Reproductive and obstetric outcomes after radical abdominal trachelectomy for early-stage cervical cancer in a series of 31 pregnancies

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Submitted on January 16, 2013; resubmitted on March 13, 2013; accepted on March 27, 2013

STUDY QUESTION: What are the reproductive and obstetric outcomes in patients undergoing radical abdominal trachelectomy (RAT) for early-stage cervical cancer?

SUMMARY ANSWER: When RAT was performed before a pregnancy achieved with fertility treatments, pregnancy rate of 36.2% was obtained and 71.4% of these women gave birth at ≥32 weeks of gestation.

WHAT IS KNOWN ALREADY: Reproductive and obstetric outcomes after radical vaginal trachelectomy (RVT) are well documented; however, these outcomes after RAT have not been well studied.

STUDY DESIGN, SIZE, DURATION: This is a retrospective cohort study of patients at a single institution who underwent RAT and became pregnant. Reproductive and obstetric outcomes of 114 patients who had undergone RAT from September 2002 to December 2010 were investigated.

PARTICIPANTS/MATERIAL, SETTING, METHODS: Women of reproductive age with early-stage cervical cancer who wished to preserve their fertility were documented.

MAIN RESULTS AND THE ROLE OF CHANCE: Patients’ median age was 33 years (25–40 years). A total of 31 pregnancies were achieved in 25 patients and 6 patients had 2 pregnancies. Eighteen of 25 patients (72.0%) had infertility problems; 17 patients conceived with IVF-embryo transfer and 1 patient with intrauterine insemination. The pregnancy rate among patients who wished to conceive was 36.2% (25/69). Among 31 pregnancies in 25 patients, 4 patients had first trimester miscarriage and 1 patient had second trimester miscarriage. Excluding the five patients who miscarried and the five ongoing pregnancies, all the 21 patients had deliveries by Cesarean section. Four patients had a preterm birth in the second trimester and 17 patients delivered in the third trimester. Of the 17 pregnancies that reached the third trimester, 2 (11.8%) were preterm births between 29 and 32 weeks, 11 (64.7%) were delivered between 32 and 37 weeks and 4 (23.5%) at ≥37 weeks of gestation.

LIMITATIONS, REASONS FOR CAUTION: Because of the retrospective data collection, not all pregnancies may have been recorded.

WIDER IMPLICATIONS OF THE FINDINGS: Prospective multicenter studies are needed to determine if the results shown in this retrospective cohort can be generalized to all patients with early-stage cervical cancer who wish to undergo the fertility-sparing RAT procedure.
**Introduction**

In recent years, cervical cancer has become the second most common malignancy in women and the number of patients diagnosed as having early-stage cervical cancer during their child-bearing years has been increasing (Jemal et al., 2011). With the recent trend of delaying child bearing, there has been an increased emphasis on fertility-sparing treatments. Since Daniel Dargent first published radical trachelectomy in 1994 (Dargent et al., 1994, 2000), the procedure, using the vaginal or abdominal approach, has been performed to provide oncological safety while preserving fertility (Abu-Rustum and Sonoda, 2007; Cibula et al., 2009; Gien and Covens, 2010; Rob et al., 2011). We have performed radical abdominal trachelectomy (RAT) in 114 patients between September 2002 and December 2010 (Nishio et al., 2009).

Previous reports indicated that radical trachelectomy results in similar oncologic outcomes as the conventional radical hysterectomy for early-stage cervical cancer (Lanowska et al., 2011; Xu et al., 2011). Many women have been reported to conceive spontaneously after radical vaginal trachelectomy (RVT). In a previous report from one institution, the 5-year cumulative pregnancy rate among women trying to conceive was 52.8% and assisted reproduction techniques (ART) were required in a minority of these patients (Plante et al., 2011). However, data for reproductive and obstetric outcomes have been particularly based on results of the RVT procedure and reports on obstetric outcome following RAT are limited (Kim et al., 2012).

Here, we evaluated the reproductive and obstetric outcomes of patients following RAT in a series of 31 pregnancies in 25 patients, which is the largest pregnant case series in RAT patients from a single institution to date.

**Materials and Methods**

**Patients**

We performed RAT according to the preoperative criteria approved by the Institutional Review Board of Keio University School of Medicine (Registration no. 20030107). All patients were fully informed about the option of choosing either RAT or radical abdominal hysterectomy. The operative criteria were shown in our previous report (Nishio et al., 2009). One hundred and fourteen consecutive women who elected to undergo RAT over 9 years between September 2002 and December 2010 were included in this study. Seventy-three (71.6%) patients had undergone cervical conization before RAT to confirm histology.

