Does radical trachelectomy (RT) during pregnancy have higher obstetrical and oncological risks than RT before pregnancy?

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Abstract
Purpose Radical trachelectomy (RT) with pelvic lymphadenectomy has become a new treatment option for young patients with uterine cervical cancer stages 1A2–1B1 who desire the preservation of their fertility. However, the application of RT for pregnant patients is still controversial. We comparatively studied both obstetrical and oncological outcomes of pregnant patients who underwent vaginal RT during pregnancy and those who underwent vaginal RT before pregnancy.

Methods Both obstetrical and oncological results of eight patients who underwent vaginal RT with pelvic lymphadenectomy during pregnancy in our institute between 2010 and 2020 (Group A), and ten pregnant patients who underwent vaginal RT with pelvic lymphadenectomy before pregnancy during the same period (Group B) were reviewed based on their medical charts.

Results There were neither significant differences in blood loss, surgical time, or surgical completeness between Group A and Group B, nor were there significant differences in obstetrical outcomes between the two groups. However, two of the eight patients in Group A had recurrence of the cancer. None of the patients in Group B has shown any signs of recurrence thus far.

Conclusion Vaginal RT during pregnancy does not affect the obstetrical prognoses of patients with early invasive uterine cervical cancer, and it might be a tolerable treatment modality for them. However, oncologically, it should be performed carefully as there is a risk of recurrence.

Keywords Radical trachelectomy · Uterine cervical cancer · Pregnancy

Introduction
Cervical cancer is one of the most commonly diagnosed malignant diseases during pregnancy worldwide [1]. It accounts for about 36% of the malignant diseases diagnosed during pregnancy in Japan [2]. The standard treatment modality for patients with invasive uterine cervical cancer stage 1A2 or higher stages was total hysterectomy irrespective of pregnancy [3, 4].

Radical trachelectomy (RT) with pelvic lymphadenectomy, originally proposed by Dargent et al. in 1988 [5], has become a new treatment option for young patients who desire the preservation of their fertility. As we reported before, we have already performed vaginal radical trachelectomy (RT) for 73 patients with early invasive uterine cervical cancer [6]. However, this operative modality is usually performed for non-pregnant patients.

RT for pregnant women is still experimental, and it is still controversial whether RT during pregnancy is a recommendable treatment modality for pregnant patients with early invasive uterine cervical cancer.

International Network on Cancer, Infertility and pregnancy (INCIP) guideline do not recommend RT during pregnancy due to its high rate gynecological and obstetrical complications [7]. National Comprehensive Cancer Network (NCCN) guidelines for cervical cancer introduced that RTs during pregnancy have been successfully performed in several institutes [8]. However, most of the reports regarding to RT during pregnancy are single case reports.

As for our institute, we have experienced 31 pregnancies in 24 patients after vaginal RT since 2003. Among them, RT during pregnancy was performed for eight patients. For pregnancy after RT, there is still a high risk of preterm birth...
and abortion in spite of progress in the management for such patients. However, does RT during pregnancy have higher obstetrical and oncological risks than RT before pregnancy? In this report, we comparatively studied both obstetrical and oncological outcomes of pregnant patients who underwent vaginal RT during pregnancy and those who underwent vaginal RT before pregnancy.

**Patients and methods**

Eight patients who underwent vaginal RT with pelvic lymphadenectomy during pregnancy in our institute between 2010 and 2020 (Group A), and ten pregnant patients who underwent vaginal RT with pelvic lymphadenectomy before pregnancy during the same period (Group B) were reviewed in this study. To exclude additional factors affecting obstetric outcome and to exclude patients who became pregnant when the standard treatment for post-RT pregnancies had not been established, patients who underwent transabdominal cerclage (TAC) and patients before 2010 were excluded from the study. The study protocol was approved by the review board and the ethics committee in our institute (approval number 05-26). Written informed consent was also obtained from each patient.

Clinical characteristics of the patients are summarized in Table 1. Various obstetrical parameters such as fetal growth, changes of uterine cervical length, infectious markers, and oncological parameters such as the results for uterine cervical cytology and tumor markers were obtained from medical records.

