—Case Reports—

Successful *in Vitro* Fertilization Pregnancy and Delivery by an Infertile Woman with Ovotesticular Disorder of Sex Development: A Case Report

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On the basis of postoperative histopathological findings, a 29-year-old nulliparous woman was diagnosed as having ovotesticular disorder of sex development (DSD). She had undergone unilateral gonadectomy at age 6 years and vulvoplasty and vaginoplasty at age 8 years. Her karyotype was 46, XX. She had dyspareunia because of a narrow vagina, but her uterus and left gonad were normal. Spontaneous ovulation was confirmed, but sexual intercourse was impossible because of dyspareunia, despite vaginal self-dilatation with a vaginal dilator. Artificial insemination was initiated; however, five cycles failed to yield a viable pregnancy. We decided to perform *in vitro* fertilization (IVF), which resulted in conception. During IVF we administered intravenous anesthesia before oocyte collection to reduce her distress due to insufficient lumen expansion after vaginoplasty. The patient delivered a healthy male infant weighing 2,558 g at 37 weeks of gestation via cesarean section, which was performed because of gestational hypertension. This is the eighth report of a viable neonate born from a patient with ovotesticular DSD after gonadectomy and the first such pregnancy achieved by IVF. Therefore, IVF may be an effective option for infertile patients with ovotesticular DSD. Additionally, to prevent dyspareunia, self-management of the plastic vagina is important during the peri- and postoperative periods of early vaginoplasty. (J Nippon Med Sch 2023; 90: 240–244)

Key words: dyspareunia, gonadectomy, *in vitro* fertilization, ovotesticular, pregnancy

Introduction

Ovotesticular disorder of sex development (DSD) is a condition of incomplete sexual differentiation, characterized by the presence of testicular and ovarian tissues in the same individual. Although rare, pregnancies have been reported in patients who had and had not undergone unilateral gonadectomy for ovotesticular DSD[1]. However, to our knowledge, the literature is limited to cases of natural pregnancies in patients with ovotesticular DSD who had undergone unilateral gonadectomy.

Here, we present a successful case of assisted pregnancy and delivery achieved by *in vitro* fertilization (IVF) in an infertile patient with ovotesticular DSD who had previously undergone unilateral gonadectomy.

Case Report

History

The patient was a 29-year-old nulligravid and nulliparous woman who initially presented to a specialist with a chief complaint of dyspareunia. She was married and desired children and was referred to our hospital for detailed clinical examination and treatment.

An abnormal vulval morphology had been noted at her birth. At age 6 years, before the surgery, an enlarged clitoris and no vagina were observed. A swelling, which was diagnosed postoperatively as ovotestis, was palpable at her right groin. Thereafter, she underwent unilateral gonadectomy at another hospital, and the diagnosis of ovotesticular DSD was confirmed histopathologically. At age 8 years, she underwent reconstructive surgery (vul-

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https://doi.org/10.1272/jnms.JNMS.2023_90-202
Journal Website (https://www.nms.ac.jp/sh/jnms/)

