Endometrial receptivity is preserved in Diethylstilbestrol-associated and other Müllerian anomalies: Evidence from tubal embryo transfer

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Abstract

Purpose To report implantation and pregnancy rates following TET in women with anomalous uteri, and to compare these with previously reported rates following trans-cervical ET.

Materials and Methods Between 1995 and 2003, 12 TET procedures were performed in seven women with Müllerian anomalies. Tubal ET was performed via laparoscopy 48 h after standard IVF in 3 cycles in two patients, whereas in 9 cycles in five patients, TET was performed 24 h or 48 h following oocyte donation.

Results Of the seven patients, 5 (71%) had a history of 15 failed cycles with trans-cervical ET. The 12 TET procedures resulted in eleven clinical pregnancies (92%; 95% CI: 63, 99%). There were seven deliveries/ongoing pregnancies (58%; 95% CI: 27%, 85%).

Conclusions We observed high implantation and ongoing pregnancy rates in women with Müllerian anomalies, suggesting that 1) endometrial receptivity in anomalous uteri is preserved, and 2) transfer efficiency is reduced but may be restored with the use of TET.

Keywords Diethylstilbestrol · Endometrial receptivity · Müllerian anomalies · Tubal embryo transfer

Capsule Tubal embryo transfer results in high implantation and live birth rates in women with diethylstilbestrol-exposed and other anomalous uteri, suggesting that endometrial receptivity is preserved.

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Congenital uterine anomalies are found in 2–3% of reproductive-age women [1]. Such anomalies, secondary to antenatal diethylstilbestrol (DES) exposure or due to sporadic abnormal Müllerian duct development, are associated with structural abnormalities of the female reproductive tract, and impaired reproductive outcome. Limited available data of pregnancy success following assisted reproductive technology (ART) in women with anomalous uteri suggest decreased implantation and ongoing pregnancy rates in such women [2–7]. In a review of published reports, the highest reported implantation and ongoing pregnancy rates following ART in DES exposed women were 13.6% and 28%, respectively [6], with rates failing to exceed 10% in the remainder of published reports.

Compared with controls, ART in women with anomalous uteri results in similar stimulation characteristics, yield of mature follicles, and fertilization and embryo cleavage rates, suggesting intact ovarian reserve; accordingly, abnormal endometrial receptivity has been proposed as the factor contributing to reduced reproductive potential in such women [3–7; 8, 9]. However, in addition to endometrial receptivity and embryo quality, the third general category of factors influencing successful embryo implantation following ART is embryo transfer efficiency [10]. Clinical experience at our center suggested that uterine anomalies were associated with an embryo transfer that was not technically difficult, yet appeared to cause an unexpectedly high level of uterine cramping. This anecdotal experience suggested to us that the anomalous uterus was associated with reduced transfer efficiency when the transfer was performed by the trans-cervical route. We hypothesized that transfer efficiency might not be reduced if the transfer were performed by the trans-tubal route. In this communication, we describe our experience with tubal embryo transfer

(TET) as a modification of standard ART technique for women with anomalous uteri.

During the years 1995–2003, seven women who had been diagnosed with a Müllerian anomaly underwent 12 TET procedures. Anomalies included T-shaped uterus secondary to DES exposure (seven transfers in three patients), T-shaped uterus in association with congenital uterine septum (three transfers in three women), and uterus didelphys (two transfers in one patient). Septa were incised hysteroscopically before fertility treatment and absence of the septa was confirmed by hydrosanography, although the T-shape of the uterus remained. All patients had bilaterally patent fallopian tubes, as confirmed by hysterosalpingography in the preoperative period. All fallopian tubes were judged to be normal in appearance at the time of laparoscopy prior to performing the TET procedure. Controlled ovarian hyperstimulation (COH) was performed using standard protocols. All recipients of egg donation underwent a practice cycle as previously described [10]. Briefly, all received a regimen of oral estradiol with graduated doses starting with 2 mg daily and increasing to 6 mg daily. On the day of egg retrieval in the donor, the recipient decreased oral estradiol to 4 mg daily; vaginal progesterone in a dose of 200 mg three times daily was added. Tubal Embryo Transfer took place on the 1st or 2nd day after egg retrieval, which corresponded to day 2 or 3 of progesterone administration, respectively. Tubal ET (mean 4.2 ± 1.0 embryos) was performed via laparoscopy 48 h after egg retrieval in 3 cycles in two patients (ages 35 and 39), whereas in 9 cycles in 5 patients, TET was performed in conjunction with egg donation (eight fresh and one frozen-thawed) (mean donor age 27.6 ± 4.3 years). In two of the egg donor cycles, embryos were transferred at the 2PN stage. In all cases, the fallopian tube was cannulated to a depth of 4 cm and the embryos were transferred to the ampulla in a volume of 50 μ L of culture medium. Tubal embryo transfers were performed unilaterally except in the patient with uterine didelphys, who underwent transfer into both fallopian tubes.

