

# Fertility preservation for young cervical cancer survivors

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About 68% of invasive cervical cancer cases diagnosed in the United States involve women of childbearing age. Current treatment options for young patients with cervical cancer may cause hormonal and/or structural modifications to the reproductive system that could compromise pregnancy potential. Although clinical guidelines are available to help preserve fertility in these patients, gaps in practice remain, suggesting that the fertility-sparing needs of cervical cancer survivors are not routinely met. The authors provide nurse practitioners with current evidence about fertility-sparing treatments and with counseling considerations for young cervical cancer survivors.

**KEY WORDS:** cervical cancer survivor, fertility-sparing treatment, pregnancy, infertility, conization, trachelectomy

Cervical cancer was once the leading cause of gynecologic cancer in the United States. Following introduction of the use of the Pap smear in the 1940s, the incidence of cervical cancer has declined dramatically.<sup>1</sup> Because use of the Pap smear is so effective and so widespread, the diagnosis of cervical cancer, when it is found, is usually made when a woman is younger (and still fertile) and when the disease is at an earlier stage (and therefore more easily treated).

In 2014, the American Cancer Society projected that 12,360 new cases of cervical cancer would be diagnosed in the U.S.<sup>2</sup> Approximately 68% of cervical cancer cases are diagnosed in women of childbearing age.<sup>3,4</sup> For young women, a diagnosis of cervical cancer once meant a hysterectomy and loss of the ability to bear a child. Today, fertility-sparing treatment (FST) options exist for women with early-stage cervical cancer, as well as more advanced fertility preservation and assisted reproductive technology (ART) approaches for those who are not candidates for FST.<sup>5</sup>

Young cervical cancer survivors may not know about FST options, and thus fear that treatment for cancer may compromise their future ability to conceive.<sup>6</sup> Survivors also tend to be anxious about pregnancy outcomes after completing cancer treatment.<sup>7,8</sup> Evidence suggests that they will want to discuss future fertility options



with their healthcare provider (HCP).<sup>9</sup> The American Society of Clinical Oncology (ASCO) and the American Society of Reproductive Medicine have published guidelines recommending that, prior to treatment, HCPs educate patients diagnosed with cervical cancer about the treatment's potential effects on their fertility, along with fertility-preservation options.<sup>10,11</sup> However, many HCPs are uninformed themselves and do not routinely offer fertility-preservation counseling prior to cancer treatment.<sup>12,13</sup> The purpose of this article is to provide HCPs with current evidence about FST for cervical cancer and with counseling recommendations for young cervical cancer survivors.

### Diagnosis and staging of cervical cancer

A Pap smear is used to screen for cervical cancer but not to make the diagnosis. A histology report from a cervical biopsy confirms the diagnosis and type of cervical cancer. After diagnosis, a workup is done to determine disease stage (*Table 1*).<sup>5</sup>

A clinical staging system is used for cervical cancer (rather than the surgical criteria used for most other gynecologic cancers). Two different staging systems are available. The International Federation of Gynecology and Obstetrics (FIGO) staging system is based on a physical examination, diagnostic procedures, and imaging studies. Stages IA1, IA2, and IB1 are considered early stages of cervical cancer.<sup>5,14</sup> In stages IA1 and IA2, cancer is confined to the cervix and diagnosed only microscopically. Stage IB1 describes cancer confined to the cervix with a clinically visible tumor  $\leq 4$  cm, stromal invasion  $< 10$  mm, and no lymph vascular space invasion.<sup>5</sup> The

## Table 1. FIGO cervical cancer clinical staging workup<sup>5</sup>

- History and physical examination
- Chest radiograph
- Complete blood count
- CT or PET-CT scan
- Cervical biopsy
- MRI as indicated
- Cone biopsy as indicated
- HIV testing as indicated
- Smoking cessation and counseling as indicated
- Cystoscopy or proctoscopy for patients in whom bladder/bowel involvement is suspected

CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; MRI, magnetic resonance imaging; PET, positron emission tomography.

## Young cervical cancer survivors may not know about fertility-sparing treatment options, and thus fear that treatment for cancer may compromise their future ability to conceive.