The clinical indications for vaginal RT in our institute, including those for pregnant patients, are as follows: (1) age $\leq 45$ years with a strong desire to preserve fertility, (2) International Federation of Gynecology and Obstetrics (FIGO) stage 1A1 with vascular space involvement, stage 1A2 or stage 1B1, (3) lesion size $\leq 2$ cm, (4) squamous histology or adenocarcinoma (including adenosquamous carcinoma), and (5) no involvement of the upper endocervical canal as determined by colposcopy or magnetic resonance imaging (MRI), and no evidence of lymph node metastasis.

All the patients except one had FIGO 2009 stages 1A2–1B1 uterine cervical cancer in this study. Vaginal RT was performed for one patient with stage IIA who strongly desired the preservation of fertility after repeated

| Patient | Age | Parity G(P) | Clinical stage | Histology$^2$ | Diagnostic conization$^3$ |
|---------|-----|-------------|----------------|--------------|--------------------------|
| Group A |     |             |                |              |                          |
| 1       | 32  | 1(0)        | 1B1            | Adeno        | +                        |
| 2       | 30  | 1(0)        | 1B1            | SCC          | –                        |
| 3       | 34  | 2(0)        | 1B1            | Adeno        | –                        |
| 4       | 32  | 2(0)        | 1B1            | Adeno        | –                        |
| 5       | 41  | 1(0)        | 1B1            | Adeno        | –                        |
| 6       | 23  | 2(0)        | IIA            | SCC          | –                        |
| 7       | 31  | 2(0)        | 1B1            | SCC          | –                        |
| 8       | 29  | 2(0)        | 1B1            | Adeno        | –                        |
| Group B |     |             |                |              |                          |
| 9       | 34  | 1(0)        | 1B1            | SCC          | +                        |
| 10      | 29  | 2(0)        | 1A2            | Adeno        | +                        |
| 11      | 36  | 1(0)        | 1B1            | SCC          | +                        |
| 12      | 37  | 2(1)        | 1B1            | SCC          | +                        |
| 13      | 31  | 1(0)        | 1B1            | SCC          | –                        |
| 14      | 29  | 2(0)        | 1B1            | Adeno        | –                        |
| 15      | 37  | 0(0)        | 1B1            | SCC          | –                        |
| 16      | 31  | 0(1)        | 1B1            | Adeno        | –                        |
| 17      | 31  | 0(0)        | 1A2            | SCC          | +                        |
| 18      | 36  | 0(1)        | 1B1            | Adeno        | –                        |
| Difference$^1$ | n.s | n.s | n.s | n.s | n.s |

$^1$“n.s” means statistically “not significant” between Group A and Group B. Differences between Group A and Group B were estimated for age, the first delivery or not, clinical stage 1B1 or others, SCC or adenocarcinoma, and the diagnostic conization was performed or not, respectively

$^2$“SCC” means squamous cell carcinoma. “Adeno” means adenocarcinoma

$^3$“+” Means diagnostic conization was done. “−” means diagnostic conization was not done
explanations to her and her family. Adjuvant chemotherapy using paclitaxel and carboplatin was used for her both during the pregnancy and after cesarean section. Assessment of pelvic lymph node metastasis was performed by laparotomy or laparoscopy at the time of vaginal RT. For pregnant patients, it was performed by magnetic resonance imaging (MRI) before the operation and lymph node sampling at the time of the operation.

Vaginal RT was performed based on a modification of the procedure of Dargent et al. Amputation height was preoperatively determined by transvaginal ultrasonography and a careful search of the lesion area by colposcopy for each patient. There were no differences of operative procedures between vaginal RT for pregnant patients and vaginal RT for non-pregnant patients.

Pelvic lymphadenectomy or lymph node sampling by laparotomy or laparoscopy was performed first, followed by vaginal RT. Briefly, a rim of vaginal mucosa was delineated circumferentially and excised so that the anterior and posterior mucosae could cover the cervix. The vesicovaginal space was defined laterally on each side. Then, the descending branches of the uterine arteries and the cardinal ligaments were cut at the level of Type II hysterectomy. After this procedure, we usually amputated the uterine cervix 10 mm below the internal os of the uterus. A nylon suture was placed around the residual cervix to support cervical strength, and Strumordor suture were placed to cover the surface of the cervix. For pregnant patients, we confirmed the fetal status by ultrasonography soon after the operation, and carefully checked the amount of bleeding from the vaginal wound, and the existence of leakage of amniotic fluid. For pregnant patients, continuous prophylactic intravenous administration of tocolytic agents was performed for at least 1 week after RT.

