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LETTER TO THE EDITOR

Male Infertility

A successful pregnancy by intracytoplasmic sperm injection using ejaculate sperm from an infertile man with 46, XX/46, XY true hermaphrodite

Yan-Wei Sha[1,*], Yan-Kun Sha[2,*], Lu Ding[1], Shao-Bin Lin[1], Zhi-Yong Ji[1], Xu Wang[1], Yue-Qiang Song[1], Ping Li[1]

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Dear Editor,

True hermaphroditism is a condition in which the gonads, genital morphology, and sexuality simultaneously show both male and female characteristics (ovaries and testes) or in which both types of gonadal tissue exist in a single gonad (known as an ovariotestis). True hermaphroditism associated with a chimeric or 46, XX/46, XY karyotype is extremely rare, and the genitalia of those affected can be characterized as female, male, or mixed.[1–3] The cause of true hermaphroditism has not been determined because the condition is relatively rare and has a diverse phenotype.[4]

The majority of masculine individuals experience varying degrees of low fertility or sterility because the chimeric karyotype prevents complete development of the male and female gonads, though there are some exceptions.[5] Dysfunctional spermatogenesis usually is characterized by severe oligospermia, asthenospermia, or azoospermia. Some masculine individuals experience dyszoospermia, leading to varying degrees of low fertility or sterility,[6] which is typically not observed in feminine patients with true hermaphroditism,[7,8] Assisted reproductive technology (ART) is an ideal alternative for true hermaphrodites.[9] In 2005, Sugawara *et al*. reported a case of successful delivery by a woman impregnated through intracytoplasmic sperm injection (ICSI) using frozen-thawed sperm obtained by testicular biopsy from an infertile 46, XX/46, XY true hermaphrodite.[10]

Here, we report a successful pregnancy obtained by ICSI using ejaculate sperm from an infertile man with 46, XX/46, XY true hermaphrodite. The patient described in this manuscript has provided written informed consent to publish this case.

In August 2014, a 33-year-old man with his wife attended our infertility clinic. In June 2007, he observed the presence of female breasts and an abnormally small penis compared with that of normal age-matched men. His blood estradiol (E2) level was 193 pg ml^{-1} (reference range: 20–47 pg ml^{-1}). The patient was preliminarily diagnosed with congenital hypospadias (penile type) and left cryptorchidism, though hermaphroditism was not ruled out. Color Doppler imaging showed normal adrenal glands. Karyotype analysis of peripheral blood using the G-staining method revealed a 46, XX/46, XY chimeric karyotype. Pelvic computed tomography (CT) indicated possible uterine and female reproductive tissue, which was later confirmed by histopathology as uterine tissue with a secretory endometrium, partial polypoid changes, and myometrium; a left ovary with an organized corpus luteum and a fallopian tube. Based on these findings, the patient was diagnosed with true hermaphroditism. In August 2014, the patient and his wife presented to our facility for the treatment of his primary sterility.

In ejaculate semen, sperm density was 1.2×10^6 ml^{-1} with about 28% motility. Sex hormone levels were as follows: FSH, 72.47 mIU ml^{-1} (reference range, 1.27–19.26 mIU ml^{-1}); LH, 30.47 mIU ml^{-1} (reference range, 1.24–8.62 mIU ml^{-1}); E2, 29 pg ml^{-1} (reference range, 1.27–19.26 pg ml^{-1}); T, 3.52 ng ml^{-1} (reference range, 1.75–7.81 ng ml^{-1}); and PRL, 23.30 ng ml^{-1} (reference range, 2.64–13.13 ng ml^{-1}). The patient was diagnosed with severe oligospermia, and ICSI was deemed as the only feasible option for conception.

Ovulation for his wife was triggered by combined administration of a gonadotropin-releasing hormone (GnRH) agonist (GnRH-a; Enantone; Takeda Osaka Plant, Osaka, Japan), recombinant FSH (r-FSH; Gonal-F; Serono Laboratory Co. Ltd., Geneva, Switzerland), highly purified menotrophin (HP-HMG; Menopur; Ferring International Center SA, Kiel, Germany), and 250 μg recombinant human chorionic gonadotropin (r-HCG; Ovidrel; Serono Laboratory Co. Ltd., Japan). GnRH-a was administered at 0.75 mg on day 4 of menstruation, followed by another 1.875 mg 28 days later. r-FSH and HP-HMG were administered daily until the dominant follicle achieved a mean diameter of 18 mm; subsequently, r-HCG was administered to induce ovulation. A vaginal ultrasound-guided follicular puncture was performed 36 h after r-HCG injection, and seven mature oocytes were retrieved. The patient ejaculated after masturbation on the day of oocyte retrieval. The semen was centrifuged at 1400 rpm for 10 min, and the sperm pellet was re-suspended to 150 μL of medium.

Three days after performing ICSI, two embryos were transferred into his wife's uterine. She was prescribed 300 mg oral progesterone to be taken twice daily (Utrogestan; Laboratories Besins International, Montrouge, France) for 12 days and 90 mg of topical 8% progesterone to be applied daily (Crinone; Fleet Laboratories

[1]Center for Reproductive Medicine, Xiamen Maternity and Child Care Hospital, Xiamen 361003, China; [2]Department of Nephrology, First Affiliated Hospital of Liaoning Medical University, Jinzhou 121000, China.
*These authors contributed equally to this work.
Correspondence: Dr. P Li (saarc2001@sina.com)
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Limited, Watford, England). Her qualitative serum HCG level 12 days after embryo transfer was 206.96 mIU ml^{-1}, which increased to 571.34 mIU ml^{-1} two days later.

At 45 days of gestation, a singleton pregnancy with fetal heartbeat was confirmed by transvaginal ultrasound. At 16 weeks, amniotic fluid analysis was performed with a normal 46, XY fetal karyotype. A healthy male child was delivered.

In most cases of the true hermaphroditism, the ovarian structures are completely developed and can secrete estrogen from the onset of puberty. Our patient was identified as a male at birth and was always treated as a boy. However, his feminine breasts, abnormally small penis, and high E2 level suggested hermaphroditism. Several urogenital surgeries resolved his abnormal micturition, and the uterine and other feminine tissues were excised, thus correcting the external and physiologic manifestations of his hermaphroditism. After surgery, his E2 level was normal, and he maintains a consistent physiologic sex and gender.

There are several cases involving male hermaphroditic patients associated with successful pregnancy and delivery.[10] In cases with azoospermia, sperm may only be obtained by testicular biopsy. In our case, there were some motile sperms found in ejaculate and so ICSI was performed with fresh ejaculate sperm.

In summary, a successful clinical pregnancy was obtained by ICSI using ejaculate sperm from an infertile man with 46, XX/46, XY true hermaphrodite. Our report suggests that sperm can be found in ejaculate in some infertile men with true hermaphrodites, and infertile men with this severe infertility condition can be treated by ICSI.

AUTHOR CONTRIBUTIONS

YWS and YKS searched literature, interpreted data and drafted the manuscript. LD and SBL carried out the semen test and the preparation of semen. ZYJ and XW conceived of the study, and participated in its design and coordination. YQS and PL put forward the design and helped preparing the manuscript and kept the quality control. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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