

# Reproductive outcomes after radical abdominal trachelectomy for cervical cancer

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**Objective:** Some patients who have undergone radical trachelectomy require *in vitro* fertilization-embryo transfer. We examine the reproductive problems in patients with cervical cancer after radical abdominal trachelectomy. **Methods:** A retrospective single-center study of the fertility treatment for the cervical cancer patients who received radical abdominal trachelectomy was performed in 17 cases. One patient had stage IA1 disease with lymph-vascular involvement, 4 had stage IA2 disease, and 12 had stage IB1 disease. Histologically, there were 9 squamous cell carcinomas and 8 adenocarcinomas. Six patients received adjuvant chemotherapy. No deaths due to disease were observed. **Results:** The median age and length of follow-up were 36 years old and 71 months, respectively. Among the 12 patients desirous of pregnancy, 9 received *in vitro* fertilization (IVF), and 8 pregnancies were confirmed in 6 patients. Seven patients had cervical stenosis, and 4 of them needed transmyometrial embryo transfer. Two cases showed spontaneous abortion in the first trimester, and five resulted in births. The remaining case is in her 17th gestational week with no abnormal findings. One case had a fetomaternal transfusion syndrome, and another had partial placenta previa and preterm premature rupture of the membranes. **Conclusions:** In this small series of cases, the pregnancy rate after radical abdominal trachelectomy was 50%; most patients received transmyometrial embryo transfer was used for cervical stenosis.

## Keywords

Cervical stenosis; Complication; Radical trachelectomy; Reproductive outcomes; Transmyometrial embryo transfer; Fertility treatment

## 1. Introduction

The incidence of cervical cancer in Japan in 2012 was 10.6/100,000 according to the data of the Center for Cancer Control and Information Services, National Cancer Center. For women with early cervical cancer, radical trachelectomy is a fertility-sparing surgery, and many subsequent pregnancies have been reported [1, 2]. There are various surgical procedures available, including vaginal, abdominal, laparoscopic, and robotic approaches, and our hospital performs surgery via the abdominal approach [2, 3]. According to a meta-analysis of 43 studies, the recurrence rate was 2.3% (1.3–3.4%), and the mortality was 0.7% (0.3–1.1%). However,

there is an issue from the perspective of fertility preservation with follow-up of 9 to 96 month after surgery, as the pregnancy rate with or without assisted reproductive technology (ART) was 20.5% (16.8–24.5%), while the abortion rate in the first and second trimesters was 24% (18.8–29.6%) [1]. As such, assisted reproductive technology is reported to be necessary in many cases [4].

Obstetrics and reproductive problems after radical trachelectomy have been reported [5, 6]. The extensive resection of the cervical stroma, parametrium, and pelvic splanchnic nerves causes issues, such as a reduction of mucus production, isthmic stenosis, and preterm delivery [5]. As a countermeasure, preservation of the bilateral uterine artery and cerclage during radical trachelectomy may lead to an improvement in the cervical condition, so we have adopted this approach in our hospital [5, 6]. About 11.3–64.5% of patients required *in vitro* fertilization-embryo transfer (IVF-ET) to achieve pregnancy, and there were cases in which transmyometrial embryo transfer was needed at the time of transplantation [5, 6]. However, there have been few reports on the complications for transmyometrial embryo transfer after radical trachelectomy.

Therefore, in the present study, we examined the reproductive problems encountered after radical abdominal trachelectomy.

## 2. Material and methods

### 2.1 Patient population

A retrospective single-center study of fertility treatment administered to cervical cancer patients who received radical abdominal trachelectomy was performed in 17 cases at Osaka Medical College Hospital between August 2010 and December 2019. The surgical indications were as follows: (1) desire for pregnancy; (2) clinical stage 1A2–1B1 (FIGO 2009 staging system); and (3) tumor size  $\leq 2$  cm. Pelvic magnetic resonance imaging (MRI) was performed in all cases as a preoperative examination, and a histological diagnosis was obtained via a diagnostic biopsy or conization. All patients underwent radical abdominal trachelectomy.

The present study was approved by the institutional review board (IRB) of Osaka Medical College. Written informed consent was obtained from all patients for radical trachelectomy and the use of their clinical records in the present study.

