

Live Birth After Intracytoplasmic Sperm Injection with Cryopreserved Sperm Retrieved from Urine in a Case of Complete Retrograde Ejaculation: A Case Report

**Anna Katrina G. Purugganan, MD, DPOGS and
Ma. Asuncion A. Fernandez, MD, FPOGS, FPSRM, FPSGE**

Center for Assisted Reproductive Medicine and Infertility, St Luke's Medical Center Bonifacio Global City

This is a case of a 37-year-old nulliparous woman, and her 53-year-old husband diagnosed with complete retrograde ejaculation and absolute azoospermia, who conceived after transfer of embryos fertilized using cryopreserved sperm retrieved from postejaculatory urine. Four embryos were thawed, then transferred in the blastocyst stage, resulting in a singleton pregnancy and delivery by cesarean section at term to a healthy baby boy weighing 3100 g. This case study shows that cryopreservation of sperm retrieved from postejaculatory urine is feasible for IVF, despite demonstration of low motility. This is more cost-effective and least invasive as the husband may avoid surgical aspiration or extraction of sperm.

Key words: cryopreservation, infertility, in vitro fertilization (IVF), retrograde ejaculation

Introduction

Retrograde ejaculation occurs when the semen goes through a dysfunctional internal vesical sphincter into the bladder, instead of going into the urethra. Infertility resulting from retrograde ejaculation occurs in less than 2% of male factor infertility, but may be as high as 18% in men with azoospermia.¹ This condition may be due anatomic abnormalities, either acquired or congenital, spinal cord lesions or other neuropathies, or may be idiopathic.² In assisting couples to conceive, sperm is recovered from the post ejaculatory urine. The urine, however, has a low pH and high osmolarity, which is toxic to the sperm. To achieve optimum pH and osmolarity to retain the viability of the sperm, several techniques have been developed, to make the urine more optimum for sperm survival. The sperm collected may be used for either intrauterine insemination or in vitro fertilization. It has been suggested that cryopreservation of sperm in patients with retrograde ejaculation may not be reliable due to

its inherent low quality due to exposure to the urine, and further diminishing its quality by cryopreservation and thawing.³

The Case

The couple consulted due to primary infertility. The wife is a 37 year old, who upon evaluation was noted to have both tubal factor (hydrosalpinges) and ovulatory dysfunction (Polycystic ovary syndrome). The husband is a 53 year old, diagnosed with prostate cancer with plans of medical management with GnRH agonist (Goserelin) and subsequent radiotherapy.

It was decided that before the husband will undergo treatment for prostate cancer, sperm will be collected to be utilized for future reproduction. On semen analysis, it revealed azoospermia. Post-ejaculatory urinalysis confirmed retrograde ejaculation. With this information, availability of sperm for an eventual in vitro fertilization by ICSI was ensured. On the day of collection, the patient

was advised to collect semen, which was again noted to have no sperm. The patient was asked to empty his bladder after ejaculation, and the total collected was handed over immediately to the andrologist. The urine sample was centrifuged then suspended in medium. Sperm recovered from the urine were then cryopreserved. Sperm concentration, motility, vitality, and morphology were assessed according to World Health Organization guidelines. Pellets were resuspended in SpermRinse solution, and the suspension of sperm obtained after centrifugation was cryopreserved. It was diluted (vol/vol) at room temperature with cryoprotectant, then was cryopreserved using Kita Zato technique.