Follow-up of the cancer was performed by periodical examination of cytology, tumor markers, CT scans, and/or MR imaging. Cytology was usually checked every 4 weeks after RT. MR imaging was performed when the recurrence was suspicious. Tumor marker examination and CT scans were not usually performed for pregnant patients.

For the management of pregnant patients after vaginal RT, there are as yet no international guidelines. Of course, there were no differences of the management methods between patients who underwent RT during pregnancy and those who underwent RT before pregnancy. Follow-up of pregnant patients after vaginal RT was performed according to a protocol described previously [6]. We recommend that patients enter hospitalization early in the second trimester of the pregnancy even if there are no signs of threatened abortion. Under hospitalization, patients undergo: (1) bed rest, (2) daily vaginal disinfection with 0.3% chlorhexidine, (3) prophylactic administration of an ulinastatin vaginal suppository, (4) routine examinations for bacterial vaginosis and maintenance of normal vaginal flora, (5) examination of the Nugent score, granulocyte elastase level and oncofetal fibronectin in vaginal secretion, (6) general blood examination, and the administration of metronidazole in cases with a Nugent score > 5, and/or that are cervical elastase or fibronectin positive, (6) routine examination of uterine cervical length using transvaginal ultrasonography, (7) long-term tocolysis using ritodrine hydrochloride, magnesium sulfate, and nifedipine for patients with abdominal pain/tension, or for those with the uterine cervical length shortened to < 2 cm, and (8) weekly administration of a hydroxyprogesterone caproate depot.

Considering the maternal physical and psychological conditions from the long-term bed rest and tocolysis, and to avoid the sudden occurrence of preterm premature rupture of membranes (pPROM), cesarean section was usually scheduled at around 35 weeks of pregnancy except for patients who required emergent cesarean section.

Standard statistical tests, including Welch t test, were used to analyze the clinicopathological data using Microsoft EXCEL 2016. A p value of less than 0.05 was considered statistically significant.

Results

Summaries of Group A and Group B are shown in Tables 1, 2, 3, 4, 5 and 6. There was no significant difference of age, stage, histology, and obstetrical factors between Group A and Group B. The average amount of bleeding at vaginal RT was 176 ml, and the average operative time was 97.5 min for Group A. The average amount of bleeding at vaginal RT was 84.4 ml, and the average operative time was 130 min for Group B (Tables 2, 4). There was no significant difference in surgical time or intraoperative bleeding between the two groups. No intraoperative problems occurred for patients and/or fetuses in either group. Genital bleeding after the operation was not marked for any patient of either group, and it usually stopped within 10 days after RT. The pathological specimens had negative surgical margins of over 10 mm for seven of the eight patients in Group A and for all the ten patients in Group B. One lymph node metastasis was detected in patient 6 with stage IIA cancer. She underwent periodic administration of paclitaxel and carboplatin until the scheduled cesarean section and also after the cesarean section as described in “Patients and methods”. No other patients in Group A and Group B showed any distant metastatic lesions. Neither patients of Group A nor those of Group B had tumor invasion to the cardinal ligaments. Depth of invasion and lymph-vascular space invasion (LVSI) are described in Table 3.

The obstetrical outcomes of Group A and Group B are summarized in Tables 5 and 6. Fetuses in each group showed
Table 2  Oncological outcomes of patients who underwent vaginal RT during pregnancy (Group A)