## 2.2 Surgical procedure

We adopted a standard radical abdominal hysterectomy approach for radical abdominal trachelectomy. Pelvic lymph node dissection is performed first, and if there is an enlarged lymph node, the lymph nodes are submitted for a frozen section examination to confirm the absence of metastasis. In cases where consent to perform a sentinel lymph node biopsy has been obtained, such as in a clinical trial, frozen section examinations of the identified lymph nodes are performed. Thereafter, both uterine arteries are identified and preserved, and the anterior part of the vesico-uterine ligament is cut while preserving the hypogastric nerve and the pelvic autonomic nerves. During the operation, the position of the internal uterine os is confirmed by ultrasonography, and the incision line is determined. The cervix amputated from the vagina with at least 2 cm of vaginal margin. Double cervical cerclage is performed with 1-0 Ethibond Excel Polyester suture (Ethicon, Johnson & Johnson, New Brunswick, NJ, USA). The vaginal cuff is sutured to the cervix with 2-0 PDS PLUS (Ethicon, Johnson & Johnson, New Brunswick, NJ, USA). Nelaton's Catheter was placed to prevent cervical stenosis (NIPRO, Osaka, Japan).

## 2.3 Postoperative management

We administer adjuvant chemotherapy or radiotherapy after radical hysterectomy for cervical cancer in patients with lymphovascular space invasion (LVSI),  $\geq 50\%$  cervical stromal invasion, lymph node metastasis, tumor of  $\geq 4$  cm in size, or a positive surgical margin. The indications for adjuvant chemotherapy for cervical cancer patients who underwent radical abdominal trachelectomy were the same as for patients who undergo radical hysterectomy. Patients who needed chemotherapy underwent egg retrieval after surgery. For all patients, permission to become pregnant was given if there were no abnormalities on MRI at six months postoperatively. Fertility treatment was started at the patient's desired timing. First, we started with general fertility treatment, moving to assisted reproductive technologies depending on the cause of their infertility.

## 2.4 Pregnancy management

Post-conception pregnancy management was performed through visits every two weeks in the first trimester and hospitalization from the second trimester. When preterm labor symptoms were confirmed, bed rest and a continuous intravenous infusion of ritodrine hydrochloride were performed. All patients underwent emergent or elective Caesarean section, and the timing was set according to the obstetric indications or at 34–36 weeks of gestation.

**Table 1. Characteristics of 17 patients who underwent abdominal radical trachelectomy.**

Total number of patients	17
Age, years	
<30	2
30–34	5
35–39	7
$\geq 40$	3
FIGO stage	
IA1	1
IA2	4
IB1	12
Lymph-vascular space invasion	6
Histological type	
Squamous cell carcinoma	9
Adenocarcinoma	8

FIGO, International federation of Gynecology and Obstetrics.

## 2.5 Statistical analyses

All of the statistical analyses were performed using the JMP software program (version 14.1.1, SAS Institute Inc., Tokyo, Japan). Continuous variables were expressed as the mean  $\pm$  standard deviation (SD).

## 3. Results

A total of 17 patients underwent radical abdominal trachelectomy, and the characteristics are listed in Table 1. The median age and length of follow-up were 36 (29–43) years old and 71 (58–85) months. There were 12 patients desirous of pregnancy as soon as possible. Of the 17 patients who underwent radical abdominal trachelectomy, one patient had stage IA1 disease with LVSI, 4 had stage IA2 disease, and 12 had stage IB1 disease. Histologically, there were eight cases of squamous cell carcinoma and nine cases of adenocarcinoma. Seven patients received adjuvant chemotherapy. Radiotherapy was performed in one patient for recurrent disease in the lymph nodes. No deaths due to disease were observed.

The obstetric outcomes of the 17 patients who underwent radical abdominal trachelectomy are shown in Tables 2,3 and Fig. 1. Among the 12 patients with an immediate desire for pregnancy, 9 received IVF, and 8 pregnancies were confirmed in 6 patients. Two of these cases ended in spontaneous abortion in the first trimester, and five resulted in births (26, 28, 34, 34, and 36 gestational weeks). The remaining case is in her 17th gestational weeks with no abnormal findings.

Six patients needed postoperative chemotherapy, and four of them underwent egg retrieval by random-start controlled ovarian hyperstimulation before chemotherapy (three patients selected oocyte cryopreservation because they were unmarried). Of the patients who underwent embryo transfer, 7 had cervical stenosis, and four of them required transmyometrial embryo transfer (Towako method [7]).

