Review Article

The Current Trend of Fertility Preservation in Patients with Cervical Cancer

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Abstract

Although the incidence of most cancers increases with age, a considerable number of patients receive a diagnosis of cancer during their reproductive years. Young women wishing to get pregnant after cancer treatment should be provided consultation for fertility preservation and possible options. In patients with cervical cancer, hysterectomy is often inevitable because the uterus is located too close to the cervix. For young patients with cervical cancer who desire to get pregnant and whose lesion is confined to the cervix, sparing the uterus and, partially, the cervix should be prioritized as much as possible, while simultaneously ensuring favorable oncologic outcomes. In this review, we explore how to choose an adequate fertility-preserving procedure to achieve a balance between favorable oncologic outcomes and fertility and management during pregnancy after a radical trachelectomy in women with early-stage cervical cancer. For patients who require hysterectomy or radiation, evaluation of the ovarian condition and laparoscopic ovarian transposition followed by the use of artificial reproduction techniques and pregnancy by surrogacy should be discussed as options to achieve a successful pregnancy.

Keywords: Cervical cancer, fertility preservation, oncologic outcome, pregnancy

Introduction

Although the incidence of most cancers increases with age, a considerable number of patients receive a diagnosis of cancer during their reproductive years. For young women wishing to get pregnant after cancer treatment, many international guidelines have been proposed that recommend evaluation of the gonadal toxicity caused by cancer treatment, consultation for fertility preservation, and discussion of options for achieving successful pregnancy following infertility.[1,2] In patients with nongynecologic tumors, the common approaches to treatment are ovarian transposition to avoid radiation exposure to the ovaries, administration of drugs to preserve ovarian function, oocyte cryopreservation, ovarian tissue cryopreservation, and transplantation. However, in patients with cervical cancer, hysterectomy is often inevitable because the uterus is located too close to the cervix. For young patients with cervical cancer who desire to get pregnant and whose lesion is confined to the cervix, sparing the uterus and, partially, the cervix should be prioritized as much as possible because surgical removal of the involved organ is the standard treatment procedure for early cervical cancer. In this review, we discuss how to choose an adequate fertility-preserving procedure to achieve a balance between favorable oncologic outcomes and fertility, management during pregnancy after a radical trachelectomy, and fertility options after a hysterectomy or radiation treatment in patients with cervical cancer.

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Epidemiology of Cervical Cancer in Young Women

In 2020, the global age-standardized incidence of cervical cancer was 13.3 cases/100,000 women-years, and the mortality rate was 7.2 deaths/100,000 women-years. With the implementation of cervical cancer screening programs in many countries, the incidence has decreased over the past three decades in Latin America, Asia, Western Europe, and Northern America.[3] However, in 146 (79%) of 185 countries, cervical cancer still ranks among the top three cancers in women younger than 45 years.[4] The age-specific annual percentage change in incidence exhibited an increasing trend for the age group of 15–49 years from 1990 to 2019, with the highest percentage change observed in high sociodemographic index regions.[5] Many women who receive a diagnosis of cervical cancer wish to preserve their reproductive function during cancer treatment.

Discussion on Fertility Preservation in Cervical Cancer Before Treatment

Wenzel *et al*. assessed the psychosocial aspects of fertility concerns and quality of life (QOL) in 231 female survivors of cancers, including lymphoma, gestational trophoblastic tumors, and cervical cancer. Patients with cervical cancer had relatively high reproductive health concerns, which were significantly associated with a lower QOL on numerous dimensions ($P < 0.001$).[6] At the time of diagnosis, a large proportion of young patients with cervical cancer are worried about the possible impact of treatment on their fertility and future chances of conception. Failure to address these concerns may negatively influence their oncologic outcomes and QOL.