American Joint Committee on Cancer created the TNM system, which is based on extent of the tumor (T), node involvement (N), and distant metastases presentation (M). Each stage in this system has sub-stages that further describe tissue involvement (*Table 2*).<sup>5,15,16</sup>

### Fertility-sparing cervical cancer treatment

The National Comprehensive Cancer Network (NCCN) recommends

cone biopsy or radical trachelectomy for treatment for up to cervical cancer stage IB1 in women who want to preserve their fertility.<sup>5</sup> This recommendation has not always existed; trends in surgical management of low-risk early-stage lesions have changed over the past 20 years. Hysterectomy was the only cure for cervical cancer stage IB1 until Dargent developed the fertility-sparing radical vaginal trachelectomy (RVT) technique in 1994.<sup>17</sup> Prior to RVT, women with stage IA1 or IA2 lesions were the only cervical cancer survivors able to preserve their fertility.<sup>15</sup>

### Cone biopsy

This term refers to a wedge-shaped excision of cervical tissue for both diagnostic evaluation and removal of abnormal tissue. Two methods of obtaining a cone biopsy with fertility sparing in mind are cold knife conization (CKC) and the loop electrosurgical excision procedure (LEEP). Cone biopsy is used to treat small lesions when there is no risk of dissecting across a gross neoplasm.<sup>5</sup> Given that adequate margins and correct orientation are

**Table 2.** Cervical cancer staging systems<sup>5,15,16</sup>

AJCC TNM stage	FIGO stage	Description
T1	I	Carcinoma confined to the cervix
T1a	IA	Microscopy-visualized invasive carcinoma with deepest invasion $\leq 5$ mm and largest extension $\leq 7$ mm
T1a1	IA1	Measured stromal invasion $\leq 3$ mm in depth and largest extension $\leq 7$ mm
T1a2	IA2	Measured stromal invasion $> 3$ mm and $\leq 5$ mm, with largest extension $\leq 7$ mm
T1b	IB	Clinically visualized lesion confined to the cervix uteri or preclinical cancers greater than stage T1a/IA2
T1b1	IB1	Clinically visualized lesion $\leq 4$ cm in greatest dimension
T1b2	IB2	Clinically visualized lesion $> 4$ cm in greatest dimension

AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynecology and Obstetrics.

obtained, CKC and LEEP are appropriate measures for cervical cancer stage IA1 without lymphovascular space invasion.<sup>5</sup>

Negligible risks exist for cervical cancer stage IA1 recurrence following this treatment.<sup>5</sup>

Potential risks regarding future fertility following a cone biopsy include cervical stenosis and preterm delivery.<sup>18,19</sup> Cervical stenosis occurs in 2%-3% of patients after CKC and in 3%-4% post-LEEP.<sup>19</sup> Because of scar tissue formation that can occur after a cone biopsy, fertility may be compromised until the tissue is removed from the cervix. Long and Leeman<sup>19</sup> reported that a history of a cone biopsy increased the odds of a preterm delivery by 2.19 (95% confidence interval, 1.93-2.49); risk correlated with the depth of the transformation zone removed. In this study, a greater risk existed for preterm delivery when a cone

## Most women who undergo radical vaginal trachelectomy are able to conceive spontaneously.

biopsy sample was thicker than 1.2 cm and larger than 6 cm<sup>2</sup>. However, Bevis and Biggio<sup>18</sup> reported that evidence for the effects of conization procedures on fertility was conflicting because of the different types of procedures performed and the varying quality of control groups.

Fanfani et al<sup>20</sup> performed a multicenter retrospective analysis of reproductive outcomes in 23 early-stage cervical cancer survivors who had undergone conization treatment. Among 10 pa-

tients who tried to conceive, 6 achieved a spontaneous pregnancy and 4 received conception assistance via *in vitro* fertilization and embryo transfer (1 of whom achieved a pregnancy). In total, 70% of the young survivors achieved a pregnancy after cone biopsy treatment.

### Trachelectomy

This fertility-sparing surgical procedure is performed to eradicate cervical cancer. In an RVT, the uterine corpus, ovaries, and Fallopian tubes are preserved, but the cervix, upper portion of the vagina, and the supporting ligaments are removed. A cerclage is placed at the location of the isthmus to close the opening of the uterus.<sup>7</sup> RVT is an option for patients with stage IA2 or IB1 lesions  $< 2$  cm in diameter. A radical abdominal trachelectomy is used for stage IB1 lesions  $> 2$  cm and  $\leq 4$  cm, and provides a larger resection of the parametria.<sup>5</sup>

Most women who undergo RVT are able to conceive spontaneously, but a small number will require conception assistance.<sup>21</sup> The 5-year cumulative pregnancy rate for women trying to conceive post-RVT is 52.8%; the cervical cancer recurrence rate after the procedure continues to be low.<sup>7</sup> Potential risks of either trachelectomy procedure with regard to future fertility include miscarriage, preterm delivery, anovulation, and isthmic stenosis.<sup>7,21</sup>

Koh et al<sup>5</sup> reported that, worldwide, more than 300 pregnancies have been confirmed following a trachelectomy for cervical cancer. Risk for second trimester miscarriage following a trachelectomy is 10%. However, 72% of women have carried a pregnancy to term. Park et al<sup>22</sup> conducted a retrospective chart review of 55 young

early-stage cervical cancer survivors who underwent laparoscopic abdominal trachelectomy. Ten of 18 patients attempting a pregnancy conceived; 6 of the 10 experienced preterm delivery. Overall, 55.6% of the survivors achieved a pregnancy, with 60% delivering preterm.

