

Case Report
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Successful Pregnancy and Delivery with Intracytoplasmic Sperm Injection in HIV-Serodiscordant Couple: the First Case in Korea

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ABSTRACT

With highly active antiretroviral therapy, human immunodeficiency virus (HIV) infection is considered to be a manageable chronic disease. The improved prognosis increases the desire of individuals with HIV to have biological offspring. With the establishment of washing protocol, no HIV transmission has been reported among more than 11,000 assisted reproduction technology (ART) cycles. Although the Acquired Immunodeficiency Syndrome Prevention Act in Korea prevents the use of HIV-infected blood, organs, tissues and semen, we recently obtained the authentic approval from the Korea Centers for Disease Control and Prevention for the practice of ART in HIV-serodiscordant couples. We report a 32-year-old HIV-seronegative female with her husband who was HIV-1 seropositive. After semen washing was performed by means of a density gradient and the swim-up technique, HIV-1 ribonucleic acid was not detected in the semen. An aliquot of processed semen was cryopreserved before ART. None of 3 cycles of intrauterine insemination was successful. After the third frozen-thawed embryo transfer following two cycles of intracytoplasmic sperm injection, an intrauterine singleton pregnancy was identified. She gave birth to a normal healthy male baby at full term by Cesarean section. She and her baby were tested for HIV during pregnancy and after delivery and the results were negative. Semen washing may be a safe ART method for HIV-serodiscordant couples who desire to have a baby in Korea.

Keywords: Human Immunodeficiency Virus; Pregnancy; Assisted Reproductive Technique; Semen Washing

INTRODUCTION

With the introduction of highly active antiretroviral therapy, human immunodeficiency virus (HIV) infection has become a manageable chronic disease.^{1,2} Currently, approximately 38 million people are infected with HIV worldwide,³ and more than 80% of infected couples are of reproductive age.⁴ The improved prognosis have increased their desire to have biological offspring, although there are other options for these couples, including the use of assisted reproduction technology (ART) with donor sperm and adoption, in addition to not having children. Since the first report of successful intrauterine insemination (IUI) with semen

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim H, Park JS, Choi YM. Formal analysis: Park WB, Park SS. Methodology: Kim H. Writing - original draft: Seong JS, Kim H, Park JS, Choi YM. Writing - review & editing: Kim H, Park JS, Park WB, Kim NJ, Oh M, Choi YM.

washing in HIV-serodiscordant couples by Semprini et al.⁵ in 1992, semen washing has been widely considered a safe method. With the establishment of a washing protocol, no HIV transmission has been reported among over 11,000 ART cycles.⁶ However, ART in HIV-serodiscordant couples has been considered to be impossible in Korea because the acquired immunodeficiency syndrome (AIDS) Prevention Act prevents the use of HIV-infected blood, organs, tissues and semen.⁷

Recently, we obtained authentic approval from the Korea Centers for Disease Control and Prevention (KCDC) for ART practice in these couples and we report the first successful pregnancy in and delivery by an HIV-serodiscordant couple in Korea.

CASE DESCRIPTION

Patient

A 32-year-old nulliparous female visited our fertility clinic with her husband for pregnancy advice in September 2015. The male partner had been diagnosed with HIV-1 after their marriage, and the couple did not have a sexual relationship afterwards. Because the couple wanted to have a baby, highly active antiretroviral therapy (HAART) therapy with elvitegravir, cobicistat, emtricitabine and tenofovir was initiated in September 2015.

First, a baseline infertility workup of the couple was performed. She had a regular menstrual cycle and no significant past medical history, except for a benign thyroid nodule and an endoscopic mucosal resection for early gastric cancer. The baseline serum hormone levels were within normal limits: luteinizing hormone 3.3 mIU/mL (1.8–11.78 mIU/mL in follicular phase), follicle-stimulating hormone 3.6 mIU/mL (3.03–8.08 mIU/mL in follicular phase), estradiol 34 pg/mL (21–251 pg/mL in follicular phase), thyroid-stimulating hormone 1.28 μ IU/mL (0.4–4.1 μ IU/mL), prolactin 22.6 ng/mL (0–25 ng/mL) and anti-Müllerian hormone 5.20 ng/mL (1–10 ng/mL). In addition, hysterosalpingography and transvaginal ultrasound showed no abnormal findings. For the husband, semen analysis revealed mild teratozoospermia according to the World Health Organization (WHO) criteria (volume of 2.0 mL [\geq 1.5 mL]; concentration of 48.1 million/mL [\geq 15 million/mL]; total motility of 41.3% [\geq 40%]; and strict morphology of 2.5% [\geq 4%]).⁸