Fertility Preservation Surgery for Early-Stage Cervical Cancer and Oncologic Outcome

When women receive a diagnosis of cervical cancer during their childbearing years, they should be provided the option of receiving a fertility-sparing strategy without compromising the outcome of the cancer treatment. Bentivegna *et al*. conducted a systematic review on 3098 women with stage IA–IIA cervical cancer, who were treated conservatively, and assessed the various techniques available to preserve fertility (Dargent's procedure; simple trachelectomy or cone resection; neoadjuvant chemotherapy with conservative surgery; and laparotomic, laparoscopic, and robot-assisted abdominal radical trachelectomy). They reported positive oncologic outcomes.[7] Another systematic review by Nezhat *et al*. on women with stage IA1–IB1 cervical cancer also reported the same result, with a mean cancer recurrence rate of 3.2% and a cancer death rate of 0.6% after a median follow-up period of 39.7 months.[8] Thus, in patients with early-stage cervical cancer, achieving favorable treatment outcomes while preserving their fertility function is possible.

Selection of Surgical Procedure

To determine whether fertility-sparing surgery (FSS) is suitable, first, lymph node metastasis should be ruled out. Thereafter, two primary factors should be considered: tumor size (FIGO 2018 1B1, IB2, and IB3) and lymphovascular space invasion (LVSI) status [Table 1]. In general, patients with stage 1A1 tumor without LVSI have a lymph node metastasis risk of <1%.[9] Accordingly, conization with negative cervical margins alone is a definitive treatment for these patients. For patients with stage 1A1 tumor and positive LVSI, the risk of lymph node metastasis is 7.8%,[9] and therefore, conization with a negative margin and pelvic lymphadenectomy (or sentinel lymph node [SLN] mapping) are the most favorable choices. Radical vaginal trachelectomy (VRT) involves the removal of the cervix, upper vagina, and supporting ligaments similar to Type B radical hysterectomy. VRT and pelvic lymphadenectomy (or SLN mapping) are the most favorable fertility-sparing options while achieving oncologic success for patients with stage 1A1 tumor and LVSI and stage 1A2-1B1 tumor [Table 2]. The ConCerv Trial prospectively evaluated the feasibility of conservative surgery on the basis of previous reports of conization samples and determined a new option. If all the relevant criteria were met (i.e., no LVSI, negative cone margins, squamous cell [any grade] or usual-type adenocarcinoma [Grade 1 or 2 only], tumor size ≤2 cm, depth of invasion ≤10 mm, and negative imaging for metastatic disease), previously performed conization with pelvic lymphadenectomy was sufficient for patients with stage 1A2–IB1 disease. The recurrence rate reported in this study was approximately 3.5%, and positive lymph nodes were found in 5% of the patients.[8] Abdominal radical trachelectomy is also a reasonable fertility-sparing strategy, and most surgeons are familiar with the procedure. It mimics Type C radical hysterectomy, provides larger parametrial resection than the vaginal approach, and is often performed on patients with stage 1B disease. Abdominal radical trachelectomy can be performed through Abdominal radical trachelectomy via laparoscopy (LRT) or Abdominal radical trachelectomy via laparotomy (ART). A systematic review by Morice *et al*.[11] demonstrated that the recurrence rates in patients with stage IB1 disease undergoing simple conization or simple trachelectomy, VRT, ART, and LRT were 4.1%, 4.7%, 2.4%, and 5.2%, respectively. Thus, ART presented the lowest rate of recurrence. Further, the recurrence rates in patients with stage IB2 disease undergoing neoadjuvant chemotherapy and conservative surgery, ART, and LRT were

Table 1: Clinical management options depending on the stage of cervical cancer for patients wishing to receive fertility-sparing surgery

Clinical stage	Management options for patients wishing to receive FSS
Stage 1A1 without LVSI	Conization
Stage 1A1 with LVSI, stages 1A2–1B1	VRT and pelvic lymphadenectomy (or SLN mapping)
Stage 1A2-1B1 and all criteria should be met (no LVSI, negative cone margins, squamous cell (any grade) or usual-type adenocarcinoma (grade 1 or 2 only), depth of invasion ≤10 mm, and negative imaging for metastatic disease)	Conization and pelvic lymphadenectomy
Stage IB2	ART or LRT; the ART group exhibited more favorable oncologic outcomes, but lower pregnancy rates. Limited data for the LRT group
Neoadjuvant chemotherapy followed by FSS	Not recommended