### Fertility preservation procedures

Most women with cervical cancer at stage IB2 or greater are not candidates for FST. Radiation therapy is most often used for patients with higher stage IB disease, often called bulky disease. Radiation therapy is also used following a primary radical hysterectomy or in conjunction with chemotherapy in advanced disease. Radiation that includes the ovaries can damage oocyte quality and sex hormone production. Chemotherapy is not used in patients with milder forms of cervical cancer who are considering FST options.

Women planning to undergo radiation still have fertility preservation options, including the ART procedures of oocyte or embryo cryopreservation prior to cancer treatment.<sup>23</sup> Cryopreservation of unfertilized oocytes, as opposed to embryos, may be considered for patients who do not have a male partner, do not wish to use donor sperm, or have religious or ethical reasons for avoiding embryo freezing. Because oocytes are highly sensitive to radiation injury, a procedure called oophoropexy (ovarian transposition) may be used. With oophoropexy, ovaries are sutured to the posterior uterus to protect them during pelvic radiation.

Before or after cancer treatment, survivors may benefit from ovarian stimulation medications that help promote follicular devel-

## Table 3. Resources

- American Cancer Society: Fertility and Women with Cancer: [www.cancer.org/acs/groups/cid/documents/webcontent/acspsc-041244-pdf.pdf](http://www.cancer.org/acs/groups/cid/documents/webcontent/acspsc-041244-pdf.pdf)
- American Society of Clinical Oncology: [www.asco.org/](http://www.asco.org/)
- Cancer Research UK: Fertility and Cervical Cancer: [www.cancerresearchuk.org/about-cancer/type/cervical-cancer/living/fertility-and-cervical-cancer](http://www.cancerresearchuk.org/about-cancer/type/cervical-cancer/living/fertility-and-cervical-cancer)
- Having-babies-after-cervical-cancer.com [www.having-babies-after-cervical-cancer.com/fertility.html](http://www.having-babies-after-cervical-cancer.com/fertility.html)
- Livestrong Foundation. Female Fertility Preservation [www.livestrong.org/we-can-help/just-diagnosed/female-fertility-preservation/](http://www.livestrong.org/we-can-help/just-diagnosed/female-fertility-preservation/)
- National Cervical Cancer Coalition: [www.nccc-online.org/](http://www.nccc-online.org/)
- Resolve: The National Infertility Association: [www.resolve.org/](http://www.resolve.org/)
- Save My Fertility: <http://www.savemyfertility.org/>
- The Oncofertility Consortium: <http://oncofertility.northwestern.edu/>

## Inform patients of their individual risk for infertility, based on disease stage and treatment, as high, medium, low, or nonexistent.

opment. However, guidelines from both the American Congress of Obstetricians and Gynecologists and ASCO indicate insufficient evidence regarding the effectiveness of gonadotropin-releasing hormone analogs to suppress and protect ovarian function during cytotoxic treatment.<sup>24</sup>

### Counseling before treatment

These counseling recommenda-

tions concerning fertility preservation were issued by ASCO: (1) Assume that patients with cancer want to discuss fertility preservation; address the possibility of infertility before cancer treatment starts and work with an interdisciplinary team to formulate a plan and make appropriate referrals; (2) Present oocyte and embryo cryopreservation as established fertility preservation methods; (3) Discuss the option of oophoropexy when pelvic radiation will be performed; (4) Inform patients of their individual risk for infertility, based on disease stage and treatment, as high, medium, low, or nonexistent; and (5) Inform patients about the use of conservative gynecologic surgery and radiation options.<sup>11</sup>

Several organizations and advocacy groups are available for young cervical cancer survivors with fertility concerns both before and after treatment (Table 3). ASCO created a **video<sup>A</sup>** that can educate young pa-

**VIEW:** Fertility preservation for young women with cancer<sup>A</sup>



**Table 4. Physical and psychological problems involving sexual function<sup>25-27</sup>**

**Physical problems**

Adhesions  
Changes in energy level  
Damage to nerves  
Decreased intimacy  
Decreased libido  
Decreased vaginal elasticity  
Difficulty with conception  
Difficulty with lubrication  
Dyspareunia  
Fatigue  
Fibrosis  
Inflammation  
Miscarriage  
Preterm delivery  
Radiation  
Risk of infertility  
Scarring  
Surgery  
Vaginal stenosis

**Psychosocial problems**

Anxiety  
Arousal difficulties  
Changes in relationships  
Depression  
Fear (of change)  
Fear (or recurrence)  
Lack of desire  
Reproductive concerns  
Sexual worry

**Drug classes that can affect libido**

Antidepressants  
Anxiolytics  
Opioids

tients about fertility preservation options and support networks.