As management during pregnancy, patients were hospitalized from 23 weeks of pregnancy, and the delivery

**Table 2. Obstetric outcome of 17 patients who underwent abdominal radical trachelectomy.**

Case	Age	Early pregnancy wish	Adjuvant chemo-therapy	Period until pregnancy wish lost	Fertility treatment	Cervical stenosis	Transmyometrial embryo transfer	Pregnancy	Live birth
1	36	+	-	43 months	-				
2	37	-	-	-	-				
3	38	+	-	61 months	IUI, IVF-ET	+			
4	38	+	+	23 months	-	+			
5	32	+	+	-	IVF-ET	+	+	+	+
6	30	+	-	52 months	-, IVF-ET	+	+	+	
7	29	+	-	-	-, IUI, IVF-ET	+		+	+
8	32	+	-	51 months	IUI, IVF-ET			+	+
9	43	+	+	32 months	IVF-ET				
10	29	-	-	-	-				
11	40	-	-	-	-				
12	35	+	+	34 months	IVF-ET	+	+	+	+
13	36	+	+	-	IVF-ET	+		+	ongoing
14	36	+	-	-	IVF-ET	+	+		
15	33	+	-	23 months	IUI				
16	41	-	-	-	-	+			
17	31	-	+	-	Oocyst cryopreservation	+			

IUI, intrauterine insemination; IVF-ET, *in vitro* fertilization and embryo transfer.

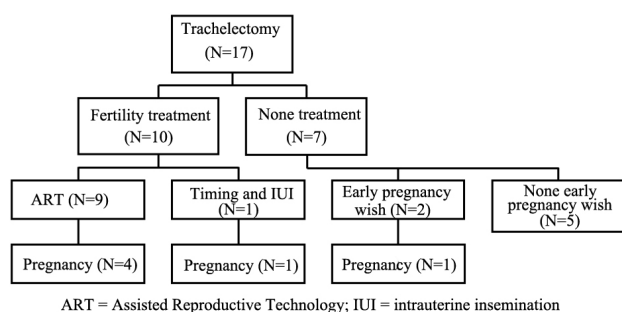
**Table 3. Pregnancy outcome of 6 patients who underwent abdominal radical trachelectomy.**

Case	Period from pregnancy permission to pregnancy establishment	Period from the start of infertility treatment to pregnancy establishment	Method of conception	Infertility cause	Gestational week	Obstetric complication	Fetal body weight (g)
5	42 months	33 months	IVF	Oligozoospermia	34	Partial placenta previa	1908
6	26 months	-	Spontaneous pregnancy	-	7	Spontaneous abortion	-
7	16 months	-	Spontaneous pregnancy	-	8	Spontaneous abortion	-
7	55 months	3 months	IUI	Asthenozoospermia	26	Preterm PROM	997
8	49 months	28 months	IVF	Asthenozoospermia	34	-	2302
8	78 months	1 month	IVF	Asthenozoospermia	36		2884
12	18 months	11 months	IVF	-	28	NRFS, Fetomaternal transfusion syndrome	1094
13	53 months	15 months	IVF		10		Ongoing

IUI, intrauterine insemination; IVF-ET, *in vitro* fertilization and embryo transfer; PROM, premature rupture of the membranes; NRFS, non-reassuring fetal status.

method was Caesarean section at 34–36 weeks of gestation. Five patients gave birth (26, 28, 34, 34, and 36 weeks of pregnancy). One patient had a complication (fetomaternal transfusion syndrome), and another had partial placenta previa and preterm premature rupture of the membranes. In case 6, which showed spontaneous abortion, it took six months for the contents to be completely discharged and absorbed.

The clinical stages of the 6 patients in whom pregnancy was not achieved were stage IA2 (n = 2) and stage IB1 (n = 4). On the other hand, the clinical stages of the 6 patients in whom pregnancy was achieved were stage IA1 (n = 1), stage IA2 (n = 2), and stage IB1 (n = 3).



**Fig. 1. The results of postoperative fertility treatment and pregnancy.** Ten postoperative patients (58%) wished to undergo fertility treatment, of whom 5 (50%) became pregnant. Five (29%) did not wish to become pregnant early after surgery.

#### 4. Discussion

In the present study, 6 of the 12 patients with an immediate desire for pregnancy after radical abdominal trachelectomy became pregnant, and 4 of them ultimately gave birth. This rate is comparable to those previously reported. In past reports, the pregnancy rates after vaginal and abdominal radical trachelectomy were  $67.5 \pm 17.6\%$  and  $41.9 \pm 19.4\%$ , respectively, and the overall pregnancy rate was  $55.4 \pm 23.9\%$  [2, 5, 8, 9]. In a recent review, the pregnancy rate was 44% in patients who underwent abdominal radical trachelectomy and 65% in patients who underwent minimally invasive radical trachelectomy. In patients who underwent abdominal radical trachelectomy and those who underwent minimally invasive radical trachelectomy, the live birth rate was 68% and 78% respectively, and the prematurity rate was 57% and 50% [10]. In Japan, minimally invasive radical hysterectomy for cervical cancer patients, including laparoscopy and robot surgery, have not been covered by public insurance. Laparoscopic radical hysterectomy for cervical cancer has been covered by public insurance since 2018. Thus, minimally invasive radical trachelectomy could not be performed in the current study. Assisted reproductive technologies were required in 9.6–36.2% of cases [5, 8, 9]. In our study, 75% of patients received IVF-ET. Many of our patients were older and had complications such as cervical stenosis; this may explain

