Medical and psychological management of recurrent abortion, history of postneonatal death, ectopic pregnancy and infertility: successful implementation of IVF for multifactorial reproductive dysfunction. A case report

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Summary

The medical and psychological treatment for a 37-year-old Caucasian G_6 P_{1051} woman who presented for evaluation of secondary infertility and recurrent pregnancy loss is described. Although one living child had been conceived without medical assistance, that delivery preceded the present evaluation by ten years and involved a different partner. With the current husband, the patient had two miscarriages and a left ectopic pregnancy. The couple had attempted controlled ovarian hyperstimulation and *in vitro* fertilization (IVF) elsewhere, but the cycle was cancelled due to poor follicular response. About one year before consultation at our institution, the couple established a pregnancy although the infant was born at 24 weeks with a cardiac anomaly, living only 40 days. Additionally, a persistent cervical lesion required cone biopsy before any fertility treatment could resume. Andrology evaluation found the husband's sperm DNA fragmentation index to be 48.6%. This constellation of stressors represented substantial emotional issues and psychological therapy/counseling was recommended. After obtaining psychological clearance, the couple underwent IVF and 16 oocytes were retrieved. Four embryos were transferred, and a healthy male infant was delivered at term. Although multifactorial infertility can be associated with very poor reproductive outcomes, the advanced reproductive technologies merit consideration during management of complex clinical challenges. Standard IVF strategies can be optimized by inclusion of thorough psychological assessment and counseling.

Key words: Infertility; Recurrent abortion; Maternal age; Sperm DNA fragmentation.

Introduction

The potentially adverse emotional impact of infertility and the assisted reproductive technologies engaged for its treatment have been described by numerous investigators [1-4]. Although the psychological stress associated with in vitro fertilization (IVF) may be profound even when the cause of infertility is known [5], patients have reported emotional anguish in the context of unexplained infertility as well. Whether or not the presence of multiple independent infertility factors is associated with differing levels of emotional stress is controversial, although the negative psychological impact of recurrent pregnancy loss has been confirmed by others [6, 7]. In this report, we chronicle the medical and psychological management of a couple referred for infertility consultation where several infertility factors were identified-any one of which alone might diminish reproductive outcome. Here we describe how a healthy term singleton delivery was achieved in the context of advanced reproductive technologies, with focused attention to the couple's emotional needs.

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Case Report

Clinical history

In April 2001, a 36-year-old nonsmoking Caucasian G_6P_{1051} woman presented to our center with her husband for reproductive endocrinology consultation to discuss infertility/recurrent pregnancy loss. A hysterosalpingogram two years earlier confirmed bilateral tubal patency and normal intrauterine contours. She was in good general health and the past medical history was unremarkable. The patient's obstetrical history included two unassisted conceptions, both commissioned by the first husband. The initial pregnancy was electively terminated early in the 1st trimester without complications in 1986. A term vaginal delivery of a healthy female infant occurred four years later. By 1996, the patient had remarried and achieved a third conception although this pregnancy was lost spontaneously in the 7th gestational week. No D&C was performed and a specific cause for the miscarriage was not identified.

Fertility treatments required postponement when low-grade cervical dysplasia was identified via Pap test and colposcopy. Trichloroacetic acid and cryoablation was performed and the lesion resolved. In February 1998, the patient had established her fourth unassisted pregnancy, although this was diagnosed initially as a 'left tubal pregnancy'. Further evaluation determined that the pregnancy was intrauterine, but no fetal cardiac activity was ever documented. The diagnosis was therefore revised to 'missed 1st trimester abortion' and the patient underwent laparoscopy/D&C without complications.

By November 1998, a fifth pregnancy was accomplished after a single 5-day course of ovulation induction with clomiphene citrate (100 mg/d). This was indeed an ectopic pregnancy situated within the left fallopian tube, and laparoscopic linear salpingostomy/ectopic excision was performed. After three additional failed pregnancy attempts with her current partner, the patient elected to pursue clomiphene therapy followed by controlled ovarian hyperstimulation and IVF. The clomiphene cycles failed, and IVF was cancelled prior to oocyte retrieval due to poor follicular response.

In November 2000, a sixth pregnancy was established (unassisted conception) and a single intrauterine pregnancy with fetal cardiac activity was identified in the first trimester. Genetic amniocentesis was performed at 19 weeks' gestation. However, six days later the patient began to note gradually increasing vaginal bleeding and 'leaky fluid'. An air ambulance was chartered and the patient was immediately flown from Istanbul to London, where a baby girl was delivered (birth weight = 650 g) in critical condition at 24 weeks' gestation. Although neonatal assessment found patent ductus arteriosus and emergency cardiac repair was performed, the baby died at age 40 days. Four months later, the couple presented in Atlanta for a second opinion and therapy.

