Gonadotropin treatment of an azoospermic patient with a Y-chromosome microdeletion

Helmy A. Selman, Ph.D., a Giovanni Cipollone, M.D., b Liborio Stuppa, M.D., c Mariella De Santo, M.D., a Karl Sterzik, M.D., d and Imam El-Danasouri, Ph.D. a,d

Spatocco Hospital, Chieti, Italy

Objective: To report on the treatment with recombinant FSH of an azoospermic normogonadotropic patient with a Y-chromosome microdeletion.

Design: Case report.

Setting: An assisted reproduction center.

Patient(s): A 32-year-old patient with azoospermia.

Intervention(s): Histological testicular biopsy, Y-chromosome screening, FSH treatment, and intracytoplasmic sperm injection.

Main Outcome Measure(s): Fertilization, embryo development, pregnancy, and delivery.

Result(s): After 6 months of treatment with gonadotropins, a small number of spermatozoa were found in the patient’s ejaculate and used for IVF, resulting in a successful twin pregnancy and the delivery of two healthy girls.

Conclusion(s): In this study, treatment with gonadotropins promoted the spermatogenesis process and led to the production of spermatozoa in a normogonadotropic azoospermic patient. (Fertil Steril 2004;82:218–9. © 2004 by American Society for Reproductive Medicine.)

Key Words: Azoospermia, human recombinant FSH, human chorionic gonadotropin, intracytoplasmic sperm injection, Y-chromosome screening

Intracytoplasmic sperm injection (ICSI) has markedly revolutionized the treatment of different forms of male factor infertility. ICSI has been successfully implemented not only in cases of patients with very low sperm count but also in those with azoospermia and only a few foci of active spermatogenesis from which mature spermatozoa could be surgically obtained.

It is well known that FSH plays a key role in spermatogenesis and sperm production (1, 2). Treatment with gonadotropins of men with azoospermia due to hypogonadotropic hypogonadism has been well documented (3–5). Several studies have shown that treatment with FSH of men with oligozoospermia improves sperm production quantitatively (6–8) and increases the spermatogonial population in oligozoospermic men with normal FSH levels (9). However, the effect of FSH administration on normogonadotropic azoospermic patients with a Y-chromosome microdeletion is still to be elucidated.

In this study, we report a patient with azoospermia, possibly due to a Y-chromosome microdeletion, who underwent FSH treatment before an IVF attempt. After the FSH therapy, a small number of spermatozoa were recovered from his ejaculate and used for ICSI, resulting in the successful delivery of two healthy girls.

CASE REPORT

A 32-year-old infertile man with a normal hormonal profile, normal testicular volume, and no historical pathology such as varicocele or cryptorchidis underwent diagnostic examinations to detect the possible causes of infertility. Semen analysis performed in our center, at 2-week intervals, demonstrated the complete absence of spermatozoa. Diagnostic histological testicular biopsy showed maturation arrest
at the spermatocyte stage. The Y-chromosome genetic screening on peripheral blood revealed the presence of a microdeletion of the DAZ, BPY2, and CDY1 genes in the azoospermia factor (AZF) region, which is probably the cause of the azoospermia.

Gonadotropin therapy was initiated with the SC administration of 75 IU of recombinant FSH (rFSH) (Puregon; Organon, Rome, Italy) on alternate days for the first 2 months. At the beginning of the third month, the rFSH dose was augmented to 150 IU on alternate days, and from the fourth month onward, 2,000 IU of hCG (Profasi; Serono, Rome, Italy) were administered IM twice weekly in addition to the rFSH.

A semen analysis was then conducted, and a small number of spermatozoa (about $0.001 \times 10^6$) were observed in the total ejaculate. Two other semen samples were collected at 15-day intervals, which showed an increase in the number of spermatozoa up to a total of $0.002 \times 10^6$, with 30% progressive motility.

In January 2002, the couple was counselled about the risk of the procedure and the possible transmission of the Y-chromosome microdeletion to their son and elected to enroll in an ICSI treatment attempt. The procedure was approved by our local institutional ethics committee, and a written informed consent was obtained from the couple.

The female partner, aged 30, with no evidence of gynecological abnormality, underwent a standard down-regulation (long protocol) for ovarian stimulation with GnRH analogue (Decapeptyl; Ipsen, Milano, Italy) and rFSH (Puregon 100; Organon). The oocyte retrieval resulted in eight oocytes, of which six were at the metaphase II stage.

The male patient continued the therapy until the date of the oocyte retrieval, when he produced a semen sample and motile spermatozoa that could be isolated and used for oocyte injection. Five of the six oocytes were fertilized, and ET took place 72 hours after injection. Three good-quality 8-cell stage embryos were replaced into the patient, resulting in a twin pregnancy as detected by the presence of fetal heartbeat 6 weeks after ET. After 36 weeks of gestation, the full-term pregnancy resulted in the successful delivery of two healthy girls with normal karyotype (46,XX).

**DISCUSSION**

Several forms of male factor infertility have been successfully treated through the introduction of ICSI, even when only a few spermatozoa are present in the patient’s ejaculate. Azoospermia is a frustrating and stressful dilemma for infertile couples as there are few treatment options.

In this study, we report a case of a normogonadotropic man with azoospermia possibly due to a microdeletion of some genes in the AZF region on the long arm of the Y-chromosome. After rFSH treatment for 6 months, a few spermatozoa were recovered from his ejaculate and used for assisted fertilization, resulting in a successful pregnancy and delivery.

The role of FSH in the treatment of hypogonadotropic hypogonadal men has been widely established (3, 5). It has been reported that administration of FSH combined with hCG rescues the spermatogenesis and sperm output in hypogonadotropic hypogonadal azoospermic men (3). Treatment of oligozoospermic patients with moderate hypospermatogenesis and a normal hormonal profile, either with urinary FSH (8, 9) or recombinant FSH (10), stimulates spermatogenesis and increases the number of spermatozoa in the ejaculate. Moreover, Foresta et al. (9) reported that FSH increases the spermatogonial population in patients with severe oligozoospermia.

In our study, the patient had a Y-chromosome microdeletion, involving the DAZ, BPY2, and CDY1 genes in the AZF region, which can be considered the cause of the spermatogenic defect. Y-chromosome microdeletion could result in several forms of infertility from severe oligozoospermia to azoosperma with complete maturation arrest of spermatogenesis. This depends on the nature and entity of the genes implicated in the deleted region (11, 12). In this study, treatment with FSH combined with hCG initiated spermatogenesis, thus facilitating successful ICSI fertilization and resulting in a pregnancy and the subsequent delivery of two healthy girls.

**References**