Healthy live birth using theophylline in a case of retrograde ejaculation and absolute asthenozoospermia

Thomas Ebner, Ph.D.,[a] Omar Shebl, M.D.,[a] Richard Bernhard Mayer, M.D.,[a] Marianne Moser, Ph.D.,[a] Walter Costamoling, M.D.,[b] and Peter Oppelt, M.D.[a]

[a] Abteilung für Gynäkologische Endokrinologie und Kinderwunsch Zentrum, Landes, Frauen, und Kinderklinik, and [b] Department of Urology, Krankenhaus der Barmherzigen Schwestern, Linz, Austria

Objective: To analyze whether the use of ready-to-use theophylline is a feasible option in a case of retrograde ejaculation and absolute asthenozoospermia.
Design: Case report.
Setting: In vitro fertilization unit of a public hospital.
Patient(s): Thirty-one-year-old nulliparous woman, and 39-year-old male with retrograde ejaculation and absolute asthenozoospermia.
Intervention(s): Retrieval of postejaculatory urine, restoration of motility using a methylxanthine, intracytoplasmic sperm injection, single-embryo transfer.
Main Outcome Measure(s): Sperm motility, fertilization, embryo quality, live birth.
Result(s): Successful fertilization and a single-embryo transfer resulted in a healthy live birth.
Conclusion(s): Theophylline turned out to be a safe, efficient agent for stimulating immotile spermatozoa in patients with retrograde ejaculation. (Fertil Steril® 2014;101:340–3. ©2014 by American Society for Reproductive Medicine.)
Key Words: Absolute asthenozoospermia, live birth, motility, retrograde ejaculation, theophylline

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The introduction of intracytoplasmic sperm injection (ICSI) into the field of assisted reproduction technologies (1) has been of great interest for the treatment of male infertility. This new technique has allowed fertilization even in couples with severe male infertility as depositing a single sperm directly into the cytoplasm bypasses all anatomic structures. The origin of the sperm has no negative effect on ICSI outcome (2), regardless of whether the male gametes were obtained by masturbation (1) or by more invasive approaches such as microsurgical epididymal sperm aspiration (3) or testicular sperm extraction (4). In addition, no matter their origin, all sperm can be cryopreserved for later usage without any impairment (5, 6).

In cases of partial or complete retrograde ejaculation, the bladder may be an alternative sperm source (7). However, the success rate in using spermatozoa from unusual sources depends on the motility of the material obtained. For example, complete sperm immotility is a common feature of the ejaculate of patients with Kartagener syndrome (8) or related cases of ciliary dyskinesia (9). Aside from such indications, absolute asthenozoospermia in ejaculated semen is associated with poorer outcomes (10). Nagy et al. (11) have indicated that use of an immotile spermatozoon in ICSI has the most strongly negative influence. Immature testicular and epididymal spermatozoa (and their reduced rate of cryosurvival) will further contribute to the presence of absolute asthenozoospermia, although acceptable results can be achieved by performing optimal sperm selection (12). Our report deals with the first live birth after employing ready-to-use theophylline to restore motility in a case of retrograde ejaculation and absolute asthenozoospermia.

Received July 30, 2013; revised September 10, 2013; accepted October 3, 2013; published online November 1, 2013.
T.E. has received consulting fees and payment for presentations from Gynemed. O.S. has nothing to disclose. R.B.M. has nothing to disclose. M.M. has nothing to disclose. W.C. has nothing to disclose. P.O. has nothing to disclose.
Reprint requests: Thomas Ebner, Ph.D., Landes Frauen und Kinderklinik, Abteilung für Gynäkologische Endokrinologie und Kinderwunsch Zentrum, Krankenhausstr. 26–30, A-4020 Linz, Austria (E-mail: thomas.ebner@gespag.at).

Fertility and Sterility® Vol. 101, No. 2, February 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.10.006

MATERIALS AND METHODS

A 31-year-old nulliparous woman (body mass index 26.3) was referred to the Kinderwunsch Zentrum Linz for ICSI treatment. She had been attempting pregnancy for 5 years. Her menses were found to be regular with a 28-day cycle and 4 to 5 days of bleeding, but occasional spotting was reported. Her medical history revealed that she had neurodermitis and hypertonia. An acute infection with salmonella at the age of 19 had resulted in renal dysfunction. An ultrasound examination showed that she had normal ovaries and uterine cavity, but both her fallopian tubes had either been removed (for adnexitis, right tube) or showed loss of function (from sactosalpinx, left tube).

Her basal hormone parameters revealed that her follicle-stimulating hormone (FSH) levels was 8.7 mIU/mL and luteinizing hormone (LH) level was (9.3 mIU/mL). Her estradiol was 37 pg/mL, and antimüllerian hormone (AMH) was 1.11 ng/mL. Her thyroid-stimulating hormone (TSH) level was also considered as unremarkable (0.57 μIU/mL). Her low testosterone (0.07 ng/mL) level was not addressed because her dehydroepiandrosterone (DHEA) level was within the normal range (1,730.0 ng/mL). Her midluteal progesterone was found to be 8.7 ng/mL. Because the patient had an elevated prolactin level (48.7 ng/mL), she was given cabergoline (a quarter of a 0.5 mg Dostinex tablet per week), but because of her history of acute renal failure, she refused the drug; a spontaneous reduction of prolactin was observed (12.5 ng/mL).

