

TRANSMYOMETRIAL BLASTOCYST TRANSFER IN A PATIENT WITH CONGENITAL CERVICAL ATRESIA

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Congenital atresia of the cervix, with or without vaginal agenesis, is a rare Müllerian developmental disorder [1,2]. The mechanisms causing cervical atresia remain unknown. Primary amenorrhoea, together with cyclic abdominal pain caused by hematometra, are the most common clinical presentations. The aims of treatments for this anomaly, which include reconstructive surgery, are firstly to relieve the symptoms and secondly to restore fertility and regular menstruation [3,4]. However, reconstructive surgery may be associated with severe complications such as pelvic inflammation or restenosis of the neocanal, which can require hysterectomy in many cases [5].

Assisted reproductive techniques (ART) increase the chances of pregnancy and childbirth in patients with congenital cervical atresia; four successful pregnancies have recently been reported in patients with this condition following *in vitro* fertilization (IVF) and transmyometrial embryo transfer (TMET) [6–9]. However, cleavage-stage embryos were transferred in all these cases.

Herein, we describe a patient with complete cervical atresia and vaginal dysgenesis who underwent a successful pregnancy with a positive fetal heartbeat after IVF treatment carried out using ultrasound-guided transmyometrial blastocyst transfer (TMBT). To the best of our knowledge, this represents the first reported case of a successful pregnancy in a patient with complete cervical atresia after TMBT.

A 33-year-old woman was referred to the outpatient clinic of the reproductive medicine center at Cathay General Hospital Hsinchu Branch in 2005 suffering from hypomenorrhea and a failure to become pregnant for

2 years. Her past history was remarkable for cyclic abdominal pain and lack of menstruation since the age of 14 years. Congenital complete cervical atresia with a short vagina was diagnosed by a gynecologist at St. Joseph's Hospital. She underwent simultaneous reconstructive surgery to create a functional uterovaginal passage and vaginoplasty to elongate the vaginal vault. Regular menstrual cycles with a period of 28 days were restored after surgery, and her cyclic abdominal pain subsided. However, she still suffered from hypomenorrhea and persistent leukorrhea with a smelly odor.

Examination at our clinic revealed normal secondary sexual maturation, including breast development and pubic hair. Her height was 160 cm and her weight was 49 kg. She had a normal female karyotype of 46,XX. Gynecologic examination demonstrated a 5-cm-long vaginal vault with no cervix and a dilated lower segment of uterus, about 2 cm in diameter with an opening to the vagina. Ultrasound examination revealed normal ovaries and a normal-sized uterus with a thin (7 mm) middle-secretory phase endometrium. Measurements of serum follicle-stimulating hormone, luteinizing hormone, estradiol, and progesterone suggested normal ovarian function, but an increased prolactin level (40.5 ng/mL) was detected. Her hyperprolactinemia resolved after treatment with bromocriptine.

Hysterosalpingography showed bilateral tubal obstruction (Figure 1). Laparoscopic examination confirmed the presence of bilateral obstructed Fallopian tubes via chromopertubation. Severe pelvic adhesion caused by chronic pelvic inflammation was also noted. The uterine body and bilateral ovaries were normal. Her husband's semen analysis was normal.

The couple received counseling regarding their fertility status, including the need for IVF-embryo transfer (ET) therapy to establish a pregnancy because of tubal occlusion; they decided to start treatment in July 2008. After pituitary downregulation with a gonadotropin-releasing hormone analog (Lupron), a total of 1,650 IU recombinant follicle stimulating hormone (Gonal-F) and



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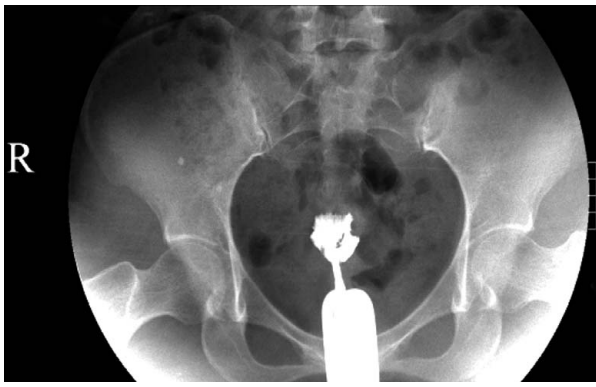


Figure 1. Hysterosalpingography image showing bilateral tubal obstruction.