**Surgical procedure**

Our surgical procedure was described previously (Nishio et al., 2009). Briefly, the conventional approach, like that used for a standard radical abdominal hysterectomy, was employed for RAT. The extent of the pelvic lymphadenectomy was identical to that in a standard radical hysterectomy including common iliac, presacral, internal/external iliac, cardinal, obturator and inguinal nodes. The bilateral uterine arteries were identified and preserved. A part of the cervix was resected together with the parametrium and ~2 cm of the vaginal wall, with nerve-sparing procedure sparing the hypogastric nerve. Once a tumor-free margin status was confirmed using frozen-sections, one or two consecutive permanent cerclages were created with nylon sutures (#0 Ethibond®, Ethicon, IL, USA) in the neo-cervix before suturing it to the vaginal stump.

**Follow-up after surgery**

All patients were followed up every month for the first 3 months, every 2 months for the next 6 months, once every 3 months during the second year, and once every 6 months during the third year. At each follow-up appointment, complications were recorded and Pap smears were taken, while colposcopic examinations were performed if any abnormal lesions were suspected. We usually advised patients to wait a minimum of 6 months after surgery before attempting to conceive. Some patients were followed up in different institutions and we asked these patients and their physicians to keep us informed of any obstetric outcomes and oncological events.

**Antepartum management**

Antepartum management was not uniform because patients were followed up by several different obstetricians at our institution or sometimes at different institutions. The type of management was determined by each obstetrician. If patients did not show any signs of threatened abortion or preterm delivery, such as abnormal genital bleeding or uterine contraction, the routine prenatal care protocol was followed in the clinic, i.e. a visit every other week in the second trimester, and thereafter once a week until delivery. At each visit, transvaginal ultrasound was performed to obtain measurements of cervical length to detect premature shortening or dilatation of the remaining cervix. Pregnant patients with abnormal findings of the neo-cervix, genital bleeding or uterine contraction were admitted for bed rest and received ritodrine hydrochloride i.v. Finally, the timing of delivery was decided by the attending obstetricians: all patients had emergent or elective Cesarean section. This study was approved by the ethical institutional board (Registration no. 20110275) and full informed consent of both patients and families was obtained.

**Statistical analysis**

Statistical analysis was performed using the Statistical package for the Social Sciences (SPSS) 19.0 (SPSS, Inc., Chicago, IL, USA). The t-test was used to compare the average time to conception between the natural conception (NC) and ART groups. P-values <0.05 were considered to denote statistical significance.

**Results**

The characteristics of the eligible 114 patients are listed in Table I. Patients’ median age was 33 years (25–40 years old) and the median follow-up period was 33 months. Among those patients, 11 (12.1%) had adjuvant treatments after surgery including chemotherapy or radiation mainly because they proved to have regional...
lymph node metastases, which had not been confirmed during surgery. None of the patients who were pregnant received adjuvant treatments. Of the 31 pregnancies, 20 (64.5%) were achieved with IVF-embryo transfer. Four of those (no. 8, 21, 24 and 30) had transmyometrial embryo transfer, i.e. using the Towako method with IVF-embryo transfer. None of the patients who were pregnant received adjuvant lymph node metastases, which had not been confirmed during surgery.

Fertility-sparing surgery for cervical cancer

Table I

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>33 (25–40)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>No. of patients according to FIGO stage</td>
<td></td>
</tr>
<tr>
<td>IA1</td>
<td>9</td>
</tr>
<tr>
<td>IA2</td>
<td>12</td>
</tr>
<tr>
<td>IB1</td>
<td>93</td>
</tr>
<tr>
<td>Lymph-vascular space invasion</td>
<td>55 (48.2%)</td>
</tr>
<tr>
<td>Stromal invasion (mm)</td>
<td></td>
</tr>
<tr>
<td>Average (range)</td>
<td>4.8 (1–13)</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>99</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>14</td>
</tr>
<tr>
<td>Adenosquamous cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Smoker</td>
<td>41 (36.0%)</td>
</tr>
</tbody>
</table>

FIGO, International Federation of Gynecology and Obstetrics.

Discussion

We report 31 pregnancies in 25 patients following RAT performed for early-stage cervical cancer at a single institution. The most important aspect in treating patients with cancer is the cure rate of the disease. Data regarding survival rates after RAT are still unavailable because the number of patients undergoing this procedure remains relatively small (Rob et al., 2011; Schneider et al., 2012) compared with conventional radical hysterectomy and therefore it is not possible to verify the safety of RAT in terms of surviving cancer.

Another important aspect of RAT is the fertility-sparing and obstetric outcome. Compared with the RVT procedure, the results of our retrospective study showed that a relatively small number of patients (n = 25, 36.2%) was able to conceive after this procedure, 9 patients had NC (13.0%) and 16 patients (23.2%) conceived with ART or IUI (Plante et al., 2011). For the RVT procedure, Plante et al. (2011) reported that 70–79% of all women attempting to conceive did so spontaneously. Although the essential procedure of preserving the body of the uterus was no different between these two procedures, the abdominal approach may affect reproductive function to a greater extent, because this procedure included the larger resection of cervical stroma, parametrium and pelvic splanchnic nerves. We usually preserved the bilateral uterine arteries; however, in most institutions the uterine arteries are resected during the parametrectomy, which is not performed in the vaginal procedure. Moreover, the uterine body is completely divided from the vaginal wall, which may result in more disruption of nerves as well as pelvic adhesions. These factors led to impairments of cervical condition, such as reduction of mucus production and isthmic stenosis (Kim et al., 2012).