The 39-year-old male partner had normal hormone parameters: TSH 1.07 μIU/mL, and FSH 3.37 mIU/mL. He had had an operation for Hirschsprung disease at the age of 10 years, which had caused complete retrograde ejaculation. Before fertility treatment, a postejaculatory urine specimen of the patient was screened for spermatozoa. The overall concentration of gametes found was 2.4 million per mL, with only 4% motile nonprogressively and 5% viable. A total of three straws were cryopreserved for further usage using glycerine as a cryoprotectant in a slow-freezing approach. Because of the reduced sperm motility, the couple requested that one straw be thawed to check the survival rate. No motile spermatozoa were observed after thawing, so we decided to attempt a fresh sperm retrieval on the day of oocyte collection.

Both partners had a normal karyotype and were seronegative for hepatitis B and C as well as human immunodeficiency virus. No infection with *Chlamydia trachomatis* or syphilis was detected.

RESULTS

In 2011, the couple started their ICSI treatment cycle. Controlled ovarian hyperstimulation was performed in an antagonist protocol applying 1,800 IU of recombinant FSH (Puregon; MSD). On the day 6 of stimulation (cycle day 8) the gonadotropin-releasing hormone (GnRH) antagonist Ganirelix (Orgalutran, MSD, Vienna, Austria) was administered in parallel until ovulation was induced with 10,000 IU of human chorionic gonadotropin (hCG, Ovitrelle; Merck Serono). The latter was scheduled when the lead follicle reached a diameter of 18 mm. A total of five follicles were visible on ultrasound with an estradiol level of 869 pg/mL. On this particular day of ovulation induction, the progesterone level was 0.3 ng/mL, and LH was 3.1 mIU/mL.

Thirty-six hours after hCG administration, the egg collection was performed via the vaginal route. A total of four cumulus-oocyte complexes were retrieved. After denudation with 80 IU/mL of hyaluronidase (Origio), the gametes were found to be mature (metaphase II), but their quality was impaired; all four showed dense central granulation (13).

At the same time, a fresh sperm probe was obtained at the Krankenhaus der Barmherzigen Schwestern, Department of Urology, from the man's postejaculatory urine following methods described elsewhere (14). Briefly, the bladder had to be voided followed by neutralization of the internal pH via catheterization. The patient was then instructed to masturbate and ejaculate, after which the urine was collected, centrifuged, and processed in BM1 medium (Ellios Bio-Media). The associated diagnosis was absolute asthenozoospermia, with a sperm count of 1.5 million per mL and a marginal viability of only 1%. The material was immediately transported from the collaborating hospital to the Kinderwunsch Zentrum. Upon arrival, the pH of the sperm solution was still 7.0, and the diagnosis of complete immotility was confirmed.

To distinguish between nonviable and immotile sperm, we applied a recently launched ready-to-use dimethylxanthine called theophylline (GM501 SpermMobil; Gynemed) to restore motility. In the method previously described elsewhere (15), we added 0.5 μL of this medium to swim-out drops on the ICSI dish containing the immotile spermatozoa. Within minutes, the addition of theophylline led to an improvement in progressive motility such that numerous previously immotile sperm revealed fast progressive motility.

Consequently, ICSI (Microtech pipettes; Gynemed) was performed 3 hours after follicular puncture, which resulted in three regularly fertilized zygotes and one monopronuclear one. It is important to note that before they were used in ICSI, the spermatozoa were washed in BM1 medium and manipulated in polyvinylpyrrolidone (PVP) to minimize the risk of carrying over theophylline to the drop containing the oocytes.

On day 2 of preimplantation development, one zygote did not cleave, which left two 2-cell embryos in culture. The next day, one of the embryos showed signs of multinucleation; the other six-cell embryo was good quality (less than 20% fragments, equally sized mononuclear blastomeres) and was transferred using a transfer catheter set (Emtrac 4.2; Gynetics).

Fourteen days after the single-embryo transfer, the woman's β-hCG concentration was found to be positive (157 mIU/mL). The associated progesterone level was 28.1 ng/mL. Three days later, she developed a mild form of ovarian hyperstimulation syndrome, which was treated conservatively because no ascites were found on ultrasound scan. A gestational sac was observed the same day, which later showed heart activity in gestational week 6. The entire pregnancy was otherwise uneventful, and ended with the spontaneous birth of a healthy girl in gestational week 37 (2,940 g, 50 cm).

DISCUSSION

Patients with retrograde ejaculation account for less than 2% of the population who present for fertility treatment (7). The