Diagnostic evaluation

Pretreatment psychological assessment included a demographic review and a summary of the marital history. The couple provided a narrative in which both strengths and weaknesses of their relationship were recorded, with special emphasis on discussing how their relationship had evolved during the challenges of infertility, ectopic pregnancy, miscarriage and death of their baby. It was felt important to confirm that they had reached closure in the grieving process after the loss of their infant daughter, to clarify how they had reached the decision to undergo their first IVF treatment, and to explore why they felt it necessary to try such therapy again despite the profound emotional strains associated with the first cycle elsewhere. Given the anguish following earlier fertility treatments, and with our acknowledgement that we could not guarantee a successful outcome after IVF at our institution, the couple were asked about their level of preparation regarding yet another disappointment. Risk of multiple gestation in the context of IVF was also discussed, and the couple developed a unified opinion on their willingness to undergo selective reduction if advised by a perinatologist. Counseling also evaluated any religious or ethical issues that could complicate IVF including registering the couple's directives for cryopreservation of any non-transferred embryos for future use, if applicable.

Screening found no mood/affect disorders in either partner, and we developed a detailed psychiatric history that failed to identify any addictive problems, sexual trauma, phobias to needles and/or surgery, or anxiety associated with office semen collection required in parallel to oocyte retrieval. The couple was also asked about their family support system and we ascertained their need for affirmation from others concerning IVF. Availability of friends/family to offer support during treatment was queried, as well as their anticipated ability to balance the special needs of IVF therapy (*e.g.*, time missed from work for office visits, blood tests, sonograms, etc.). We were careful to disclose the need for restriction of sexual activity during certain phases of IVF treatment (*i.e.,* protected or no intercourse for the month prior to and immediately following embryo transfer until serum hCG measurement), and the couple expressed understanding of this policy. We also explored what (if any) plans the couple might have to disclose the role of IVF in the birth(s) of any children conceived using this technology, and if that private decision would also be shared with friends, family, or colleagues. From these data, a comprehensive report itemizing all relevant psychological factors was compiled and reviewed by nursing and medical staff at our institution.

Physical examination of the female was unremarkable; her BMI was 28 kg/m^2. Blood type was O positive and rubella immunity was confirmed by immunoassay. Ovarian reserve was estimated by cycle day #3 serum FSH and E_2 measurements which were 6.0 mIU/ml and 15 pg/ml, respectively. This was corroborated by a serum inhibin-β of 167 pg/ml. Hysterosalpingogram films were reviewed and no intrauterine abnormalities were noted. While other basic laboratory test results were within the normal reference range, the patient was found to have a previously undetected heterozygous mutation for the prothrombin G20210A allele [8]. Genetic counseling was offered to discuss the significance of this abnormality. Concurrently, another cervical intraepithelial lesion was identified on Pap test and gynecologic oncology consultation was again engaged. Definitive therapy with cone biopsy was undertaken with clear margins on excision.

The partner took no daily medications and was also in good general health. Semen analysis showed no evidence of infection or inflammation. The overall spermatozoa concentration was 52 M/ml. Sperm motility was 43% and normal forms morphology was 20% (strict criteria). For the 5.1 ml sample submitted for analysis, the absolute spermatozoa count (forward progressive motility) was ~114 million. Although high DNA stainability was normal at 9.3%, sperm chromatin structure assay [9] suggested a poor fertility prognosis with DNA fragmentation at 48.6%. A specific cause for the sperm chromatin abnormality could not be identified after formal urology consultation. Due to the elevated sperm DNA fragmentation, use of anonymous donor sperm was offered as an alternative gamete source (in the event that the husband's specimen was unsuitable for use during treatment), but this option was declined.