LVSI: Lymphovascular space invasion, VRT: Vaginal radical trachelectomy, SLN: Sentinel lymph node, FSS: Fertility-sparing surgery, ART: Abdominal radical trachelectomy via laparotomy, LRT: Abdominal radical trachelectomy via laparoscopy

Table 2: Oncologic and reproductive outcomes after various surgical procedures

Study	Procedure	Simple trachelectomy/ cone resection	Radical vaginal trachelectomy	ART	LRT	Neoadjuvant chemotherapy
Bentivegna *et al*.[10]	Pregnancy rate (%)	56	57	44	65	77
Stage IA-IIA	Live birth rate (%)	74	67	68	78	76
	Prematurity rate (%)	15	39	57	50	15
	Recurrence rate (%)	1.8	3.8	3.8	4.7	4.3
Nezhat *et al*.[8]	Pregnancy rate (%)	65	68	42	42	
Stage 1A1–1B1	Live birth rate (%)	86	63	66	66	
	Prematurity rate (%)	25	35	31	31	
	Recurrence rate (%)	1.4	3.7	3.6	3.3	
Morice *et al*.[11]	Pregnancy rate (%)	56.3	58.7	36	46.4	
Stage IB1	Live birth rate (%)	88	71	66.6	62	
	Recurrence rate (%)	4.1	4.7	2.4	5,2	
Morice *et al*.[11]	Pregnancy rate (%)			36	46.4	74.5
Stage IB2	Live birth rate (%)			66.6	63.3	78.7
	Recurrence rate (%)			4.8	10.5	13.2

ART: Abdominal radical trachelectomy via laparotomy, LRT: Abdominal radical trachelectomy via laparoscopy

13.2%, 4.8%, and 10.5%, respectively. The recurrence rate observed in the group of patients treated with LRT should be interpreted with caution because this group comprised only 57 patients. Under laparoscopy, preserving the ascending branches of the uterine arteries and separating the ligaments surrounding the cervix and vaginal area becomes easier. However, LRT is a more complex procedure because both transabdominal and vaginal routes are necessary to remove the whole cervix and make corpus-vagina anastomosis.[12] Not all surgeons have adequate patient volume to get familiar with this procedure, and this reason may compromise the outcome. Standardized surgery in LRT and high-volume surgeons in laparoscopic radical hysterectomy may improve the outcome.[13] About LRT, the surgeon also should monitor the risk of LVSI. According to the finding by Huang *et al*., in their retrospective study, the rate of LVSI is higher in laparoscopic radical hysterectomy than in abdominal radical hysterectomy (36.8% vs. 19.8%, $P < 0.05$); however, they cannot confirm that the recurrence rate is related to LVSI.[14]

The recurrence rates were significantly higher in the neoadjuvant chemotherapy and conservative surgery groups than in the laparotomic approach group (13.2% vs. 4.8%; $P = 0.001$).[11] Therefore, the suitability of using neoadjuvant chemotherapy to reduce tumor size and conservative surgical treatment for patients with a large cervix should be validated experimentally. The ongoing NEOCON-F/CONTESSA trial assesses the effectiveness and safety of neoadjuvant chemotherapy followed by FSS in stage IB2 cervical cancer which will provide further evidence. In a review by Di Donato *et al*., only 48 patients who had a cervical tumor ≥4 cm in size (Stage IB3) underwent FSS and exhibited 5-year disease-free survival and overall survival rates of 92.4% and 97.6%, respectively. By contrast, the 5-year disease-free survival rate was only 74.7% in high-risk patients (G3, nonsquamous histology, and diameter ≥5 cm).[15] Due to the limited evidence, we do not recommend the use of FSS in stage IB3 patients.

Fertility Results and Pregnancy Outcomes after Conservative Treatment

Bentivegna *et al*. conducted a systematic review in 2016 to evaluate the fertility results and obstetric outcomes in patients with stage 1A-IIA cervical cancer subjected to FSS.