Semen washing

After authentic interpretation by the KCDC and Institutional Review Board (IRB) approval (IRB No. 1407-153-597) of Seoul National University Hospital., sperm cryopreservation began being practiced in June 2016 before IUI and intracytoplasmic sperm injection (ICSI). The husband met the inclusion criteria in our institution as follows: 1) healthy, 2) a no clinical symptom, 3) cluster of differentiation 4 (CD4)⁺ T cell count > 200/mm³ (tested at least 2 times for 4 months), 4) stable blood viral load (ribonucleic acid [RNA] titer of less than 50 copies/mL in more than 2 consecutive measurements over 3 months), 5) RNA viral load of less than 1,000 copies/mL in the seminal fluid and an undetectable viral load in the final fraction after semen washing, and 6) HIV-1 infection.

The serum CD4 T-cell count of the husband was 870/mm³ and HIV-1 RNA was not detected in the semen after washing. The whole sperm preparation procedure in our clinic was carried out in a Class II biosafety cabinet to isolate infected specimens per recommendation of the American Society for Reproductive Medicine.⁴ Semen washing was based on the

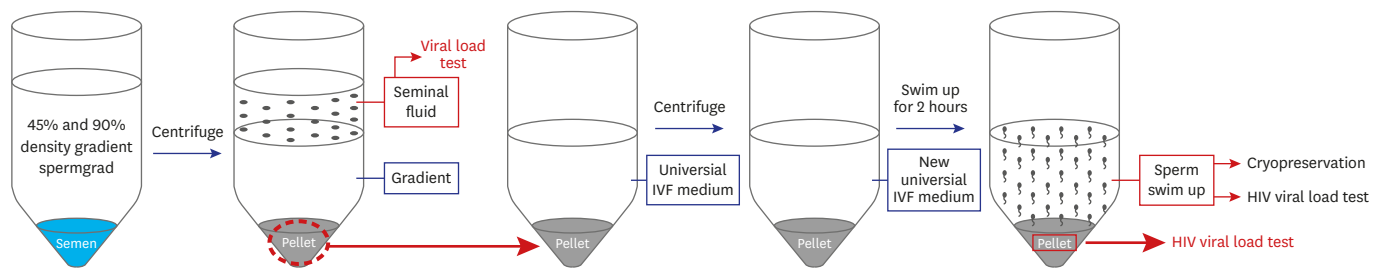


Fig. 1. The method of sperm washing. IVF = in vitro fertilization, HIV = human immunodeficiency virus.

method described by Semprini et al.⁵ (Fig. 1). Briefly, samples were processed with 45% and 90% density gradients (SpermGrad, VitroLife, Göteborg, Sweden) after liquefaction and centrifuged at 400 g for 30 minutes. Then, the supernatant was tested for viral load and the sperm pellet was recovered and resuspended in universal in vitro fertilization (IVF) medium. The tube was incubated for two hours for use in the swim-up technique. Following swim-up, an aliquot of this supernatant was sent to the laboratory for HIV RNA test, and Cobas® (Roche Diagnostics Ltd, Burgess Hill, UK) was used. The remaining washed sperm was cryopreserved for further procedures. Cryopreservation of sperm was performed before every IUI and ICSI attempt with the protocol described above, and HIV-1 RNA was not detected in either the serum or the semen in each session.

ART and successful delivery

The results of the IUI and ICSI cycles are summarized in Tables 1 and 2. A total of 3 cycles of IUI with frozen-thawed sperm were not successful. Beginning in June 2017, two cycles of ICSI were attempted, but a fresh embryo transfer (ET) cycle was not performed due to the highly suspected risk of ovarian hyperstimulation syndrome (OHSS) with the excessive number of follicles. Instead, frozen-thawed embryo replacement (FER) was attempted three times with estradiol valerate (Progynova, Schering AG, Berlin, Germany) beginning on the 3rd day of the menstrual cycle and vaginal progesterone (Lutinus; Ferring, Parsippany, NJ, US) was added from 5 days before ET. After the third FER, serum human chorionic gonadotropin level was 111.7 mIU/mL (0-10 mIU/mL in non-pregnant women) 11 days after ET and an intrauterine singleton pregnancy was identified by transvaginal ultrasonography at 5 weeks of gestational age.

Table 1. IUI regimens and outcomes

Date	Regimen	CC, mg	FSH, IU/day	Days of stimulation	Outcomes
June 2016	CC+hMG+IUI	50	75	10 days	Not pregnant
September 2016	CC+hMG+IUI	50	150	10 days	Not pregnant
February 2017	CC+IUI	50		7 days	Not pregnant

IUI = intrauterine insemination, CC = clomiphene citrate, FSH = follicle stimulating hormone, hMG = human menopausal gonadotropin.