| No | RT (wks.) | Operative time (min.) | Bleeding (ml) | Bleeding > 10 days | Depth (mm) | LVSI | Free margin | Current status | Recurrence (timing) | Special remarks                      |
|----|-----------|-----------------------|---------------|-------------------|------------|------|-------------|---------------|-------------------|-------------------------------------|
| 1  | 16 W      | 93                    | 150           | –                 | –          | > 10 mm | NED         | 10 years       | –                 |                                     |
| 2  | 15 W      | 110                   | 360           | –                 | 5          | 7–8 mm  | NED 4 years | 4 years        | Residual cervix (24 weeks of preg.)|                                     |
| 3  | 18 W      | 58                    | 105           | –                 | 7          | > 10 mm | NED 3 years | –             | –                 |                                     |
| 4  | 26 W      | 76                    | 125           | –                 | 3.5        | > 10 mm | NED 3 years | –             | –                 |                                     |
| 5  | 16 W      | 121                   | 264           | +                 | 3          | > 10 mm | NED 3 years | –             | –                 |                                     |
| 6  | 10 W      | 147                   | 320           | –                 | 10         | > 10 mm | NED 2 years | –             | –                 | Chemotherapy during pregnancy      |
| 7  | 13 W      | 43                    | 20            | +                 | 0          | > 10 mm | NED 10 months | –             | –                 |                                     |
| 8  | 16 W      | 132                   | 70            | –                 | 6          | > 10 mm | Under treatment | Residual cervix (2 months after delivery) | –                 |                                     |

1“RT” means pregnancy weeks when RT was performed
2“Bleeding > 10 days” means the existence of genital bleeding after vaginal RT
3“LVSI” means “Lymph-vascular space invasion”
4“NED” means “clinically no evidence of disease”
5“*”There was no statistical significance between Group A and Group B
normal growth over the course of pregnancy. The cervical length measured by transvaginal ultrasonography was mostly stable during follow-up for both groups, and there were no differences of the changes in the cervical length. Markers for genital tract inflammation such as the granulocyte elastase level and the oncofetal fibronectin level in the vaginal secretions were also mostly within the normal ranges over the pregnancy for both groups. Control of the preterm labor was successful with the administration of tocolytic agents and bed rest. As mentioned in “Patients and methods”, cesarean section was scheduled at around 35 weeks of pregnancy. However, for one patient who had recurrence during pregnancy (patient 2), cesarean section with abdominal radical hysterectomy (RH) was performed at 26 weeks of pregnancy. In addition, for a patient with a twin pregnancy (patient 15), one with pPROM (patient 17), and one who underwent chemotherapy during pregnancy (patient 6), cesarean section was performed at around 30 weeks of pregnancy.

As described in Table 2 and Table 4, two of the eight patients in Group A had recurrence of the cervical cancer, although none of Group A has recurred so far (Table 3). Patient 2 had recurrence in the residual cervix 9 weeks after RT, at 24 weeks of pregnancy. She underwent cesarean section with RH at 26 weeks of pregnancy. She also received concurrent chemoradiation therapy (46 Gy/25 fr. to the whole pelvis with 6 courses of weekly administration.

| Table 3 | Cytological results and decisions after cytology in patients who underwent vaginal RT during pregnancy (Group A) |
|---------|----------------------------------------------------------------------------------------------------------------|
| 1st cytology | Histology | Cytology after RT | Cytology after delivery |
| 1 | Adenoca | Adenoca | NILM | NILM |
| 2 | SCC | SCC | HSIL (9 wks after RT) | NILM |
| 3 | ASCH | Adenoca | NILM | NILM |
| 4 | Adenoca | Adenoca | NILM | NILM |
| 5 | ASCH | Adenoca | NILM | NILM |
| 6 | HSIL | SCC | NILM | NILM |
| 7 | HSIL | SCC | NILM | NILM |
| 8 | AGC | Adenoca | NILM | NILM (4 wks after delivery) |

1 “1st cytology” means the first cytology after pregnancy. “adenoca.” means adenocarcinoma. “SCC” means squamous cell carcinoma. “ASCH” means atypical squamous cells, cannot exclude HSIL. “HSIL” means high-grade squamous intraepithelial lesion. “AGC” means atypical glandular cells

2 “Histology” means the result of punch biopsy after cytology

3 “Cytology after RT” means the result of the first cytology after RT. “NILM” means negative for intraepithelial lesion or malignancy