Several months after completion of the husband's treatment, the wife was prepared for IVF. Controlled ovarian hyperstimulation was administered by utilizing an antagonist protocol applying total of 5175 IU of recombinant FSH (Puregon), starting on day 3 of her cycle. On the day 5 of stimulation (cycle day 8) the GnRH antagonist Cetrorelix was administered in parallel with the Puregon. On day 10 of stimulation, there were 15 follicles <10mm, with the leading follicle measuring 21.5mm, with an estradiol level of 2518 pg/mL. Stimulation was continued until day 12, when ovulation was induced with 10,000 IU of human chorionic gonadotropin. A total of twenty one follicles were visible on ultrasound. Thirty-four to thirty-six hours after hCG administration, transvaginal oocyte retrieval was performed. A total of sixteen cumulus-oocyte complexes were retrieved. After denudation, proceeded with intracytoplasmic sperm injection with 12 oocytes using the thawed cryopreserved sperm. Eventually, 7 were fertilized (three Grade 2, four Grade 3 embryos). On Day 2, three embryos were transferred (two Grade 2, one Grade 3 embryos). The remaining 4 embryos were cryopreserved. Unfortunately, the wife was not able to get pregnant during that cycle. Pregnancy was achieved after the frozen-thawed embryo transfer one year after the first transfer. All cryopreserved embryos were thawed, and were transferred on day 5 (blastocyst). Fetus was singleton, without congenital anomalies. Wife developed gestational diabetes, which was controlled by diet alone. The rest of the pregnancy

was unremarkable and was carried to term. Delivered by primary cesarean section to a live boy without complications, and weighing 3.1 kg.

Discussion

In this case report, we describe the first live birth in the Philippines achieved using intracytoplasmic sperm injection of cryopreserved sperm retrieved from urine in a man with complete retrograde ejaculation. Retrograde ejaculation occurs in <2% of male factor infertility. There are several factors causing retrograde ejaculation which are enumerated in Table 1.

Table 1. Etiology of retrograde ejaculation

Neurogenic
Spinal cord injury
Cauda equina lesions
Multiple sclerosis
Autonomic neuropathy (juvenile diabetes)
Retroperitoneal lymphadenectomy
Sympathectomy
Colorectal and anal surgery
Pharmacological
Antihypertensives
Alpha1-adrenoceptor antagonists
Antipsychotics
Antidepressants
Bladder neck incompetence
Congenital defects of hemitrigone
Bladder extrophy
Bladder neck resection
Prostatectomy
Congenital dopamine beta-hydroxylase deficiency
Urethral obstruction
Ectopic ureterocele
Urethral stricture
Urethral valves or veru montanum hyperplasia

G. Colpi. EAU Guidelines on Ejaculatory Dysfunction. European Urology, January 2014

The husband was diagnosed with prostate cancer and he subsequently underwent radiotherapy. Prior to treatment, the husband was

advised to preserve his semen for future reproductive use. His semen analysis yielded a result of azoospermia and upon further evaluation he was noted to have retrograde ejaculation supported by postejaculation urinalysis. Objective of treatment for retrograde ejaculation is restoration of antegrade ejaculation either medically or surgically, or spermatozoa can be recovered from the urine. For this case, additional assessment for the etiology and subsequent appropriate medical management may delay the treatment for his prostate cancer.

Retrieval of sperm from the urine should procure adequate viable sperm from the postejaculatory urine for insemination, IVF, or intracytoplasmic sperm injection (ICSI). There are several treatment options available for retrograde ejaculation, but there is scarcity of supporting data to conclude which method will be ideal to achieve pregnancy. There are three different methods for urinary sperm retrieval: centrifugation and resuspension of postejaculatory urine specimens, the Hotchkiss or modified Hotchkiss technique, and ejaculation on a full bladder.⁴ The Hotchkiss technique entails emptying the bladder, then washed with Ringer's lactate through a catheter, and then a small amount of Ringer's lactate is left within the bladder before withdrawing the catheter. The contents of the bladder right after ejaculation are obtained by either voiding or catheterization, and the suspended spermatozoa are used for intrauterine insemination.⁵ The same procedure is performed in modified Hotchkiss technique but sterile culture medium for gametes is instilled instead of Ringer's lactate solution.

