

Ovarian hyperstimulation can reduce uterine receptivity.

A case report

J. H. Check, J. K. Choe, A. Nazari, D. Summers-Chase

*The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden,
Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology,
Division of Reproductive Endocrinology & Infertility, Camden, New Jersey (USA)*

Key words: Ovarian hyperstimulation; Adverse uterine environment; Embryo cryopreservation; Deferred transfer.

Introduction

A previous study of viable pregnancy rates (PRs) after six months of therapy for women with luteal phase defects with normal follicular maturation found that progesterone (P) supplementation in the luteal phase was far more efficacious than clomiphene citrate or human menopausal gonadotropins (hMG) (74% vs 4%) [1]. Interestingly, during a second 6-month therapeutic trial, 60% of those women failing to conceive during the first 6-month trial of follicle maturing drugs had a viable pregnancy following P treatment [1]. The markedly different PRs may have been solely secondary to follicle maturing drugs not being sufficient to correct luteal phase deficiency when the follicle is mature, or possibly the follicle maturing drugs may have somehow created a hostile uterine environment.

Support for the concept that follicle maturing drugs may create a hostile uterine environment was provided by a shared oocyte study demonstrating twice the PR per transfer in oocyte recipients than the donors who provided the oocytes [2]. The medication and not merely a more intrinsic hostile uterine environment in donors versus recipients was suggested by subsequent PRs following frozen embryo transfer (ET) which was similar in both donors and recipients [2]. The same conclusions were reached in another comparative study of a shared oocyte program only this time the donors had salpingectomies for hydrosalpinges if present [3].

The case presented here provides further support for the concept that follicle maturing drugs may create an environment that is not conducive for implantation.

Case Report

A 38-year-old woman presented with a 10-year history of primary infertility. She had oligomenorrhea with irregular menses and was diagnosed as having polycystic ovarian syndrome based on ultrasound findings, hirsutism with mild androgen elevations, and a 2:1 luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio. She had been treated for infertility for all 10 years. A hysterosalpingogram and laparoscopy showed normal tubes, absence of endometriosis, and con-

firmed the diagnosis of polycystic ovaries. The semen analysis was normal as were post-coital tests. After failing to conceive after many cycles of ovulation induction with clomiphene citrate and gonadotropins she tried in vitro fertilization (IVF). She failed to conceive despite 10 IVF cycles including the last 6 cycles where 12 embryos were transferred (in the first four cycles a total of 20 embryos were transferred). Each cycle the patient had a tendency to hyperstimulate and in 2 cycles she had a full blown syndrome of ovarian hyperstimulation syndrome (OHSS).

She decided to try another cycle of IVF at our IVF center. To minimize the risk of OHSS, and because we hypothesized that the gonadotropins could have produced a hostile uterine environment for implantation, we planned to cryopreserve all embryos for subsequent frozen ET.

The patient was treated with .05 mg once daily of leuprolide acetate from day 2 of her menstrual cycle with 150 U hMG (Humegon, Organon Inc.) in the p.m. and 150 U recombinant FSH (Gonal-F, Serono Inc.) from day 4. After 5 days the hMG was reduced to 75 U and on day 14, the last day of gonadotropin therapy, she was reduced to 75 U of each. Her serum estradiol level was 4,512 pg/mL on the day that 10,000 U human chorionic gonadotropin was given IM.

There were 38 eggs (all deemed mature) retrieved; 28 were fertilized and 27 of these were fertilized and frozen at the 2-pronuclear stage. The embryos were cryopreserved and thawed using a simplified freezing technique with a one-step removal of cryoprotectant [4]. All embryos had assisted embryo hatching performed prior to transfer [5-8].

The patient was treated with a graduating dose of oral micronized estradiol beginning at 2 mg x 5 days from day 2 of the cycle then 4 mg x 4 days, then 6 mg for 5 days when the estradiol dosage stayed the same and P in the form of 200 mg vaginal suppositories was started twice daily along with 100 mg IM daily.