**Counseling after treatment**

A woman who has undergone FST for cervical cancer faces many challenges. She may experience distress, depression, anxiety, and/or fear, and, depending on her own innate coping ability and her support system, may require psychological assessment and referral. HCPs can evaluate patients for these psychological reactions with tools such as the **Functional Assessment of Cancer Therapy-Cervical Cancer Subscale<sup>B</sup>** and the **NCCN Distress Thermometer for Patients<sup>C</sup>**, and make referrals as needed.

Cervical cancer and its treatment can adversely affect sexual health, causing problems such as decreased libido, fatigue, vaginal stenosis, and dyspareunia (Table 4).<sup>25-27</sup> Many women hesitate to

mention sexual problems on their own, so HCPs need to inquire about them and make referrals to a counselor who specializes in sex therapy, a gynecologist, or a physical therapist who specializes in pelvic pain and sexual dysfunction.\* Many of the physical and psychological complaints involving sexual function resolve within the first year after treatment but may last up to 2 years or longer.<sup>25,26</sup>

With regard to dyspareunia in particular, asking patients whether they experience it is the first step

*\*Editor's Note:* In the current issue of *Women's Healthcare: A Clinical Journal for NPs*, Tammy M. DeBevoise, PT, DPT; Angela F. Dobinsky, PT, DPT; Caitlin B. McCurdy-Robinson, PT, DPT; Christina M. McGee, PT, DPT, ATC, LAT; Cody E. McNeely, PT, DPT; Sara K. Sauder, PT, DPT; and Kimberlee D. Sullivan, PT, DPT, WCS, BCB-PMD present a feature-length article on pelvic floor physical therapy.

in helping resolve the problem. Nonpharmacologic and pharmacologic treatments, along with alternate positioning during intercourse, can be offered. HCPs can recommend over-the-counter vaginal moisturizers and lubricants to assist with vaginal dryness, dyspareunia, and sexual stimulation. In addition, prescription-strength topical lidocaine, estradiol vaginal cream, or ospemifene may help.

Undergoing ART can be arduous for women who endure painful and costly treatments. As of 2008, only 15 states have mandates that require health insurance carriers to provide full or partial coverage of costs related to infertility treatments.<sup>28</sup> Most couples or individual women pay for infertility treatments out of pocket. Each ART cycle requires a woman to invest her body, mind, time, and money to realize her dream of motherhood, and she may be placing herself at risk for developing anxiety and depression.<sup>29-31</sup>

Even if a woman succeeds in achieving pregnancy through ART, the process is often fraught with anxiety.<sup>32,33</sup> Young female cancer survivors have reported that they have a hopeful yet worried outlook on fertility and motherhood.<sup>34</sup> This worry is especially true for cervical cancer survivors who have had trachelectomy surgery, as reported by Lloyd et al,<sup>7</sup> wherein several participants described how they were fearful during pregnancy and attempted to be "model" pregnant women who followed every recommendation to reduce risks associated with preterm labor and miscarriage.

Consultations with specialists in reproductive endocrinology and/or high-risk obstetrics may be helpful. Pregnancy loss after infer-

tility treatment can be devastating to these women, who view their pregnancy as “precious” and a “miracle,” and can have a profound impact on their psychological well-being.<sup>7</sup> HCPs should promptly refer these cancer survivors to mental health counselors who specialize in infertility and pregnancy loss.

## Conclusion

Sixty-eight percent of cervical cancer cases diagnosed in the U.S. involve reproductive-aged women.<sup>2</sup> Many of these women desire future pregnancies and want to discuss treatment options and future fertility. An interdisciplinary care approach for these women is necessary, with an emphasis placed on both successful cancer treatment and fertility preservation. FST options are available for women with early-stage cancer up to IB1. Fertility preservation procedures are available for women who are not candidates for FST. National guidelines are available regarding treatment and counseling for reproductive-age women with cervical cancer. The role of HCPs such as women’s health nurse practitioners is to educate young cervical cancer patients and survivors about their treatment options, manage pre- and post-treatment care, and provide referrals to specialists as needed. ●

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## Web resources

- A. <https://www.youtube.com/watch?v=N51GRc8fQXA>
- B. [www.facit.org/FACITOrg/Questionnaires](http://www.facit.org/FACITOrg/Questionnaires)
- C. [www.nccn.org/patients/resources/life\\_with\\_cancer/pdf/nccn\\_distress\\_thermometer.pdf](http://www.nccn.org/patients/resources/life_with_cancer/pdf/nccn_distress_thermometer.pdf)

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