825 IU human menopausal gonadotropin (Merional) were used for controlled ovarian hyperstimulation. Transvaginal oocyte retrieval was performed 36 hours after an intramuscular injection of 10,000 IU human chorionic gonadotropin (hCG, Pregnyl). The endometrial thickness on the day of ovum retrieval was 12 mm. Nine oocytes were retrieved, five of which were fertilized. After 68 hours, four 8-cell embryos were selected for transfer. Embryo transfer was initially attempted through the uterovaginal canal, because we had previously successfully inserted a metal uterine probe via this canal into the uterine cavity. However, embryo transfer by this approach failed because it was difficult to insert the soft embryo-transfer catheter through the tortuous uterovaginal canal without the support of a cervical clamp. We therefore extended the embryo culture to day 5, and three out of four 8-cell embryos developed to one early blastocyst and two full expanded blastocysts. All the three blastocysts were transferred via TMBT under general anesthesia using a 5 MHz endovaginal ultrasound probe and a “Towako” embryo transfer catheter. The “Towako” needle with its stylet was passed through the anterior vaginal fornix under ultrasound guidance, then through the myometrium of the anterior uterine wall with its adjacent endometrium, and into the endometrium of the posterior wall. The needle was then pulled back gently into the uterine cavity and the stylet was removed. A catheter loaded with the embryos was introduced into the needle and the embryos were transferred by gentle injection. Transvaginal ultrasound showed the presence of an echogenic air bubble in the posterior endometrium of the uterus where the blastocysts and culture medium were deposited (Figure 2). Luteal support was maintained with daily intramuscular progesterone-in-oil injections of 50 mg and vaginal progesterone gel (Crinone 8%) 90 mg twice daily.

A positive pregnancy test with a serum β -hCG level of 173.89 mIU/mL was obtained 10 days after TMBT.

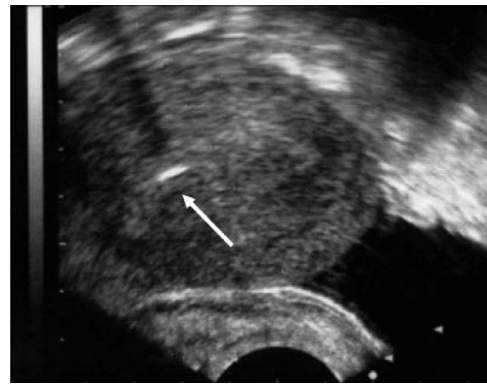


Figure 2. The process of transmyometrial blastocyst transfer under ultrasound guidance. Transvaginal ultrasound showing an echogenic air bubble in the posterior endometrium of the uterus where the blastocysts and their culture medium were delivered (arrow).

At 25 days after TMBT, serum β -hCG was 6,375 mIU/mL and an intrauterine gestational sac, about 1.1 cm in size, was detected by transabdominal ultrasound. A fetal pole with a crown-rump length of 5.2 mm and the presence of a fetal heartbeat were detected 1 week later (Figure 3). The fetal crown-rump length had increased to 8 mm at 39 days after TMBT. However, fetal cardiac activity was absent and a missed abortion was diagnosed. Evacuation of the intrauterine mass by laparotomy, whole-body or local injection of methotrexate, oral mifepristone (RU486) therapy or conservative observation were discussed as potential management options for the abortion; the couple chose oral mifepristone therapy. The patient received 600 mg mifepristone and 600 mg misoprostol (U-miso) orally on day 44 post-TMBT. Vaginal bleeding began on the day after medication. Six days after medication, serum β -hCG was 1,110 mIU/mL and sonography revealed a 3.5-cm hematoma within the lower part of the uterus (Figure 4). Vaginal bleeding had ceased 16 days after medication and serum β -hCG had decreased to 20 mIU/mL. No signs or symptoms of infection occurred throughout the medication period.

The probability of spontaneous pregnancy is low in patients with congenital cervical atresia, even following successful canalization surgery. This could be attributable to the lack of normal endocervical canal glandular function, severe endometriosis, or tubal problems secondary to the anomaly. Only three spontaneous pregnancies in patients with this disease have previously been reported [10–12].

