie D, Holzworth G. Comparison of two ovarian hyperstimulation regimens for poor responders in an in vitro fertilization program. *Infertility In Press.*
2. Howles CM, Macnamee MC, Edwards RG. Short term use of an LHRH agonist to treat poor responders entering an in vitro fertilization programme. *Hum Reprod* 2:655-656;1987.
3. Macnamee MC, Howles CM, Edwards RG, Taylor PJ, Elder KT. Short-term luteinizing hormone-releasing hormone agonist treatment: prospective trial of a novel ovarian stimulating regimen for in vitro fertilization. *Fertil Steril* 52:264-269;1989.
4. Serafini P, Stone B, Kerin J, Batzofin J, Quinn P, Marrs RP. An alternate approach to controlled ovarian hyperstimulation in "poor responders": pretreatment with a gonadotropin-releasing hormone analog. *Fertil Steril* 49:90-95;1988.
5. Cummins JM, Yovich JM, Edirisiugte WR, Yovich JL. Pituitary down-regulation using leuprolide for the intensive ovulation management of poor prognosis patients having in vitro fertilization (IVF)- related treatments. *J In Vitro Fert Embryo Transf* 6:345-352;1989.
6. Dor J, Seidman DS, Ben-Shlomo I, Levran D, Karasik A, Mashiach S.

The prognostic importance of the number of oocytes retrieved and estradiol levels in poor and normal responders in in vitro fertilization (IVF) treatment. *J Assist Reprod Genet* 9:228-232;1992.

7. Garcia JE, Padilla SL, Bayati J, Baramki TA. Follicular phase gonadotropin-releasing hormone agonist and human gonadotropins: a better alternative for ovulation induction in in vitro fertilization. *Fertil Steril* 53:302-305;1990.

8. Check JH, Adelson HG. Case Report: Opposite responses to the addition of leuprolide acetate to human menopausal gonadotropin therapy in two perimenopausal women. *Int J Fertil* 35:343-346;1990.

MONDUZZI  EDITORE

VIA FERRARESE, 119/2
40128 BOLOGNA

TEL. (051) 370337 - FAX (051) 370529
TELEX 512654 MONDBO I