The overall fertility, live birth, and prematurity rates after the fertility-sparing procedures were 55%, 70%, and 38%, respectively. The pregnancy rate was higher in patients who received VRT and LRT than in those who received ART. The live birth rate was similar among different FSS procedures. The prematurity rate was significantly lower in patients who had undergone a simple trachelectomy/cone resection or neoadjuvant chemotherapy followed by FSS than in those who had undergone other conservative surgeries. Most second-trimester fetal losses and premature deliveries were related to premature rupture of membranes.[10] In 2020, another systematic review by Nezhat *et al*. reported similar results – the overall fertility, live birth, and prematurity rates after these procedures were 55.4%, 67.1%, and 31.0%, respectively. The highest pregnancy rate (67.5%) was observed in the VRT group. Only 20% of pregnancies after FSS required treatment with assisted reproductive technology. The median follow-up period after FSS was 39.7 months,[8] and the follow-up period was not sufficiently long in most studies (<2 years in many studies). Although such short follow-up durations may be appropriate for evaluating reproductive and obstetric outcomes, they cannot truly reflect the long-term oncologic outcomes.

Cerclage

During pregnancy, the cervix provides strong support that keeps the baby in the uterus. Cervical incompetence is a major cause of preterm labor after FSS. In the FSS procedure, after trachelectomy is performed, the surgeon often places a cervical cerclage around the isthmus with a Hegar dilator placed in the canal to prevent further stenosis and preterm labor in the future. Despite the use of cervical cerclage, preterm labor has still been reported in more than 30% of pregnancies after a trachelectomy.[8,10] To the best of our knowledge, until now, no randomized study has compared the obstetric outcomes between patients with and without cervical cerclage after a trachelectomy. However, in a review by Nezhat *et al*., almost all patients in the VRT and LRT groups and most patients in the ART group receive a cerclage.[8] In the present clinical setting, we suggest performing cerclage routinely during a trachelectomy.

Pregnancy Management after Trachelectomy

Before and after a trachelectomy, the patient and her family should be informed about the high risk of preterm delivery and preterm premature rupture of membranes after surgery. Moreover, fertility problems such as cervical stenosis and hematometra, thinning of the endometrium, and Asherman's syndrome have also been reported after FSS. On average, 10.5% of patients who undergo radical trachelectomy have cervical stenosis. In addition, the incidence rates of cervical stenosis were 8.6% and 3.0%, respectively, in patients who received cervical cerclage and those who did not (P = NS). In the presence of antistenosis devices, the incidence of stenosis was 4.6%, and in their absence, the incidence was 12.7% ($P < 0.001$).[16] Most cases of cervical stenosis can be resolved through surgical dilatation, but some require assisted reproductive technology.

On conception after FSS, the incidence rate of miscarriage in the first trimester was approximately 12.8%.[10] If miscarriage occurred before 12 weeks of gestation, determining whether dilatation and curettage (D and C) should be performed is critical. D and C in women who have undergone FSS presents high risks of losing the prophylactic cerclage or developing endometritis. Therefore, expectant management without D and C may be considered the first-line treatment for the first-trimester miscarriage after FSS. In a report by Bernardini *et al*., 3 of 22 pregnancies after a radical trachelectomy resulted in first-trimester abortions; none of which required D and C.[17] However, if D and C is performed, care should be taken to not remove the cerclage.

The incidence rate of miscarriage in the second trimester after FSS was 5.7%.[10] If a miscarriage occurs, vaginal delivery should be avoided due to the risk of cervical laceration caused by cerclage.[18]

Regarding perinatal management, Kasuga *et al*.[19] suggested outpatient visits every 2 weeks after 18 weeks of gestation. Moreover, they recommended the use of transvaginal ultrasound to evaluate the cervical length at every hospital visit. A cervical length of <13 mm may be a strong predictor of preterm delivery during the second trimester.[20] Thus, if a short cervix is found during the examination, the physician may recommend more frequent outpatient visits or hospital stays. Whether vaginal progesterone should be used in patients with FSS is controversial due to limited relevant data,[21] but it may be considered.