Treatment approach

In November 2001, ovulation induction commenced at our institution with 300 IU/d rec-FSH (Gonal-F®, Serono Laboratories Inc.; Rockland, MA). Terminal serum E2 was 1191 pg/ml, and three follicles with mean diameter ≥ 17 mm were noted on transvaginal sonogram after 8 days of gonadotropin therapy. Timed intercourse occurred within 30 hours of 10,000 IU hCG, injected subcutaneously [10], but no pregnancy occurred. Five months later the couple started IVF after pituitary downregulation with 5 IU/d leuprolide acetate (Lupron®, TAP Pharmaceuticals; Lake Forest, IL). Downregulation was discontinued on the fourth day of gonadotropin treatment, when serum $E_2 > 200$ pg/ml. Ovulation induction followed a "step-down" protocol beginning with 225 IU/d rec-FSH + 150 IU/d hMG (Repronex®, Ferring Pharmaceuticals; Albuquerque, NM), with use of hMG alone as follicular recruitment concluded. Gonadotropin therapy was accompanied by oral aspirin (81 mg/d) and heparin (10,000 IU/d), the latter given as divided daily subcutaneous injections.

Following a 10-day ovarian stimulation phase, terminal E_2 was 1959 pg/ml and hCG was administered when six follicles reached ≥ 17 mm mean diameter (total follicle count was approximately 14). Transvaginal ultrasound-guided needle aspiration yielded 16 oocytes, although only seven were developmentally mature. These fertilized normally *(2pn)* by conventional insemination; donor sperm was not used. On the third post-fertilization day, four embryos (4,4,5,7-cell stage) were placed *in utero* via a 6.8 Fr transcervical catheter (Echotip®, Cook IVF; Bloomington, IN) with abdominal sonographic

guidance. No assisted-embryo hatching was performed and none of the non-transferred embryos were of sufficient quality to warrant cryopreservation. Supplementary progesterone and estrogen were administered post-transfer as previously described [11].

Two weeks after embryo transfer, serum hCG was 164 mIU/ml and progesterone was 35.5 ng/ml; 48 hours later, serum hCG was 273 mIU/ml. The patient returned at ~six weeks' gestation for a transvaginal sonogram, and a single intrauterine gestational sac with one fetal pole (cardiac rate = 153/min) was identified. There was no vaginal bleeding or uterine cramping following examination, and the obstetrical course proceeded without complications. Although estrogen and progesterone were discontinued after the 12th gestational week, heparin + aspirin therapy was maintained without dosage adjustment until five days before delivery with no adverse effects. For this pregnancy, a genetic amniocentesis was not done. At $38^{1}/_{2}$ weeks' gestation, a spontaneous vaginal delivery occurred resulting in the birth of a healthy 3,288 g male infant (Apgar 9 and 9, at 1 min and 5 min). Both mother and baby were discharged home in good condition following two days of hospitalization; they continue to do well eight months later.

Discussion

Optimal management of multifactorial infertility represents an important clinical challenge for reproductive endocrinologists. Previous investigators have surveyed the emotional stress associated with infertility [12], ectopic pregnancy loss [13], recurrent miscarriage [6], and death of a newborn [14]. That men and women process the stress of infertility in different ways has also been recognized in earlier research [15]. Evoking severe anxieties for many patients, these factors require clinical competencies that go well beyond technical proficiency in ovulation induction, oocyte retrieval, or embryo transfer. The present report illustrates ho advanced reproductive technologies – in concert with comprehensive and compassionate psychological counseling – form the basis of successful fertility therapy resulting in a satisfactory outcome.

Psychological counseling for couples about to undergo assisted-reproductive treatments may follow several formats, but should always attempt to capture the relevant aspects of both partners' emotional condition before IVF begins. At our institution, a meeting for at least an hour with a licensed clinical psychologist is required of most couples to accomplish this. Assessments obtained from such consultations are summarized for easy entry to the record for review by the medical and nursing team.

This couple presented to our institution already aware of several issues that prefigured a poor pregnancy outcome. Perhaps more importantly however, additional findings were discovered during evaluation that required further interpretation, counseling and treatment. Specific concerns were the detection of a premalignant cervical lesion, the identification in the partner of a high sperm chromatin fragmentation index, and the awareness that the female had a genetic mutation associated with a hypercoagulable condition – the latter two representing potential independent causes for spontaneous abortion.

Clinical application of prophylactic heparin and/or aspirin for thrombophilic conditions during pregnancy has been described previously [16, 17], although their implementation in this case could be regarded as a liberal use of these reagents given the equivocal nature of the abnormality identified (*e.g.,* heterozygous prothrombin gene mutation). Accordingly, the use of heparin and low-dose aspirin in this setting was carefully discussed with the couple and they agreed to this treatment. While aspirin therapy near term is generally not recommended, in this case ongoing perinatal assessments judged its extended use acceptable. The couple's choice not to have anonymous donor sperm available in the event of (partner) specimen inadequacy at the time of oocyte retrieval was deliberate, but not without risk. Fortunately this contingency was not realized. Indeed, the husband's fresh semen parameters on the day of oocyte retrieval were of sufficient quality that intracytoplasmic sperm injection was considered unnecessary. Although the risk of chromosomal anomalies among parturients at age ≥ 35 is well-known, for this pregnancy our couple understandably declined genetic amniocentesis because of their previous experience.

