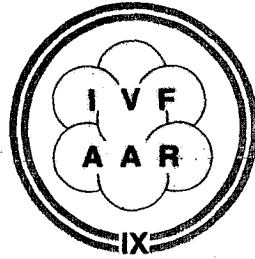


REPRINTED FROM:



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

An ultra-short use of leuprolide acetate works as well as longer use to prevent premature luteinization following controlled ovarian hyperstimulation (1)

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

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

SUMMARY

The present study evaluated whether an ultra-short course of leuprolide acetate (LA) (3 days at 1mg/day s.c.) could effectively inhibit premature luteinization following hyperstimulation with human menopausal gonadotropin for in vitro fertilization vs longer use of LA. At the time of human chorionic gonadotropin, the mean sera estradiol was 1369pg/mL and the progesterone was 1.0ng/mL in the ultra-short LA vs 1475pg/mL and 0.95ng/mL, respectively in the long LA technique. An average of 14.1 follicles were punctured with 11.3 oocytes retrieved with ultra-short LA vs 14.8 and 12.6 with long LA. An average of 28.2 amps of hMG was used with ultra-short LA vs 40.9 for long LA. The cancellation rate for premature luteinization with ultra-short LA was 3 cycles vs 0 for long LA. Failed fertilization was 7.5% for ultra-short LA and 6.0% for long LA.

INTRODUCTION

Premature luteinizing hormone (LH) surges prior to maturation of the leading follicle(s) causes premature luteinization, resulting in poor fertilization and pregnancy rates (PRs) (2). Though it may happen even in natural cycles (3), the use of ovulation stimulating drugs increases the chance of premature luteinization (2,4). Besides poor fertilization related to atresia of oocytes (5), there may also be reduced viability of the embryos when fertilization does occur (6).

Controlled ovarian hyperstimulation (COH) used for in vitro fertilization (IVF) is even more likely to cause premature luteinization. Fleming and Coutts found it in 51% of patients treated exclusively with human menopausal gonadotropin (hMG) for COH (2). Attempts to inhibit premature luteinization from COH were made using gonadotropin-releasing hormone agonists (GnRH-a); one of the first reports combined buserelin and hMG (7).

Two protocols using GnRH-a with gonadotropins have been used for COH, a long protocol where hMG is only used after complete pituitary suppression (8-10), and a short protocol where the gonadotropins are used concomitantly with GnRH-a or shortly after (11). The benefit of the latter is that the initial agonistic actions of the GnRH-a helps increase the number of follicles recruited (so called flare-up effect). A randomized study comparing the long vs short protocol found only small differences in the clinical outcome (12). There was no difference in number of oocytes obtained in short vs long protocol or estradiol (E_2) level at times of hCG. The duration of treatment and the amount of hMG employed was also similar (12).

MATERIALS AND METHODS

During a 6 month interval, all infertility patients desiring IVF-ET were offered the opportunity to participate in a prospective and randomized study in order to compare the ultra-short vs the long LA/hMG hyperstimulation protocols. Participation entailed being randomly assigned to a treatment group; one group received the ultra-short LA hyperstimulation protocol, the other receiving the long LA hyperstimulation protocol. The randomization was based on the last digit of the patient's social security number, odd received short, even assigned to long. Furthermore, patients were asked to agree to alternate the hyperstimulation regimen received if they were to require other IVF cycles in the 6 month period. Those patients who were willing to enlist in the study received a 25% reduction in the charge for IVF. The only IVF-ET patients excluded from this study were participants in our donor oocyte program.

The short LA/hMG protocol consisted of starting the GnRH-a on day 2 subcutaneously at 1 mg/day for 3 days only, and then stopped, and then starting hMG at 4 ampules (75 IU)/day on day 3. The GnRH-a for the long protocol may be administered in early follicular phase (day 1 or day 2) or in mid-luteal phase (13). The "long" leuprolide for our study was initiated in the luteal phase on day 21 and continued for at least 10 days before starting the hMG at 4 ampules/day. The hMG was not started unless the serum E_2 was $<30\text{pg/mL}$ and the serum progesterone (P) was

<1.5ng/mL. When the hMG was started, the LA was reduced to 0.5mg daily.