the high ART rate in our study. Postoperative complications reportedly include vaginal scarring, neo-cervical encroachment, cervical stenosis, and dyspareunia [5, 9, 11], with reported incidence rates of 50%, 54%, 58%, and 33%, respectively [9, 11]. The period before pregnancy is permitted differs among each study [5, 11]. In our hospital, we give patients permission to start attempting to become pregnant at six months postoperatively and conduct an infertility examination if pregnancy does not occur even after one and a half years, or when the patient wishes to undergo such an examination. If the infertility examination reveals no particular issues, general fertility treatment is performed for three to six cycles and then shifted to assisted reproductive technologies. However, it may be best to perform infertility examinations early after surgery because of the risk of recurrence and complications.

In the review of the relevant literature, among 805 patients who had stage IA2 disease, lymph node metastasis was detected in 35 (5%) patients [12]. The rate of lymph node metastasis was 12% in the patients with LVSI and 1% in the patients without LVSI; LVSI is a negative prognostic factor for recurrence and nodal metastasis in cervical cancer [12]. Although the details of the management of fertility sparing surgery for patients with LVSI is unknown, no recurrence was reported in patients who received fertility preserving surgery including conization (n = 20) and simple trachelectomy (n = 59) in IA1 patients with LVSI in a systematic review [13].

Although a recent report showed that the incidence of cervical stenosis was 4.3% [2]. It was observed in 10 of 17 patients (59%) at our institution. The method of the assessment of cervical stenosis varies depending on the study. Furthermore, we defined cervical stenosis as a case in which physicians at our facility could not visually confirm the cervical canal [14]. Measures against cervical stenosis include preventive measures such as Smit-sleeve for trachelectomy, confirmation by menstrual colposcopy, and cervical dilation [2, 15]. Cervical dilatation was performed for cervical stenosis; however, the patients experienced strong pain during embryo transfer and IUI. For this reason, transmyometrial embryo transfer was performed in 4 patients with cervical stenosis; 2 of those patients achieved pregnancy. Cervical stenosis can increase the rate of ART.

The success of implantation also depends on atraumatic embryo transfer, which is difficult to perform in patients with cervical stenosis [7, 16]. As a solution, we perform transmyometrial embryo transfer, but there have been a few reports of complications [7, 16], including bleeding, injury to adjacent organs, infection, and junctional zone contractions [17, 18]. In the four cases encountered in the present study, there were no obvious complications due to transmyometrial embryo transfer, but complications of partial placenta previa and fetomaternal transfusion syndrome were recognized during gestation. Previous reports have described cases of transmyometrial embryo transfer showing placenta pre-

via and placenta accreta [5]. It may be necessary to consider complications during pregnancy in patients receiving transmyometrial embryo transfer.

In the current study, post-conception pregnancy management involved visits every two weeks in the first trimester and hospitalization from the second trimester. A recent study showed that cervicovaginal fluid quantitative fetal fibronectin was effective for predicting spontaneous preterm birth in asymptomatic women who underwent cervical surgery [19]. The American College of Obstetrics and Gynecology recommends against conducting direct clinical management solely by positive predictions such as fetal fibronectin testing or short cervix in women with acute symptom [20]. On the other hand, high negative predictions can rule out women who are unlikely to give birth within 14 days after the test, reducing unnecessary intervention [21].

## 5. Conclusions

The pregnancy rate for patients after radical trachelectomy was 50%; however, most patients received IVF. If the patient is older or has cervical stenosis, early aggressive fertility treatment intervention is considered desirable. Transmyometrial embryo transfer was used for patients with cervical stenosis; however, it may be necessary to consider pregnancy complications associated with this approach. Although our series of cases is small the clinical stage of the cancer did not seem to impact the patient's ability to achieve pregnancy or birth.

## Abbreviations

IVF-ET, *in vitro* fertilization-embryo transfer; FIGO, International federation of Gynecology and Obstetrics; MRI, magnetic resonance imaging; IRB, institutional review board; ART, Assisted Reproductive Technology; IUI, intrauterine insemination.

## Author contributions

HK, TT, and MO made the conception and design of study. TT, HM, YK, SF and YT acquired the data. TT, KT and KK analyzed and/or interpreted the data. HK, TT and MO drafted the manuscript. TT, KT, KK, MH and MO revised the manuscript critically for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The present study was approved by the Osaka Medical College Research Review Board (2014-18), and all patients provided written informed consent.

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## Conflict of interest

The authors declare no conflict of interest.

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