In summary, medical and psychological therapies in reproductive medicine are complementary and approach complex clinical problems from different vantage points. When properly integrated, a clinicopsychological treatment plan as portrayed in this report can enable a successful outcome even when the challenges are complex and initially appear hopeless.

References

[1] Taymor M.L., Bresnick E.: "Emotional stress and infertility". *Infertility,* 1979, *2,* 39.

[2] Zucker A.N.: "The psychological impact of reproductive difficulties on women's lives". *Sex Roles,* 1999, *40,* 767.

[3] Jakobovits A.A., Szekeres L.: "Interactions of stress and reproduction – a personal view". *Zentralbl. Gynakol.*, 2002, *124,* 189.

[4] Hjelmstedt A., Widstrom A.M., Wramsby H. *et al.*: "Personality factors and emotional responses to pregnancy among IVF couples in early pregnancy: a comparative study". *Acta Obstet. Gynecol. Scand.,* 2003, *82,* 152.

[5] Lee T.Y., Sun G.H., Chao S.C.: "The effect of an infertility diagnosis on the distress, marital and sexual satisfaction between husbands and wives in Taiwan". *Hum. Reprod.*, 2001, *16,* 1762.

[6] Craig M., Tata P., Regan L.: "Psychiatric morbidity among patients with recurrent miscarriage". *J. Psychosom. Obstet. Gynecol.*, 2002, *23,* 157.

[7] Klier C.M., Geller P.A., Ritsher J.B.: "Affective disorders in the aftermath of miscarriage: a comprehensive review". *Arch. Womens Ment. Health*, 2002, *5,* 129.

[8] Pihusch R., Buchholz T., Lohse P. *et al.*: "Thrombophilic gene mutations and recurrent spontaneous abortion: prothrombin mutation increases the risk in the first trimester". *Am. J. Reprod. Immunol.*, 2001, *46,* 124.

[9] Larson K.L., DeJong C.J., Barnes A.M. *et al.*: "Sperm chromatin structure assay parameters as predictors of failed pregnancy following assisted reproductive techniques". *Hum. Reprod.,* 2000, *15,* 1717.

[10] Sills E.S., Drews C.D., Perloe M. *et al.*: "Periovulatory serum human chorionic gonadotropin (hCG) concentrations following subcutaneous and intramuscular nonrecombinant hCG use during ovulation induction: a prospective, randomized trial". *Fertil. Steril.*, 2001, *76,* 397.

[11] Sills E.S., Perloe M., Kaplan C.R. *et al.*: "Uncomplicated pregnancy and normal singleton delivery after surgical excision of heterotopic (cornual) pregnancy following in vitro fertilization/embryo transfer". *Arch. Gynecol. Obstet.*, 2002, *266,* 181.
[12] Hsu Y.L., Kuo B.J.: "Evaluations of emotional reactions and coping behaviors as well as correlated factors for infertile couples receiving assisted reproductive technologies". *J. Nurs. Res.*, 2002, *10,* 291.
[13] Schaper A.M., Hellwig M.S., Murphy P. *et al.*: "Ectopic pregnancy loss during fertility management". *West. J. Nurs. Res.*, 1996, *18,* 503.
[14] Ritsher J.B., Neugebauer R.: "Perinatal bereavement grief scale: distinguishing grief from depression following miscarriage". *Assessment,* 2002, *9*, 31.
[15] Laffont I., Edelman R.J.: "Psychological aspects of in vitro fertilization: a gender comparision". *J. Psychosom. Obstet. Gynecol.*, 1994, *15*, 85.
[16] Riyazi N., Leeda M., de Vries J.I. *et al.*: "Low molecular weight heparin combined with aspirin in pregnant women with thrombophilia and history of preeclampsia or fetal growth restriction: a preliminary study". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1998, *80,* 49.
[17] Tzafettas J., Mamopoulos A., Anaplotis A. *et al.*: "Thromboprophylaxis throughout pregnancy in women with previous history of recurrent miscarriage of unknown etiology". *Clin. Exp. Obstet. Gynecol.*, 2002, *29*, 267.

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