Table 2. ICSI regimens and outcomes

Date	Regimen	FSH, IU/day	Oocytes	Day of ET	No. of transferred embryos	No. of cryopreserved embryos	Outcomes
June 2017	D(L)+FSH	150→225	8			6	All cryopreserved (due to OHSS risk)
July 2017	ERT+FER			Day 3	2		Not pregnant
July 2017	ERT+FER			Day 3	2		Not pregnant
December 2017	D(L)+FSH	225	7			4	All cryopreserved (due to personal reasons)
December 2017	ERT+FER			Day 3	2		Intrauterine pregnancy

ICSI = intracytoplasmic sperm injection, FSH = follicle stimulating hormone, ET = embryo transfer, D(L) = GnRH agonist long protocol, ERT = estrogen replacement therapy, FER = frozen embryo replacement, OHSS = ovarian hyperstimulation syndrome.

Obstetric problems were not observed during antenatal follow-up. The patient gave birth to a 3.685 kg normal healthy male baby at 41⁺¹ weeks of gestational age by cesarean section. She requested cesarean delivery after induction of labor was unsuccessful twice. The couple was tested for HIV at 2 weeks, 3 months and 6 months following each IUI and ICSI cycle, and HIV-1 RNA was not detected in either partner. The baby was also tested for HIV until 3 months after birth, and the results were negative.

Ethics statement

This case report with a waiver of informed consent was approved by the IRB (IRB No.1907-091-1048) of Seoul National University Hospital.

DISCUSSION

This is the first case of successful delivery after ART in an HIV-serodiscordant couple in Korea. In 1987, the Korean government legislated the Prevention of AIDS Act⁷ and mandated that HIV-1-infected individuals be tested and report their status to public health centers every month. According to article 25 of this law, it is illegal to use HIV-infected blood, organs, tissues and semen. Therefore, ART practice or any actions to become pregnant in HIV-serodiscordant couples have been considered impossible. In contrast to this article, the Korean Constitution indicates that all citizens shall be assured of human worth and dignity and have the right to pursue happiness.⁹ In the United States of America, US state laws do not limit a serodiscordant couple's right to use infertility services, such as the IUI of sperm from an HIV-positive male partner because HIV-positive individuals are covered under the Americans with Disabilities Act.¹⁰ Over sixty percent of the infertility clinics in the US have reported that they are able to offer ART services for HIV-serodiscordant couples.¹¹

In September 2013, before the initiation of the practice, we asked the authentic opinion of the KCDC whether ART could be practiced in HIV-serodiscordant couples in Korea. They responded that infertility services for serodiscordant couples with the purpose of childbearing are not in violation of the law because the KCDC had considered a similar issue before, namely, the compulsory abortion and sterilization policies by the Korean government for Hansen's disease patients in leprosariums until the 1990s.¹² They also described that the AIDS Prevention Act was enacted not only for prevention of AIDS but also for protection and support of HIV-infected people. Moreover, they considered the level of current medical practice and both pregnancy and delivery as basic human rights. Afterwards, the IRB approved the practice and it could be started.

The early initiation of antiretroviral therapy has significantly reduced the rates of HIV sexual transmission, being as high as 0.1% for the female partner of an HIV-seropositive male after an act of unprotected intercourse.^{13,14} However, this low risk is not negligible and does not rule out the possibility of HIV transmission.^{15,16} ART is acceptable in preventing the horizontal and vertical transmission of HIV between these patients and in achieving pregnancy safely.¹⁷ Semen washing in combination with IUI or ICSI has been used for 30 years to decrease the risk of transmission.¹⁶ Basically, semen washing involves the separation of motile sperm from seminal plasma or non-seminal cells that may harbor virus. This procedure can be achieved by centrifugation with density gradient followed by the use of swim-up technique.¹⁶ A recent meta-analysis reported that there was no HIV transmission in 11,585 ART cycles with the use of semen washing among 3,994 women.⁶ In the present

case, the serum HIV test results for both the partners and the baby were negative after the predefined period.

In the present case, ICSI following three IUI cycles attempts was used instead of conventional IVF. Some have argued that ICSI uses only a single sperm that is injected directly into the oocyte and can minimize the risk of transmission.¹⁸ However, the overall pregnancy rates of IUI cycles were similar to those of ICSI cycles, and HIV transmission was not observed in a systematic review.⁶ Therefore, we proceeded with ICSI after the failure of the IUI cycles in the present case, as well as in healthy couples.

To summarize, we report the first successful pregnancy in and delivery by a couple with ART treatment that comprised a HIV-seropositive male in Korea. In this regard, this study presents a safe ART method for HIV-serodiscordant couples who desire to have a baby.

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