ART, however, should enhance the chances of pregnancy in patients with congenital cervical atresia and five successful pregnancies have been reported in patients with this disease using ART. One patient became pregnant after zygote intra-Fallopian transfer [13] and three



Figure 3. Transabdominal ultrasound on day 32 after transmyometrial blastocyst transfer showing a positive fetal heart beat and a fetal crown rump length of 0.52 cm.

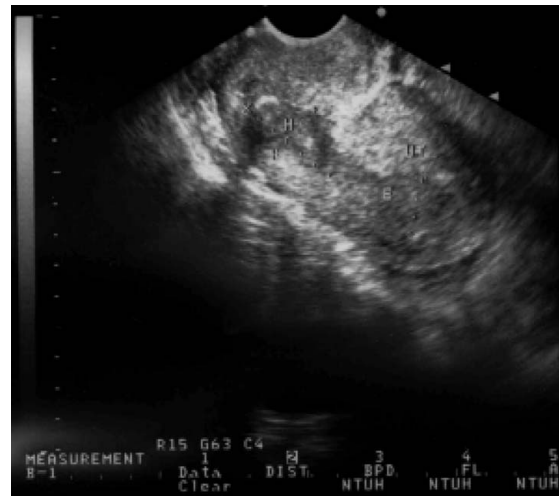


Figure 4. Six days after mifepristone and misoprostol medication (50 days post-transmyometrial blastocyst transfer), a 3.5-cm hematoma can be detected within the lower part of the uterus. No gestational sac or fetus can be detected (H = hematoma; UT = uterus; E = endometrium).

Table. Summary of assisted reproductive techniques used in pregnant women with congenital cervical atresia

Authors	Type of ART	Embryo stage	Outcome
Thijssen et al [13]	ZIFT	–	Delivery at 38 wk gestation
Anttila et al [6]	TMET	4-cell	Delivery at 32 wk gestation
Lai et al [8]	TMET+TET	8-cell	Delivery at 36 wk gestation
Suganuma et al [7]	TMET	Cleavage stage	Missed abortion and blighted ovum
Xu et al [9]	TMET	Cleavage stage	Delivery at 30 wk gestation
Present study	TMET	Blastocyst	Missed abortion and FHB (+)

ART=assisted reproductive technology; ZIFT=zygote intra-Fallopian transfer; TMET=transmyometrial embryo transfer; TET=transtubal embryo transfer; FHB=fetal heart beat.

conceived after TMET with fresh or frozen-thawed embryos [6,7,9]. One pregnancy was reported after TMET and transtubal ET [8]. Cleavage-stage embryos were selected for TMET in all these cases (Table).

ET at the blastocyst stage is known to be associated with a higher implantation rate and a lower multiple pregnancy rate compared with transfer at the cleavage stage. In addition, blastocyst transfer provides opportunities to select more viable embryos and to place the embryos into a more synchronized uterine environment [14]. The current case represents the first pregnancy in a patient with congenital cervical atresia arising from IVF-TMET using blastocysts, rather than cleavage stage embryos. Although this case resulted in a missed abortion, our experience supports the possibility of pregnancy using TMBT in patients with congenital cervical atresia.

Management of a missed abortion in patients with congenital cervical atresia has also rarely been reported. Traditional dilatation and curettage is difficult to perform in such patients because of the lack of cervix.

Although surgery, such as laparotomy or laparoscopy, can be performed to remove the remaining intrauterine mass, only one case of a patient having a complete abortion using conservative observation without surgery or medication has been reported [7].

In the present case, the patient decided to terminate the missed abortion with mifepristone and complete evacuation of the intrauterine mass occurred 16 days after medication, with no signs of infection. To the best of our knowledge, this is the first report of successful termination of a missed abortion with mifepristone in a woman with congenital cervical atresia. However, a long follow-up period is required between administration of the medication and expulsion. We suggest that surgical treatments to manage this condition, such as laparoscopy or laparotomy, should only be offered as last choices.

In conclusion, TMBT can result in pregnancy in patients with congenital cervical atresia. Medical treatment with mifepristone offers a viable alternative method of termination for missed abortion in these patients.

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