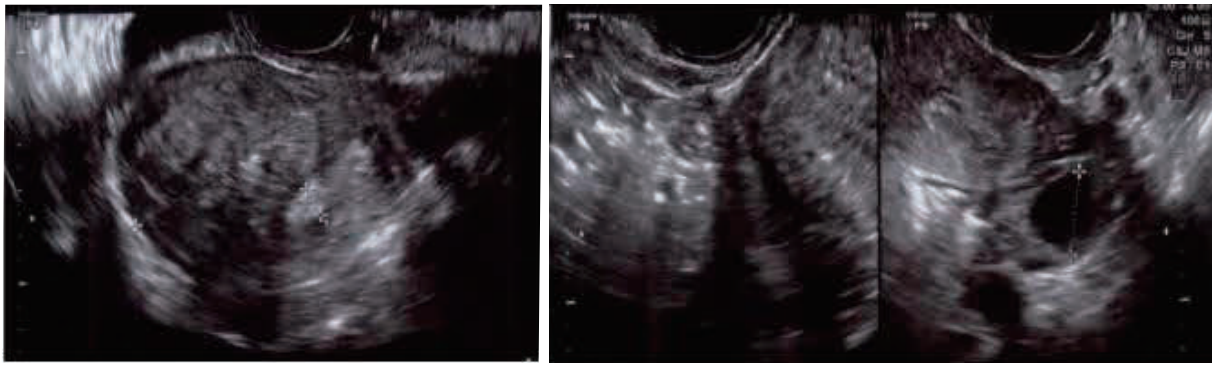

Fig. 1 Images of transrectal ultrasonography
Left: Uterus with adenomyosis. Right: Left ovary with visible antral follicles; the right ovary could not be identified.

voplasty and vaginoplasty). Unfortunately, the records of that procedure are unavailable and further details could not be ascertained.

Physical Examination (at First Visit)

The patient's height and weight were 157 cm and 52 kg, respectively, and the external features (breasts and pubic hair) appeared feminine. She had female genitalia, with distinct labia majora, labia minora, and a clitoris; the constructed vagina was located anterior to the labia minora, which were fused. On pelvic examination, the patient's vagina was narrow, allowing for the insertion of only one finger. Her uterus was of normal size and anteverted.

Investigations

Transrectal ultrasonography revealed an 83-mm-long uterus with an endometrial thickness of 4.5 mm. In addition, an enlarged area caused by adenomyosis (35 mm) was observed in the uterus. The left gonad measured 31 mm and the antral follicles were visible; the right gonad could not be identified (**Fig. 1**). The patient declined hysterosalpingography.

The patient's serum hormone levels during menstruation were as follows: luteinizing hormone, 3.8 mIU/mL; follicle-stimulating hormone, 7.7 mIU/mL; estradiol (E_2), 29.0 pg/mL; anti-Müllerian hormone (AMH), 1.98 ng/mL; total testosterone, 0.35 ng/mL; thyroid-stimulating hormone, 1.94 μIU/mL; free triiodothyronine, 3.1 pg/mL; free thyroxine, 1.5 ng/mL; and prolactin, 10.5 ng/mL. In addition, tests for immunoglobulin (Ig)A and IgG antibodies against *Chlamydia trachomatis* yielded negative results. Her karyotype was 46, XX.

Analysis of her partner's semen showed a semen volume of 1.6 mL, sperm count of 107 million/mL, and sperm motility of 72%.

Treatment and Course

We proceeded to expand the vagina with a vaginal dilator. The patient began to self-dilate once it reached a diameter of 20 mm, achieving further expansion to 30 mm in 6 months. Although spontaneous ovulation was confirmed, sexual intercourse was impossible because of the associated pain. Because of the dyspareunia, artificial insemination was initiated; however, five cycles failed to yield a viable pregnancy. Thus, we decided to perform IVF for idiopathic infertility.

Two cycles of oocyte retrieval were performed. The gonadotropin-releasing hormone antagonist protocol (0.25 mg daily when the leading follicle is 14-15 mm) was used in both IVF cycles. The E2 and progesterone (P4) levels of each cycle were 2,606 pg/mL and 0.56 ng/mL and 2,731 pg/mL and 0.05 ng/mL, respectively, on the day of human chorionic gonadotropin (hCG) administration. Both oocyte retrieval procedures were performed transvaginally at 36 h after hCG injection. Oocytes were harvested under intravenous anesthesia with transvaginal ultrasound guidance. Eight and nine oocytes were retrieved in each cycle. The retrieved oocytes were prepared for conventional IVF. The two cycles of oocyte retrieval yielded a total of six frozen blastocysts.

We conducted various tests before embryo transfer (ET). Hysteroscopy revealed some shrinkage of the uterine cavity (lumen); the oviducts were visible bilaterally (**Fig. 2a**). No findings indicative of chronic endometritis were observed. The biopsied endometrial tissue was stained by using cluster of differentiation 138-immunohistochemistry and viewed under high-magnification microscopy. One or more plasma cells were observed in four of 10 fields in total, leading to a diagnosis of chronic endometritis. We administered doxycycline hyclate (Vibramycin; Pfizer Inc., New York, NY, USA). In addition, uterine adenomyosis was confirmed by contrast-enhanced pelvic magnetic resonance imaging (MRI) (**Fig. 2b**).