We acknowledge the benefits of the vaginal approach. However, since 2002 we have chosen to use the abdominal approach because most gynecologic oncologists in Japan are familiar with the abdominal radical procedure, as this method requires no specialist training and allows an adequate resection of the involved parametrial and vaginal tissue. Moreover, it is difficult to perform the vaginal procedure without adequate training or familiarity with the vaginal approach.
We are aware that reproductive specialists were important in helping patients to become pregnant and ~70% (17/25) patients required reproductive intervention. Twenty-two pregnancies (71.0%) were achieved following ART or IUI. The time to conception for the assisted conception group was longer than for the NC group. Except for one case, all patients in the NC group fell pregnant within 2 years after surgery. This result indicated that RAT patients may require ART if they do not conceive within 2 years following surgery.

Preterm deliveries may occur as a result of lack of mechanical support of the residual cervix or ascending infection followed by chorioamnionitis. We had seven pPROM cases in our pregnant series. Two of these pregnancies (no. 1 and 18) did not have cerclage during RAT procedure. Five pregnancies with the cerclage procedure had pPROM and terminated before <32 weeks of gestation (no. 2, 3, 4, 16 and 21). Blood samples revealed that all of these patients had elevated white blood cell counts and C Reactive Proteins (CRPs), which could be caused by an ascending bacterial infection from the neo-cervix, mainly because cervical resection causes loss of the mucous barrier. However, the reasons why only these patients had chorioamnionitis should be elucidated.
We have chosen to place the prophylactic permanent cerclage during the surgery to maintain the mechanical support of the residual cervix, because two patients without cerclage during surgery delivered in the second trimester. Jolly et al. (2007) reported that maintenance of the permanent cerclage could be important for successful deliveries as only one patient terminated delivery at <32 weeks of gestation (Jolley et al., 2007): in that study, 6 of all 21 (28.6%) pregnancies were preterm deliveries at <32 weeks of gestation. Among RVT patients, 5–29% patients had a premature delivery at <32 weeks of gestation (Plante et al., 2005).

Isthmic stenosis is reported to occur in up to 15% of RVT patients (Boss et al., 2005; Wong et al., 2009). In our case series, some patients required isthmic dilation before or during embryo transfer and four patients with inadequate dilation of cervix required the Towako methods. As Wong et al. (2009) stated, all patients should be informed of this complication and reproductive clinicians should try to ensure access to uterine cavity before treatment begins.

To the best of our knowledge, the pregnant case series in this report after RAT is the largest reported to date from a single institution. In conclusion, the pregnancy rate following RAT for women with early-stage cervical cancer was 36.2 and 70% of patients required ART in order to conceive. With an appropriate patient selection, and pre-operative and post-operative counseling, RAT is a promising fertility-sparing procedure for women with early-stage cervical cancer. We also demonstrated here that patients should be informed of, and counseled on, infertility issues and obstetric risks before and after surgery, including the risk of pPROM and subsequent preterm labor.

Figure 1 (a) Transvaginal ultrasound image for one pregnant patient after RAT. (b) Schematic of the transvaginal ultrasound shown in (a). The ‘neo-cervix’ is shown and the permanent cerclage is identified.

Figure 2 Length of the ‘neo-cervix’ during the course of pregnancy of nine patients with early-stage cervical cancer who had undergone RAT.

Acknowledgement

We thank Dr K. Tsukazaki, Dr N. Hirao, Dr T. Matsumoto, Dr M. Nakamura, Dr A. Ohno, Dr I. Murakami and Dr S. Nishio for helping in revising the manuscript. We also appreciated patients and clinicians who provided their obstetric outcomes.

Authors’ roles

H.N. and T.F. designed this study, analyzed the data and wrote the manuscript. J.S. was responsible for the selection of data and participated in critical discussions. N.K. and M.T. contributed to be involved in obstetric practice of patients and participated in the interpretation of the results. T.H. contributed to be involved in fertility treatment of patients and participated in the interpretation of results. K.M. and K.M. contributed to participate in obstetric practice of patients, participated in the interpretation of the results and helped preparing manuscripts. H.T., T.I., K.T. and T.F. participated in collection of data and gynecologic practice of patients. Y.T. contributed to be involved in fertility treatment of patients. Y.Y. and D.A. contributed toward writing the manuscript. All authors approved the final version of the manuscript.

Funding

No external funding was either sought or obtained for this study.

Conflict of interest

None declared.
References