The efficacy of the protocols were evaluated by comparing the mean sera E_2 and P levels at the time hCG was administered; the number of ampules of hMG required; the number of failed IVF cycles due to premature luteinization; the number of failed IVF cycles due to zero fertilization; the mean number of follicles punctured; mean number of oocytes recovered; mean number of embryos transferred; mean number of embryos available for cryopreservation; the mean survival rate after thawing; and, finally, the number of pregnancies and subsequent live births realized. An IVF cycle was considered to result in pregnancy only if the Beta hCG level reached 5000mIU/mL and a gestational sac was seen on ultrasound.

Statistical analysis of the data from the first IVF cycle included Student's t-tests to compare the mean sera E_2 , and P levels, number of follicles punctured, number of eggs retrieved, fertilization rate, number of embryos transferred, and the number of ampules of hMG administered between the two treatment protocols; chi-square analysis to compare the PRs. For those patients undergoing two IVF cycles, one with the short protocol and one with the long protocol, statistical comparison between the results of their two cycles were performed using paired t-tests and McNemar's test for related proportions. A .05 level of significance was used.

RESULTS AND CONCLUSIONS

One hundred and six women entered this study in the 6 month interval. Fifty-six underwent IVF using the long LA/hMG protocol (long), 50 underwent IVF using the ultra-short LA/hMG protocol (short). Fourteen of the women underwent a second IVF cycle within the 6 month study period in which they used the alternate hyperstimulation protocol used in the first cycle. The average age for the women in the group using the long protocol was 33.7 (± 4.06) years, as compared to 34.1 (± 4.79) for those in the short protocol group. The average number of previous IVF cycles where a successful pregnancy did not occur was .3 for those in the long protocol group, and 1.1 for those in the short protocol group.

Two cycles were cancelled for premature luteinization in the group receiving ultra-short LA vs none with long LA. The mean sera E_2 and P levels at the time of hCG were the same in both treatment groups. There were also no differences in the mean number of follicles punctured, oocytes retrieved, fertilization rates, or number of embryos transferred in the two groups. Neither technique provided any advantage for cryopreserving additional embryos.

There were 4 pregnancies in the short group and 9 pregnancies in the long group. Allowing for abortions, the live birth rate was 8.8% for short vs 12.96% for long.

A previous prospective randomized study was published comparing the long to the short flare-up protocol using LA as the agonist (12). In contrast to Frydman et al.'s data, Garcia et al. found a reduction in the amount of pure FSH and hMG used with the short vs long protocol (14). They found an average difference of 11 ampules between short (lowest) and long protocol (14), and we found a difference of somewhat over 12

ampules. Other researchers have also found that when GnRH-a is added to hMG therapy more of the latter is required to accomplish follicle maturation (15). The use of the ultra-short protocol would have saved the patient at least \$500 per cycle in the United States.

Our data found a very small incidence of premature luteinization with the ultra-short protocol (and no significant difference from the long one) using LA as the GnRH-a, thus supporting the conclusions from Bourn Hall using the ultra-short protocol with buserelin as the GnRH-a (16). These two data suggest that in early follicular phase a mere 3 days of use of GnRH-a is all that is necessary to inhibit premature luteinization. A randomized study comparing ultra-short protocols to flare-up is needed to determine whether the ultra-short protocol offers any other benefits than reduction in frequency of GnRH-a injections and reduced cost of GnRH-a.