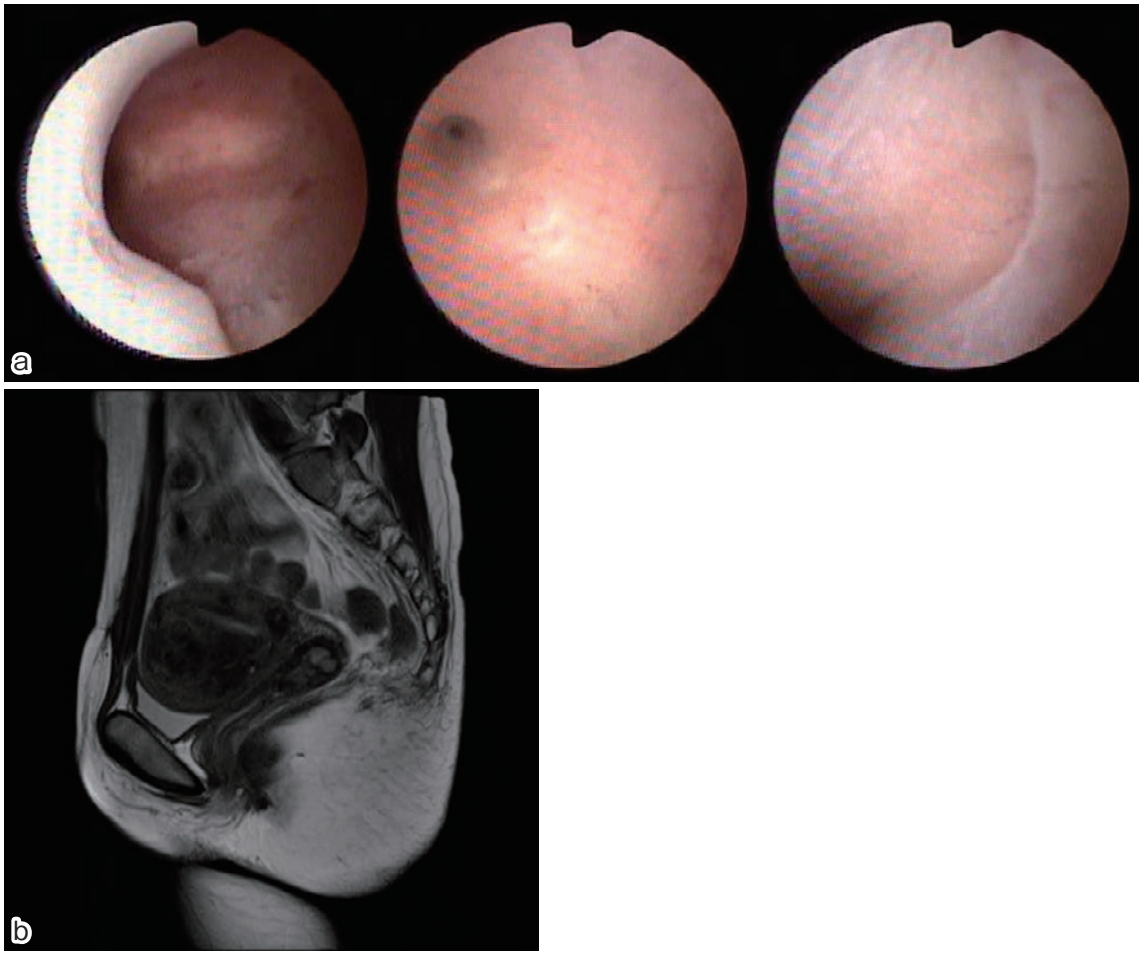

Fig. 2 Imaging findings before embryo transfer
a) Hysteroscopic image of the uterine cavity. Left: Uterine cavity (lumen). Center: Right oviduct. Right: Left oviduct. b) A T2-weighted enhanced magnetic resonance image of the pelvis shows the uterus with adenomyosis.