Jefferys, et al., compared several management of retrograde ejaculation. The study compared the outcomes of either medical or surgical management, and different methods of urinary sperm retrieval, by measuring pregnancy rate and live birth rate. Two surgical techniques have been described: collagen injections into the bladder neck to achieve antegrade ejaculation and testicular sperm extraction. Both achieved pregnancies, but the number of participants in these studies is small and testicular sperm extraction has a potential risk of subsequent testicular scarring.⁴

Medical management of retrograde ejaculation with the use of either sympathomimetics or anticholinergics or both, has also been widely discussed in the literature. Patients respond well to α -agonists and have been reported to produce antegrade ejaculation in 50% of men with neurogenic retrograde ejaculation.⁶ This would allow natural conception after ejaculation has reverted to antegrade fashion, albeit the studies of medical management have reported pregnancy outcomes, hence, it is not possible to reach any conclusions about efficacy.

Prostate cancer itself and the radiation therapy will have a negative effect on the patient's ejaculation. In a study with 364 prostate cancer patients who underwent radiation, 72% lost the ability to ejaculate in an antegrade fashion, and as much as 89% of the patients experienced anejaculation within 5 years.⁷ The husband's sperm was not assessed prior to exposure to the urine, it cannot be known whether the negative effects on the sperm motility and viability is due to the exposure to the urine or if it is inherent to his condition. With this, it was decided that once sufficient sperm for several cycles of ICSI have been collected then cryopreserved, the husband would immediately undergo radiotherapy and receive GnRH agonist.

The least invasive option for sperm retrieval would be just to collect the sperm from the postejaculatory urine. He was advised to masturbate with a full bladder, and collect his urine immediately after ejaculation. In some studies, it has been found that this method yielded a higher pregnancy rate compared to the two previously mentioned urinary sperm retrieval.⁴ This method was utilized in our patient. However, due to the combined effects of osmotic stress, low pH, and urea toxicity, the spermatozoa found in the pellet after urinary centrifugation will almost always be non-viable.⁸ To reduce the adverse effect of urine on the sperm, appropriate medium may be instilled into the bladder, such as the Hotchkiss technique. This entails instillation of the medium through a catheter into the bladder before ejaculation. However, due to patient's discomfort with catheterization, as well as the risk for infection, an alternate method to adjust the

urine condition is by ingestion of alkalinizing agents, such as sodium bicarbonate. A pregnancy has been reported through intravaginal insemination of semen separated from alkalinized urine. After collection of urine-semen mixture, it was noted that the first fraction consisted of a thick gelatinous mass. This fraction consisted entirely of unliquefied semen with a concentration of 80 million/mL highly motile sperm.⁹ Nonetheless, it is not possible to use the collected semen with poor parameters for intrauterine insemination and conventional IVF, which require sufficiently motile sperm. The sperm obtained in these cases should be used in intracytoplasmic sperm injection.

In this case, the husband was diagnosed with prostate cancer and would thereafter undergo radiotherapy. It was then expected the quality of his sperm may decline after completing treatment for prostate cancer¹⁰, thus contributing to the decision to store his sperm prior to radiotherapy. Sperm was retrieved from alkalinized postejaculatory urine, which was then cryopreserved. Cryopreservation of human sperm has been known to be detrimental to the sperm quality. The most reported effect is decrease in sperm motility, which may be due to several factors, including intracellular ice crystals formation during cryopreservation and osmotic damage due to extensive cell shrinkage.¹¹ The presence of female factors such as hydrosalpinges and ovulatory dysfunction and the sperm's poor motility contributed to the decision of doing ICSI instead of intrauterine insemination and conventional IVF.

Conclusion

Due to limited studies and less ideal quality of publications, there can be no direct comparisons between successes of each method and their effect on the pregnancy rate. In males presenting with azoospermia, it is vital to request for postejaculatory urinalysis to rule out retrograde ejaculation. Once this diagnosis is made, further evaluation is important to determine the etiology of this condition to aid in the course of the management, whether he will proceed with medical

or surgical therapy. If reproduction is the objective, several methods for sperm recovery from the urine are feasible. It is best to individualize the treatment catering to both husband and wife, after thorough evaluation. All available options may be offered to the couple, but the safest and least invasive should be the first choice.

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