Our results are detailed in Table 1. Of the seven study patients, 5 (71%) had a previous history of 15 failed cycles with trans-cervical ET (nine with donated oocytes, six with autologous oocytes). The 12 TET procedures resulted in eleven clinical pregnancies (92%; 95% CI: 63–99%). There were seven term deliveries (58%; 95% CI: 27–85%). The per embryo implantation rate was 37%. The miscarriage rate was 30%. There were no ectopic pregnancies. Implantation and pregnancy outcomes in the DES-associated and other Müllerian anomaly groups were similar (p =NS, Fisher's Exact test). The pregnancy rate among cycles utilizing autologous oocytes was 100% (3/3) whereas among cycles utilizing donor eggs, the pregnancy rate was 67% (6/9). Our results and historical controls are summarized in Table 2. For

Table 1 Summary of cycles

Patient #	Age	# Previous failed cycles	Type of Uterine Anomaly	Infertility Diagnosis	Donor Egg	# Cycle Tubal Embryo Transfer	# Embryos Transferred	Quality of Embryos Transferred	# Implantations	# Babies Born
1	43	4	T-shaped (DES exposure)	DOR ¹	Yes	1	3	2PN x3	2	2
2	45	0	T-shaped (DES exposure)	POF ²	Yes	1	3	6B,3B,6C	1	1
3	37	0	T-shaped (DES exposure)	POF	Yes	1	2	3	0	0
					Yes	2	5	3BC,4AB,6BC, 6BC,6BC	1	1
					Yes	3	5	3C,3C,3BC, 2BC,3BC	1	0
					Yes	4	5	2CD,2D,2C, 5BC,3CD	1	0
					Yes	5	4	2A,3B, 100% frag,4A	1	1
4	51	3	T-shaped (post-metropoelasty)	Ovarian Failure	Yes	1	3	4B, 4B, 4B	1	1
5	54	2	T-shaped (post-metropoelasty)	Ovarian Failure	Yes	1	4	2PN x4	3	0
6	35	1	T-shaped (post-metropoelasty)	Severe male factor	No	1	4	2B,4B,2B,5B	2	2
7	39	5	Didelphys	Unexplained	No	1	6	5B,6B,2B,5C, 4B,3B	3	1
					No	2	5	4B,4B,4C, 4BC,4BC	2	0 ⁴ f

¹ DOR = Diminished Ovarian Reserve,

² POF = Premature Ovarian Failure

³ Data not recorded

⁴ Twin implantations, one in each horn. One lost spontaneously, one terminated secondary to chromosomal anomaly.

Table 2 Implantation and pregnancy rates following *trans-cervical ET* (historical controls) and *tubal ET* (current study) in women with Müllerian anomalies

Study	Anomaly	No. patients	No. transfers	Implantation rate	Clinical preg rate/ET	Ongoing preg rate/ET
Lavergne et al. [3]	Septate, Unicornuate, Bicornuate	38	103	5.8%*	13.6%*	8.7%
Heinonen et al. [2]	Unicornuate, Didelphic, Septate	17	47	8.8%	18.0%	8.2%
Attia et al. [4]	Septate, Bicornuate, Didelphic, DES exposed	37	55	-	8.3%*	8.3%*
Karande et al. [5]	DES exposed	46	149	7.4%*	15.3%	8.3%*
Noyes et al. [6]	DES exposed	38	50	13.6%	32.0%	28.0%
Pal et al. [7]	DES exposed	17	27	2.3%*	12.5%*	8.0%*
Current study (TET)	DES exposed	3	7	25.9%	85.7%	57.1%
	Other Müllerian anomalies	4	5	50.0%	100%	60.0%
	All anomalies	7	12	36.7%	91.7%	58.3%

* $p < 0.05$ (vs. internal control group with normal uteri)

simplicity of data presentation, we have combined the data from donor oocytes and autologous oocytes.

To our knowledge, this is the first report of the use of TET for ART in women with anomalous uteri. In contrast to previous studies, our data suggest that implantation and ongoing/delivery rates in such women are not diminished when TET is utilized. However, the series is small and the confidence intervals are quite broad, as detailed above.

Lower implantation and pregnancy rates previously reported following ART in women with uterine anomalies were suggested to be a function of reduced receptivity of the Müllerian-derived endometrium [2–7]. Although studies evaluating biochemical markers of endometrial receptivity are lacking, limited available data suggest adequate endometrial thickness obtained following standard controlled ovarian hyperstimulation in ART cycles in women with anomalous uteri. In a report by Noyes et al., despite a higher tendency towards a solid endometrial pattern, and a significantly thicker endometrial lining noted in non-DES compared with DES-exposed patients undergoing COH, DES-exposed uteri still reached a mean endometrial thickness of 10.1 mm (versus 11.1 mm in non-DES exposed) on the day of hCG administration [6]. In a later report, Pal et al. found no difference in endometrial thickness following COH between DES-exposed women (10.0 mm) compared with infertile controls (10.0 mm) [7]. The relatively high implantation rate noted in our study population, compared with prior reports, suggests preserved endometrial receptivity in women with anomalous uteri, implicating other factors for the previously reported diminished implantation rates.

Müllerian developmental defects may result in a spectrum of anomalies as a result of lack of duct fusion, septum resorption, or canalization. This often results in a structural compromise of the uterine cavity, which has been implicated in pregnancy loss associated with such anomalies.

Moreover, constriction and distortion of the endometrial cavity often encountered in anomalous uteri can potentially also impact on embryo transfer efficiency by resulting in difficult or traumatic ET when the trans-cervical route is utilized. This is avoided with a TET, provided at least one normal fallopian tube is present. Since pregnancy and implantation rates are similar between TET and trans-cervical ET in the general infertile population [11], one possible explanation for high implantation and pregnancy rates observed in our study cohort is unimpaired transfer efficiency of tubal transfer in women with anomalous uteri.

In conclusion, we observed high implantation and delivery rates in women with DES exposure and other Müllerian anomalies, suggesting that 1) endometrial receptivity in uteri with these anomalies is apparently preserved, and 2) transfer efficiency is optimized by the use of TET. Our series is quite small, as these patients are relatively rare. Larger-scale randomized studies comparing the trans-cervical and trans-tubal routes of embryo transfer are needed to validate our preliminary findings.

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