REFERENCES

1. Check JH, Nowroozi K, Chase JS. Comparison of short versus long-term leuprolide acetate-human menopausal gonadotrophin hyperstimulation in in-vitro fertilization patients. *Hum Reprod* 7:31-34;1992.
2. Fleming R, Haxton MJ, Hamilton MP, McCure GS, Black MP, MacNaughton MC, Coutts JR. Successful treatment of infertile women with oligomenorrhea using a combination of LHRH agonist and exogenous gonadotrophins. *Br J Obstet Gynaecol* 92:369-373;1985.
3. Check JH, Chase JS, Nowroozi K, Dietterich C. Premature luteinization: treatment and incidence in natural cycles. *Hum Reprod* 6:190-193;1991.
4. Zimmerman R, Buhnet HW, Weise HC, Leidenberger FR. Preliminary report about a modified gonadotropin (human menopausal gonadotropin/human chorionic gonadotropin). Treatment in infertile patients with premature luteinization. *Fertil Steril* 41:714-718;1984.
5. Lobo RA, diZerega GS, Marrs RP. Follicular fluid steroid levels in dysmature and mature follicles from spontaneous and hyperstimulated cycles in normal and anovulatory women. *J Clin Endocrinol Metab* 60:81-87;1985.
6. Stanger JD, Yovich JL. Reduced in-vitro fertilization of human oocytes from patients with raised basal luteinizing hormone levels during the follicular phase. *Br J Obstet Gynaecol* 92:385-393;1985.
7. Porter RN, Smith W, Craft IL, Abdulwahid NA, Jacobs HS. Induction of ovulation for in vitro fertilization using buserelin and gonadotropins. *Lancet* 2:1284-1285;1984.
8. Neveu S, Hedon B, Bringer J, Chinchole MM, Arnal F, Humeau C, Cristol P, Viala JL. Ovarian stimulation by a combination of a gonadotropin-releasing hormone agonist and gonadotropins for in vitro fertilization. *Fertil Steril* 47:639-643;1987.
9. Smitz J, Devroey P, Braeckmans P, Camus M, Khan I, Staessen C, Van Waesberghe L, Wisanto A, Van Steirteghem AC. Management of failed cycles in an IVF/GIFT programme with the combination of a GnRH analogue and hMG. *Hum Reprod* 2:309-314;1987.
10. Wildt L, Diedrich K, Van Der Ven H, Hasani SA, Hubner H, Klasen R. Ovarian hyperstimulation for IVF controlled by GnRH agonist administered in combination with human menopausal gonadotropin. *Hum Reprod* 1:15-19;1986.

11. Barriere P, Lopes P, Boiffard JP, Pousset C, Quentin M, Sagot P, L'hermine A, Lerat MF, Charbonnel B. Use of GnRH analogues in ovulation induction for in vitro fertilization: benefit of a short administration regimen. *J In Vitro Fert Embryo Transfer* 4:64-65;1987.
12. Frydman R, Belaisch-Allart J, Parneix I, Forman R, Hazout A, Testart J. Comparison between flare up and down regulation effects of luteinizing hormone-releasing hormone agonists in an in vitro fertilization program. *Fertil Steril* 50:471-475;1988.
13. Meldrum DR, Wisot A, Hamilton F, Gutlay AL, Kempton W, Huynh D. Routine pituitary suppression with leuprolide before ovarian stimulation for oocyte retrieval. *Fertil Steril* 51:455-459;1989.
14. 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.
15. Lewinthal D, Taylor PJ, Pattinson HA, Corenblum B. Induction of ovulation with leuprolide acetate and human menopausal gonadotropin. *Fertil Steril* 49:585-588;1988.
16. Macnamee MC, Howles CM, Edwards RG, Taylor PJ, Elder KT. Short-term luteinizing hormone-releasing hormone agonist treatment: prospective trial of a novel ovarian stimulation regimen for in vitro fertilization. *Fertil Steril* 52:264-269;1989.

MONDUZZI  EDITORE

VIA FERRARESE, 119/2
40128 BOLOGNA

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