Eight embryos were thawed and 5 were transferred. Two embryos cleaved to 7 cells within 72 hours with $\leq 25\%$ fragmentation, one 6-cell embryo with $< 25\%$ fragmentation, and a 5-cell with 50% fragmentation and one 2-cell embryo with 50% fragmentation. She conceived that cycle and successfully delivered a viable full-term child.

Discussion

The woman described previously had 92 embryos transferred on stimulated cycles and none implanted. It is the equivalent of 30 embryo transfer cycles in most IVF centers. Thus it seems highly unlikely that her conceiving

Revised manuscript accepted for publication May 15, 2000

on the first frozen transfer of 5 frozen/thawed embryos, without ovarian hyperstimulation, resulting in a successful pregnancy, was merely fortuitous. Hence, this case clearly demonstrates that in some women the stimulation of multiple follicles for the purpose of oocyte retrieval may create a hostile environment for implantation. Though there have been other data supporting this concept (mostly using data comparing PRs in recipients versus donors) [2, 3, 9, 10], other researchers did not reach the same conclusions [11, 12].

Previous data showed that the main androgen to rise following controlled ovarian hyperstimulation for IVF was androstenedione but this was not associated with a decrease in PRs [13]. However, possibly the androgen levels are more important in cases of polycystic ovarian syndrome [14-16]. Androgens were not measured during any of the controlled ovarian hyperstimulation cycles in this patient.

It is clear that the case presented herein, a 38-year-old woman who had 38 eggs retrieved with the serum estradiol over 4000 pg/mL, was clearly a high responder. Some researchers suggest that the women most likely to develop a problem with uterine receptivity are the high responders [10], related to high estradiol and progesterone levels in the pre-implantation period. The same group has claimed to improve receptivity by using a FSH step-down regimen to decrease the pre-implantation serum estradiol levels [17]. However, based on this case report, a more appropriate option may be to defer transfer and cryopreserve all embryos. This maneuver may not only improve the implantation rate, but would significantly reduce the risk of severe ovarian hyperstimulation syndrome.

Decreased uterine receptivity may not necessarily be related to high estradiol and P levels in the pre-implantation period seen in high responders [18]. There has been some data presented that suggested that the use of follicle stimulating drugs may adversely affect uterine receptivity even in non-IVF cycles where the attempt was not to hyperstimulate but to stimulate only one mature follicle if possible [1]. Recent data show that implantation failure may be associated with the failure to develop a homogeneous hyperechogenic (HH) endometrial echo pattern 3 days after transfer in stimulated cycles [19]. Though high responders most likely elected to have fresh ET deferred, this study suggests that other patients than high responders may also be subject to uterine receptivity defects [19].

Based on the success of this case with frozen ET, and the aforementioned study of showing lower implantation rates with the mid-luteal non-HH echo pattern, we are presently engaged in a prospective study where normal or low responders who demonstrate a non-HH pattern 3 days after transfer will be randomized to another fresh ET vs cryopreservation of all embryos with deferring transfer to 2 months later. Unfortunately, this study could only include patients who had no frozen embryos available for transfer after the first IVF-ET cycle. This study will take a long time to complete since most patients have some frozen embryos available after their first IVF-ET

cycle. Hopefully, this case report will encourage some other IVF centers to join together with this prospective study so that the question of whether frozen ET can be an answer to uterine receptivity problems in stimulated cycles can be more definitively answered.