A frozen-thawed single embryo was transferred 5 days after the initial P4 application. Embryo transfers were performed under real-time transvaginal and transabdominal ultrasound guidance, using a KITAZATO ET Catheter (Kitazato Corp., Tokyo, Japan). She conceived after the second frozen-thawed ET.

A pregnancy-related follow-up examination was performed at Nippon Medical School Hospital. An elective cesarean section was initially scheduled for week 38 because of her past history of reconstructive surgeries. The patient's pregnancy course was unremarkable until week 36, when she developed gestational hypertension without signs of pre-eclampsia such as proteinuria or severe hypertension; she delivered the infant via cesarean section at week 37 (male, 2,558 g), 1 week earlier than scheduled because of concerns regarding progression of gestational hypertension. Her systolic and diastolic blood pressures before delivery were <160 and <100 mm Hg, respectively, and returned to normal after 1 day. Intraoperative findings showed extensive adhesion of the uterus to the peritoneum, and her left gonad was detected as an ovary of regular size. The infant's Apgar scores at 1 and 5 min after the delivery were 7 and 9, respectively. On the first day, he needed respiratory care in the growing care unit, from which he was discharged a day later.

This article does not contain any studies of human and animal subjects performed by any of the authors. The patient provided informed consent to use the clinical results for our research.

Discussion

We describe our treatment of a case of ovotesticular DSD in an infertile woman who had undergone unilateral gonadectomy as a child. IVF resulted in conception and live birth. To date, there have been few reports of pregnancies in such cases; this is only the eighth successful delivery documented among women with this condition post-gonadectomy. The seven previous cases resulted from natural conception, making this the first case in the literature of IVF pregnancy and viable delivery reported

Table 1 Pregnancies and births after gonadectomy in persons with ovotesticular disorder of sex development

Studies	Karyotype	Age (years) at gonadectomy	Age (years) at vulvoplasty	Age (years) at vaginoplasty	Age (years) at pregnancy	Delivery	Infant
Narita et al., 1975 [2]	46, XX	25	25	None	34	Cesarean section	Male
Williamson et al., 1981 [3]	46, XX	6	6	None	18	Vaginal	Male
Minowada et al., 1984 [4]	46, XX	14	4	None	24	Vaginal	Male
Starceski et al., 1988 [5]	46, XX	0	1	15	23	Cesarean section	Male
Pereira et al., 1991 [6]	46, XX	13	None	None	Unknown	Vaginal	Male
	46, XX	13	None	None	Unknown	Vaginal	Male
Schultz et al., 2009 [7]	46, XX	0	0	None	21	Vaginal	Male
Present Case	46, XX	6	8	8	30	Cesarean section	Male

in a patient with ovotesticular DSD post-gonadectomy.

Successful birth by a woman with ovotesticular DSD after gonadectomy is rare. Zeki et al. reported 26 pregnancies among women with ovotesticular DSD[1], specifically, seven and 19 cases of pregnancy in patients with ovotesticular DSD who had and had not undergone gonadectomy, respectively (**Table 1**). Only one of the seven women had undergone vaginoplasty, at age 15 years, while continuing dilation therapy; intercourse was initially painful after colporrhaphy, and pelvic inflammation occurred because of intercourse[5]. However, she conceived naturally at age 22 years, and her child was delivered by cesarean section.

The existing literature, including the report by Zeki et al., suggests that ovotesticular DSD is not involved in gestational hypertension. Because our patient had no history of hypertension or known risk factors, such as obesity or family history, the development of gestational hypertension was considered incidental.