4 “Cytology after delivery” means the result of the first cytology after delivery

| Table 4 | Oncological outcomes of patients who underwent vaginal RT before pregnancy (Group B) |
|---------|----------------------------------------------------------------------------------------------------------------|
| Operative time (min.) | Bleeding (ml) | Bleeding > 10 days | Free margin | Current status | Recurrence (timing) | Special remarks |
| 9 | 188 | 100 | – | > 10 mm | NED 9 years | – |
| 10 | 154 | 300 | – | > 10 mm | NED 6 years | – |
| 11 | 114 | 20 | – | > 10 mm | NED 5 years | – |
| 12 | 115 | 40 | – | > 10 mm | NED 5 years | – |
| 13 | 114 | 20 | – | > 10 mm | NED 4 years | – |
| 14 | 147 | 130 | – | > 10 mm | NED 3 years | – |
| 15 | 74 | 84 | – | > 10 mm | NED 2 years | – Twin pregnancy |
| 16 | 55 | 60 | – | > 10 mm | NED 1 years | – |
| 17 | 127 | 70 | – | > 10 mm | NED 2 years | – |
| 18 | 213 | 20 | – | > 10 mm | NED 8 months | – |

1 “Bleeding > 10 days” means the existence of genital bleeding after vaginal RT

2 “NED” means “clinically no evidence of disease”

3-4 There was no statistical significance between Group A and Group B
of CDDP) after delivery. Her child has normal growth thus far, and she is alive without further recurrence. Patient 8 showed no abnormal cytology over the pregnancy. At the time of cesarean section, we could not find any abnormal masses around the uterus, and the washing cytology of the abdominal cavity was also negative. Her postpartum genital condition was good. However, in a postpartum checkup 1 month after the cesarean section, ascites retention at the Douglas pouch, and a slight elevation of tumor marker CA125 were detected. As MR imaging of the uterus detected an abnormal mass deep in the residual cervix, and the cytology showed adenocarcinoma, we diagnosed recurrence of the cancer. She underwent six courses of chemotherapy with paclitaxel and docetaxel, and then she received hysterectomy and the partial bladderctomy due to invasion of the tumor to her bladder. Then, she received concurrent chemoradiation therapy (50 Gy/25 fr. to the whole pelvis with 6 courses of weekly administration of CDDP) after the hysterectomy. Her child’s growth is quite normal thus far. None of patients in Group B has shown any signs of recurrence.

Table 5 Obstetrical outcomes of patients who underwent vaginal RT during pregnancy (Group A)

| Patient | Delivery (weeks) | Baby weight (g) | Apgar score (1 min./5 min.) | CAM (placenta) | Highest BV score1 | pPROM | Shortening rate of Cx (%)2 | Tocolysis |
|---------|------------------|-----------------|-----------------------------|----------------|------------------|-------|---------------------------|-----------|
| 1       | 34               | 2112            | 8/9                         | –              | 7                | + (34w) | 26                        | Ritodrine hydrochloride |
| 2       | 26               | 882             | 4/8                         | –              | 2                | –      | 46                        | Ritodrine hydrochloride |
| 3       | 35               | 2156            | 7/9                         | –              | 4                | –      | 17                        | Ritodrine hydrochloride |
| 4       | 35               | 2328            | 8/8                         | –              | 5                | –      | 49                        | Ritodrine hydrochloride |
| 5       | 35               | 2400            | 8/9                         | –              | 0                | –      | 35                        | Ritodrine hydrochloride |
| 6       | 30               | 1188            | 7/8                         | –              | 0                | –      | 0                         | Isoxsuprine hydrochloride |
| 7       | 36               | 2248            | 8/9                         | –              | 6                | –      | 29                        | Nifedipine |
| 8       | 35               | 2390            | 8/9                         | –              | 8                | –      | 8                         | None |
| Average | 33*              | 1963*           | 7/8*                        | *              | 4*               | *      | 26.3*                     |          |

1^”Highest BV score” means the highest BV score during pregnancy
2^”Shortening rate of Cx” means (cervical length in the early pregnancy—minimum cervical length during pregnancy)/cervical length in the early pregnancy
3^&* There was no statistical difference between Group A and Group B