References

- [1] Check J. H., Nowroozi K., Wu C. H., Adelson H. G., Lauer C.: "Ovulation-inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects". *Int. J. Fertil.*, 1988, 33, 252.
- [2] Check J. H., O'Shaughnessy A., Lurie D., Fisher C., Adelson H. G.: "Evaluation of the mechanism for higher pregnancy rates in donor oocyte recipients by comparison of fresh with frozen embryo transfer pregnancy rates in a shared oocyte programme". *Hum. Reprod.*, 1995, 10, 3022.
- [3] Check J. H., Choe J. K., Katsoff D., Summers-Chase D., Wilson C.: "Controlled ovarian hyperstimulation adversely affects implantation following in vitro fertilization-embryo transfer". *J. Assist. Reprod. Genet.*, 1999, 16, 416.
- [4] Baker A. F., Check J. H., Hourani C. L.: "Survival and pregnancy rates of pronuclear stage human embryos cryopreserved and thawed using a single step addition and removal of cryoprotectants". *Hum. Reprod. Update*, 1997, 2 (CD-ROM).
- [5] Cohen J., Elsner C., Kort H., Malter H., Massey J., Mayer M. P. et al.: "Impairment of the hatching process following IVF in the human and improvement of implantation by assisted hatching using micromanipulation". *Hum. Reprod.*, 1990, 5, 7.
- [6] Tucker M. J., Cohen J., Massey J. B., Mayer M. P., Wiker S., Wright G.: "Partial zona dissection of the zona pellucida of frozen thawed human embryos may enhance blastocyst hatching, implantation, and pregnancy rates". *Am. J. Obstet. Gynecol.*, 1991, 165, 341.
- [7] Cohen J., Alikani M., Trowbridge J., Rosenwaks Z.: "Implantation enhancement by selective assisted hatching using zona drilling of human embryos with poor prognosis". *Hum. Reprod.*, 1992, 7, 685.
- [8] Check J. H., Hoover L., Nazari A., O'Shaughnessy A., Summers D.: "The effect of assisted hatching on pregnancy rates after frozen embryo transfer". *Fertil. Steril.*, 1996, 65, 254.
- [9] Paulson R. J., Sauer M. V., Lobo R. A.: "Embryo implantation after human in vitro fertilization importance of endometrial receptivity". *Fertil. Steril.*, 1990, 53, 870.
- [10] Simon C., Cano F., Valbuena D., Remohi J., Pellicer A.: "Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients". *Hum. Reprod.*, 1995, 10, 2432.
- [11] Meldrum D. R.: "Female reproductive aging-ovarian and uterine factors". *Fertil. Steril.*, 1993, 59, 1.
- [12] Al-Khatib R. A., Fakh H.: "Artificial hormonal replacement cycles have no advantage over hyperstimulated cycles in a gamete intrafallopian transfer oocyte donation program". *Fertil. Steril.*, 1995, 63, 1255.
- [13] Check J. H., Nowroozi K., Chase J. S., Dieterich C.: "Effect of increased mid-cycle androgen levels following controlled ovarian hyperstimulation during IVF on fertilization/pregnancy rates". *ARTA*, 1991, 3, 85.
- [14] Dupon C., Rosenfield R. L., Cleary R. E.: "Sequential changes in total and free testosterone and androstenedione in plasma during spontaneous and clomid-induced ovulatory cycles". *Am. J. Obstet. Gynecol.*, 1973, 115, 478.
- [15] Lawrence D. M., McGarrigle H. H. G., Radwanska E., Swyer G. M.: "Plasma testosterone and androstenedione levels during monitored induction of ovulation in infertile women with "simple" amenorrhoea and with the polycystic ovary syndrome". *Clin. Endocrinol.*, 1976, 5, 609.
- [16] Schumert Z., Spitz I., Diamant Y., Polishuk W. Z., Rabinowitz D.: "Elevation of serum testosterone in ovarian hyperstimulation syndrome". *J. Clin. Endocrinol. Metab.*, 1975, 40, 889.

- [17] Simon C., Garcia Velasco J. J., Valbuena D., Peinado J. A., Moreno C., Remohi J. *et al.*: "Increasing uterine receptivity by decreasing estradiol levels during the preimplantation period in high responders with the use of a follicle-stimulating hormone step-down regimen". *Fertil. Steril.*, 1998, 70, 234.
- [18] Pellicer A., Valbuena D., Cano F., Remohi J., Simon C.: "Lower implantation rates in high responders: evidence for an altered endocrine milieu during the preimplantation period". *Fertil. Steril.*, 1996, 65, 1190.
- [19] Check J. H., Dieterich C., Lurie D.: "Non-homogeneous hyperendogenous pattern three days after embryo transfer associated with lower pregnancy rates". *Hum. Reprod.*, In press.