Cesarean section (CS) should be performed to prevent cervical laceration. A transverse incision made during CS at the lower region of the uterus is recommended to avoid bladder injury. However, during this procedure, varices may be found at the site of uterovaginal anastomosis, and bleeding may occur.[22] In addition, the risk of uterine artery injury should be considered. The decision regarding classical CS or high-transverse CS is usually made at the physician's discretion; however, the high bleeding rates in this procedure should also be considered. CS is usually considered at 37 gestational weeks without labor signs or if symptoms such as vaginal bleeding, uterine contraction, and membrane rupture occur after 34 gestational weeks. After delivery, hematometra or pyometra may occur, and hence, follow-up is recommended.

Ovarian Preservation

Other important concerns related to fertility preservation in patients with cervical cancer are the possibility of ovarian

metastasis and preservation of the ovarian function during cancer therapy. The risk of ovarian metastasis is not high in patients with stage I–IIA cervical cancer; however, it is even higher for those with nonsquamous cervical carcinoma.[23-25] The incidence of ovarian metastasis in patients with cervical cancer was 0.22% for stage IB, 0.75% for stage IIA, and 2.17% for stage IIB squamous cell carcinoma; the corresponding values were 3.72%, 5.26%, and 9.85%, respectively, for adenocarcinoma.[25] Another review by Cheng *et al*. indicated that the incidence of ovarian metastases was 0% in stage IA, 2.8% in stage IB, 3.4% in stage IIA, and 11.8% in stage IIB cervical adenocarcinoma.[26] To the best of our knowledge, data on the incidence of ovarian metastasis in patients with advanced cervical cancer are insufficient. For patients with cervical cancer who want to preserve their fertility, ovarian preservation may be advised to patients with the clinical stage of their tumor <IIA or stage IIB for squamous cell carcinoma.

Ovarian Transposition

In patients identified as having an intermediate-risk disease based on final pathology results after a hysterectomy according to the criteria stated by Sedlis *et al*., adjuvant radiotherapy is indicated.[27] Patients with stage IIB squamous cell carcinoma of the cervix often receive concurrent chemoradiation for primary treatment. In both treatment strategies, if the ovary is exposed to radiation, it loses its function. Ovarian function, and thereby fertility, can be preserved through ovarian transposition. Because ovarian transposition is often a prophylactic procedure, the possibility of ovarian failure after this procedure should be discussed with the patient. According to the review by Laios *et al*., in the group that underwent ovarian transposition alone, 9% of the women lost their ovarian function, and 1% of the women exhibited metastases to the transposed ovaries. In the external beam pelvic radiotherapy and ovarian transposition group, ovarian function was preserved in 61% of women, and no metastases to the transposed ovaries were reported in that group.[28] Because ovarian function is not completely preserved after ovarian transposition, ovarian tissue cryopreservation should be also considered during ovarian transposition.

Surrogacy and Uterine Transplantation

For women without a uterus or whose uterus has been exposed to pelvic radiation, the fertility option with the highest success rate is surrogacy.[29,30] Oocytes are often retrieved from the ovary through the transabdominal approach, and conception is achieved through artificial reproduction techniques, with the involvement of a surrogate mother. Uterine transposition is another option; however, the source of the donor, numerous complications, and long-term use of immunosuppressants may limit its use.[31]

Conclusion

In young women with early cervical cancer, FSS can provide favorable oncologic and reproductive outcomes. Simple trachelectomy, conization, and VRT provide more favorable reproductive outcomes in women with stage IA and IB1 tumors; whereas ART provides more favorable oncologic outcomes in women with stage IB tumors; however, the obstetric outcomes are not favorable. Further antenatal care is required after FSS due to high abortion and preterm rates. In addition to conization or trachelectomy, ovarian transposition should be discussed as an option before FSS is performed. Patients who are indicated for a hysterectomy or pelvic radiation may still become pregnant through surrogacy or uterine transplantation if their ovarian function is preserved.

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