Table 6 Obstetrical outcomes of patients who underwent vaginal RT before pregnancy (Group B)

| Patient | Delivery (weeks) | Baby weight (g) | Apgar score (1 min./5 min.) | CAM (placenta) | Highest BV score1 | pPROM | Shortening rate of Cx (%)2 | Tocolysis |
|---------|------------------|-----------------|-----------------------------|----------------|------------------|-------|---------------------------|-----------|
| 9       | 33               | 2294            | 6/6                         | +              | 8                | –      | 21                        | Ritodrine hydrochloride |
| 10      | 34               | 2520            | 7/8                         | –              | 6                | –      | 13                        | Ritodrine hydrochloride |
| 11      | 35               | 2126            | 8/9                         | –              | 3                | –      | 42                        | Isoxsuprine hydrochloride |
| 12      | 35               | 2470            | 8/9                         | –              | 1                | –      | 27                        | Ritodrine hydrochloride |
| 13      | 34               | 3226            | 5/7                         | –              | 1                | –      | 22                        | Ritodrine hydrochloride |
| 14      | 35               | 2412            | 7/9                         | –              | 2                | –      | 44                        | Ritodrine hydrochloride |
| 15      | 30               | 1224/1499       | 8/9 5/8                     | –              | 3                | –      | 50                        | Ritodrine hydrochloride |
| 16      | 36               | 2588            | 6/9                         | –              | 0                | –      | 44                        | Ritodrine hydrochloride |
| 17      | 31               | 1684            | 8/9                         | –              | 0                | + (31w) | 17                        | None |
| 18      | 37               | 2160            | 8/9                         | –              | 10               | –      | 0                         | None |
| Average | 34*              | 2200*           | 7/8*                        | *              | 3.4*             | *      | 28*                       |          |

1^”Highest BV score” means the highest BV score during pregnancy
2^”Shortening rate of Cx” means (cervical length in the early pregnancy—minimum cervical length during pregnancy)/cervical length in the early pregnancy
3^&* There was no statistical difference between Group A and Group B

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Discussion

This study compared the obstetrical and oncological outcomes of patients who underwent vaginal RT during pregnancy with those of patients who underwent vaginal RT before pregnancy in a single institute.

Pregnancy after RT itself has an extremely high risk of preterm birth [6, 9, 10]. As is well known, the uterine cervix works not only as a mechanical support of the fetus but also as a barrier against intrauterine infection [11]. Large excision of the uterine cervix with RT might contribute to a decrease in such load-bearing capacity, along with an increased risk of infection by intravaginal bacteria, resulting in miscarriage or preterm birth. RT during pregnancy might have additional obstetrical and oncological risks. These possible risks include: (1) miscarriage and preterm birth due to the burden of the radical surgery during pregnancy, (2) the occurrence of pPROM due to chorioamnionitis (CAM) induced by cervical infection after RT during pregnancy, (3) massive bleeding of the pregnant uterus during the operation, and (4) increase of the recurrence of the cancer.

For (1), Ungar et al. reported a high rate of postoperative miscarriage when RT was performed in the first trimester of pregnancy [12]. A recent report by Douligeris et al. also showed a high abortion rate after abdominal RT during pregnancy [13]. Fetuses in the first trimester may not be able to tolerate the surgical stress of RT [14], although our patient number 6, who underwent vaginal RT at 10 weeks of pregnancy, did not show any signs of threatened abortion after the operation. On the other hand, we believe that the late second to the third trimester of pregnancy is too late to undergo RT. Aoki et al. reported that it was better to perform RT between 15 and 19 weeks of pregnancy [15]. We agree with their policy. Manipulation of the enlarged uterus during the operation can be a stress to the intrauterine fetus and it sometimes causes uterine contractions, and an enlarged uterus also becomes an obstacle to performing pelvic lymphadenectomy. We also performed vaginal RTs during the second trimester of pregnancy before 20 weeks of pregnancy, except for one case in which cancer was detected in the third trimester of pregnancy. We experienced no fetal losses thought to be associated with the operation during pregnancy. Furthermore, RT is performed through either the abdominal or vaginal route. As we reported previously, vaginal RT for pregnant patients seems to have an advantage over abdominal RT in terms of the direct stress on the fetus in the uterus because vaginal RT does not need complicated intra-abdominal procedures [16]. Vaginal RT during pregnancy does not seem to affect the fetal condition as long as the operation is performed early in the second trimester of pregnancy before 20 weeks of pregnancy.