Address reprint requests to:
 JEROME H. CHECK, M.D., Ph.D.
 7447 Old York Road
 Melrose Park, PA 19027 (USA)

European Academy of Gynaecological Cancer
European Society of Gynaecological Oncology

CONTINUING MEDICAL EDUCATION

BUDAPEST, HUNGARY

December 1-2, 2000

Applied surgical anatomy for gynaecological oncologists: basic and advanced surgical elements

FRIDAY DECEMBER 1, 2000

Opening address Péter Bősze (Hungary)

Session 1

Surgical elements beyond the scalpel, Moderator *László Vimpláti (Hungary)* - Preoperative assessment, cellular response to surgical trauma, intraoperative and postoperative fluid and electrolyte balance, *László Vimpláti (Hungary)* - Preoperative preparation, *Attila Artnér (Hungary)* - Physiology of management of the postoperative patient, *Hugh H. Allen (Canada)* - Wound healing and suture materials, *Róbert Póka (Hungary)*.

Session 2

Anatomy of the parametrium and paracolpium as it relates to radical hysterectomy, Moderator *Péter Bősze (Hungary)* - Anatomy of the parametrium/paracervix and paracolpium: classification of the cardinal ligament excision (e.g. "paracervical lymphadenectomy"), *Daniel Dargent (France)* - Anatomy and definition of radical hysterectomy (Piver) classification, *László Ungár (Hungary)* - Proximal, modified radical hysterectomy: anatomical considerations, *Javier Magrina (USA)*.

Session 3

Anatomy of the pelvic side wall: surgical relevance, Moderator *John H. Shepherd (UK)* - Introduction, *John H. Shepherd (UK)* - Anatomy of the pelvic side wall as seen by a vascular surgeon, *Csaba Dzsinih (Hungary)* - Technique of pelvic wall clearance, *László Pálfalvi (Hungary)*.

Session 4

Anatomy of the pelvic nodes and their relevance to cervical, endometrial and ovarian carcinoma, Moderator *Raimund Winter (Austria)* - Anatomy and classification of the pelvic lymph nodes, *Raimund Winter (Austria)* - How do I do the pelvic lymphadenectomy in cervical, endometrial and ovarian carcinoma?, *John H. Shepherd (UK)*, *László Pálfalvi (Hungary)* and *Attila Artnér (Hungary)* - Discussion.

Session 5

Anatomy of the paraaortic nodes and their relevance to cervical, endometrial and ovarian carcinoma, Moderator *László Ungár (Hungary)* - Anatomy and classification of the paraaortic lymph nodes, *László Pálfalvi (Hungary)* - How do I do the paraaortic lymphadenectomy in cervical, endometrial and ovarian carcinoma?, *Raimund Winter (Austria)*, *Javier Magrina (USA)*.

SATURDAY DECEMBER 2, 2000

Session 6

Anatomy for creating urinary pouches, Moderator *Javier Magrina (USA)* - Indiana pouch, *Javier Magrina (USA)* - Ilium conduit, *Hugh H. Allen (Canada)* - The Budapest pouch, *László Ungár (Hungary)*.

Session 7

Anatomy of the vulva and groin nodes: surgical relevance, Moderator *Daniel Dargent (France)*, Anatomy of the vulva as relates to the excision of the primary tumor, *Daniel Dargent (France)*, Anatomy of the groin as relates to lymph node dissection, *Péter Bősze (Hungary)* - Flaps used for vulvar reconstruction, *Hugh H. Allen (Canada)*.

Session 8

Approach to difficult pelvic tumors, Moderator *Hugh H. Allan (Canada)*, Methods of approach to spleen and liver, *Hugh H. Allan (Canada)*, The way I remove a fixed pelvic mass and ovarian metastases in the upper abdomen: technical and anatomical considerations, *Daniel Dargent (France)*, *John H. Shepherd (UK)*, *Javier Magrina (USA)*.

Show from the operating theatre Case-debate. *Hugh H. Allen (Canada)*.

Closing remarks. *Hugh H. Allen (Canada)*

INFORMATION: Péter Bősze, M.D.

1301 Budapest, PO. Box 46, Fax 36 1 4290318,
 E-mail bosze@mail.matav.hu or mail@primed-x.hu

Free of charge