In all reported cases, including the present case, the neonate was male. There are two hypotheses as to why children delivered by women with ovotesticular DSD are male. First, the functional ovary in ovotesticular DSD is usually located on the left side[8]. Venous drainage of the ovaries makes the left ovary warmer than the right ovary, which may favor sperm with a Y chromosome. The second hypothesis is related to possible characteristics of maternal embryo disorders in fertilization and embryonic development[7]. Embryos formed by oocytes fertilized by sperm carrying an X chromosome may not survive, because of a genetic disorder involving the sex chromosomes or autosomes. For example, an abnormal maternal X chromosome with Y genes may not pair well with a normal paternal X chromosome at fertilization. Possibly, pairing of an abnormal X with a shorter Y chromosome during early embryogenesis may not be a problem in this rare condition. As this was the first such case where IVF was performed, the detailed results would support these theories. In our patient, there was no obvious abnormality in fertilization or embryonic development; nevertheless, our findings are insufficient to rule out the latter hypothesis, mainly because preimplantation genetic testing was not performed. Four frozen blastocysts remain, and the patient desires additional children. Although there is risk associated with repeated cesarean sections, it is important to confirm the sex of subsequent children or to examine the chromosomes in miscarried tissue if the pregnancy ends in abortion.

In cases of vaginal hypoplasia, reconstructive surgery is one option for ovotesticular DSD, although practitioners should also consider self-management in the peri- and postoperative periods. Vulval and vaginal morphologies are diverse in ovotesticular DSD. Although no precise taxonomy has been established, the three types usually discussed are masculine, feminine, and ambiguous. Takezaki et al. reported that most patients with ovotesticular DSD with one ovary and one ovotestis have a feminine vulva and are raised as girls[9]. Similarly, our patient was born with one ovary and one ovotestis and was raised as a girl. An interview with the patient revealed that she received a diagnosis of ovotesticular DSD at age 6 years, which was based on histopathological findings after unilateral gonadectomy. However, surgical and pathological records were unavailable and further information could not be obtained. She also underwent vulvoplasty and vaginoplasty at age 8 years. Despite our efforts to dilate the vaginal cavity 20 years after this reconstructive surgery, the persistence of painful intercourse necessitated a strategic shift to artificial insemination. Opinions differ on the optimal timing of vaginoplasty.

Jong et al. recommend that it should be performed during the neonatal period, when the internal and external genitalia are relatively well developed, because of the high estrogen environment in the uterus[10]. Specifically, the timing should be based on patient compliance with self-management postoperatively and the presence of a willing sexual partner in the present or near future. Mekaru et al. performed vaginal reconstruction for a 26-year-old woman with Mayer-Rokitansky-Küster-Hauser syndrome but reported that her vaginal cavity shrank after the procedure because of negligent self-management during periods without a sexual partner[11].

The present outcome was a successful IVF pregnancy and relatively early delivery. This is potentially good news for infertile women with ovotesticular DSD. Typically, IVF is not considered until a woman reaches the age of 30 years; however, our patient's AMH titer was approximately half the standard value for women her age, but comparable to the expected value for a woman her age with only one functional ovary, suggesting a healthy ovarian reserve[12]. Indeed, her course was favorable for a woman of her age, leading to pregnancy 9 months after the first IVF procedure. This indicates that unilateral gonadectomy is unlikely to materially affect IVF outcomes for patients with ovotesticular DSD.

Practitioners should be aware that insufficient lumen expansion after vaginoplasty complicates oocyte collection and ET. Technical difficulties due to a short, inelastic neovagina have been reported during oocyte retrieval[13,14]. Our patient associated transvaginal procedures with pain and fear; thus, we administered adequate intravenous anesthesia before oocyte collection to reduce her distress. In addition, contrast-enhanced pelvic MRI and hysteroscopy were performed before ET. The latter was successfully performed with combined transvaginal and transabdominal ultrasonography.

In conclusion, this is the first case report of a successful IVF pregnancy and viable delivery by an infertile patient with ovotesticular DSD who had previously undergone unilateral gonadectomy. Early vaginoplasty may be ineffective for reproductive-age patients with ovotesticular DSD, because the vaginal cavity needs to be dilated to prevent dyspareunia. IVF is an effective option to achieve successful conception and birth for infertile patients with ovotesticular DSD.

Acknowledgements: The authors would like to thank Editage (www.editage.jp) for English language editing.

Conflict of Interest: None declared.

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(Received, January 29, 2021)
(Accepted, November 22, 2021)
(J-STAGE Advance Publication, January 25, 2022)