With regard to (2), both uterine contracture and uterine cervical infection can be a cause of pPROM. Manipulation of the uterus can be a cause of continuous uterine contraction after the operation. We usually performed continuous intravenous administration of tocolytic agents for several days after RT during pregnancy. These treatments were effective and no patients in Group A experienced abortion due to uterine contraction after RT. Is the surgical wound of the uterine cervix a focus of infection, leading to pPROM from CAM by intravaginal bacteria? As shown in Table 4, genital bleeding of the patients in Group A was almost stopped within 10 days after RT, regardless of its timing. We performed meticulous bacterial vaginosis (BV) and preterm marker examinations, as well as blood tests, as we mentioned in “Patients and methods”. Treatment of BV in normal pregnant women is still controversial. However, such routine examinations and treatment that starts at the timing of BV seem to be useful to prevent the occurrence of cervical and intrauterine infections in patients after RT [17]. The surgical wound of the uterine cervix seems not to be a cause of intrauterine infection that leads to pPROM as long as we conduct meticulous postoperative prophylaxis.

With regard to (3), uterine surgery during pregnancy is associated with enlarged blood vessels, and therefore, we thought the amount of bleeding was likely to increase. However, in the present study, there was no significant difference in surgical time or intraoperative blood loss between the two groups. Yoshihara et al. also reported that there were no significant differences in the amount of bleeding during the operation among RT before pregnancy, RT during pregnancy, and RH [18]. We believe that RT during pregnancy does not increase the risk of massive intraoperative bleeding as long as it is performed during the appropriate period of pregnancy.

We found two recurrences (25%) in the eight patients who underwent RT during pregnancy. However, all the patients who underwent RT before pregnancy were free of recurrence during follow-up. Yoshihara et al. reported that there was no difference in oncological prognoses among abdominal RT before pregnancy, abdominal RT during pregnancy and abdominal radical hysterectomy (RH). It is said that pregnancy has no effects on the progression of the cervical cancer [19], and of course, it is generally accepted that there is no difference in oncological outcomes between vaginal RT and abdominal RT [20]. However, Capilna et al. reported that abdominal RT during pregnancy had better oncological results than vaginal RT during pregnancy [21]. They reported that 2 of 10 patients (20%) had recurrences after vaginal RT, though none of 11 patients did so after abdominal RT. Vaginal RT is less stressful for the fetus than abdominal RT because there is no laparotomy or strong traction of the uterus. However, vaginal RT is a more conservative operation than abdominal RT. Vaginal RT resects the
parametrium at the level of type II hysterectomy, whereas abdominal RT can provide wider resection up to the level of type III resection [22]. Does such a conservative procedure of vaginal RT affect the recurrence of the cancer? None of the patients in this study had parametrial invasion, and it is widely accepted that the oncological prognoses of vaginal RT and abdominal RT are the same as long as the indication of the operation is appropriate. Considering that the site of recurrence was the residual cervix in both cases, we should have ensured a greater cancer-free margin for the operation for pregnant patients, though doing so might lead to an increase in preterm birth.

RT during pregnancy is still an experimental treatment because of the lack of large trials and randomized studies. In a PubMed search, as of September 2020, we found that only 28 cases of abdominal RT and 9 cases of vaginal RT had been reported [18, 23]. However, we believe that RT for pregnant patients with early invasive uterine cervical cancer is a promising treatment modality. What is important is to conduct careful management for patients who undergo RT during pregnancy to detect recurrence as early as possible. It is said that management of uterine cervical cancer during pregnancy depends on five factors: the stage of the disease, nodal status, histological subtype of the tumor, term of pregnancy, and the desire to preserve fertility [24]. It might be useful to decide the management of pregnant patients with uterine cervical cancer based on these factors. The demand for the preservation of fertility among young patients with uterine cervical cancer is increasing. This study is only a small study in a single institute. It is not easy to get clinical evidences in the treatment of pregnant women with invasive cervical cancer. We believe future multicenter randomized trials to obtain a consensus on the indications, operative timing, and operative technique are important.

Author contributions SS, SI, TM, and TS designed the research. All the authors attended the management of each patients as a treatment team. SS, YF, MK, and MS analyzed data. SI and TS supervised the research. SS, SI, and TS wrote the manuscript. All the authors have read and approved the manuscript.

Funding Not applicable.

Availability of data and materials Data will be available from corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This study adhered to the tenets of Declaration of Helsinki, and the study design was reviewed and approved by the Sapporo medical university’s review board and the ethics committee (approval number: 05–26). Permission to access and to use these data was also approved.

Consent to participate A written informed consent to participate in the study and to publish the report was obtained from each patient.

Consent for publication Not applicable.

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