Cervical neoplasia in pregnancy. Part 2: current treatment of invasive disease

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Although the incidence of cervical cancer in the United States has declined sharply, many young women are diagnosed with the disease every year. Naturally, coincident pregnancies will occur in this subset of reproductively active patients. Although the treatment of cervical cancer has evolved under the drive of multicenter, randomized trials, the same level of evidence does not exist for the treatment of this malignancy in pregnancy. Treatment algorithms are therefore proposed as a series of modifications to the guidelines intended for the nonpregnant patient, taking into account the tremendous social, ethical, and emotional dilemmas specific to each trimester at presentation.

Key words: cervical cancer, pregnancy, treatment management

In 2008, it is estimated that approximately 11,000 women in the United States will be diagnosed with cancer of the uterine cervix, in contrast to more than 493,000 worldwide. With more than 40% of these cases occurring in women of child-bearing age, the diagnosis of this disease during pregnancy is well described. In fact, cervical cancer is one of the most common cancers diagnosed during pregnancy, with an incidence of 1.5 to 12 per 100,000 pregnancies.

Given the critical role that the cervix plays in the continuation of a successful term pregnancy and the vulnerability of the fetus to common cancer treatment modalities, this situation can pose an exceedingly difficult dilemma for both the diagnosing and the treating physician. These unique ethical considerations, and the rarity of the disease, make large, randomized, controlled trials in this group of patients far more difficult, if not impossible, to perform. As a result, there is a noticeable absence of such data to support definitive treatment guidelines. The recommendations brought forth by this or any other review should be based on a thorough and updated survey of the published literature and would not, by any means, seek to define absolute conclusions with regard to treatment of such women.

There is a significant body of work that has been performed, mostly in smaller numbers, regarding procedures evaluated in both the diagnosis and the treatment of cervical cancer in pregnant women. Although the studies are limited in size, they do provide applicable information regarding the efficacy and, perhaps more importantly, the risks of such modalities.

In our companion review (see page 3), we examined the implications of preinvasive cervical disease in pregnancy, with an emphasis on both diagnosis and natural course of the disease. Several conclusions were drawn that are important to the present discussion. First, the progression from preinvasive disease to cervical carcinoma during the course of a pregnancy is rare. In fact, there is a surprisingly high rate of regression from high-grade intraepithelial neoplasia to low grade and from low-grade lesions to normal histology during pregnancy and delivery. As such, it is imperative that a proper histologic diagnosis be made in situations of possible invasive disease. To that end, cervical biopsy has not been shown to be associated either with excess bleeding or pregnancy complications.

Although endocervical curettage has not been definitively proven to cause complications in pregnancy, it has been evaluated only in small, nonrandomized trials.

It is therefore our conclusion that colposcopically directed biopsy should be performed in which cervical intraepithelial neoplasia (CIN) III or greater is suspected and that large-loop electrosurgical excision procedure of the transformation zone (LLETZ) and other excisional procedures be used with caution, generally in the setting of an unwanted pregnancy. Furthermore, endocervical curettage in pregnant patients should be avoided.

Signs and symptoms

Lee et al reported no symptoms in any patient with a stage IA lesion, whereas others have reported postcoital vaginal bleeding or spotting in 59% of patients and a vaginal discharge in 29% of patients with stage IB lesions during pregnancy. Sood et al reported on 30 patients with stage I disease. The majority of patients, 63%, presented with an abnormal Papanicolaou smear, whereas 20% presented with postcoital bleeding. Certainly, patients with advanced or metastatic disease while pregnant can have any number of symptoms including pelvic pain, flank pain, sciatica, chronic anemia, and even intestinal obstruction and/or respiratory distress. However, with modern screening programs, such delayed presentations are becoming increasingly less common.

Staging

Staging of cervical cancer, using the International Federation of Gynecology and Obstetrics (FIGO) schema (Table 1), is based on clinical examination and bi-
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TABLE 1

FIGO staging of cervical cancer\textsuperscript{70}

| Stage | Lesion | Description | 
|-------|--------|-------------|
| I     | Lesion is confined to the cervix. | 
| IA    | No visual lesion is identifiable. Abnormality is identified only by microscopic examination. Depth of invasion is no greater than 5 mm and lesion is no wider than 7 mm in diameter. | 
| IA1   | Stromal invasion is no greater than 3 mm in depth and no wider than 7 mm in diameter. | 
| IA2   | Stromal invasion is between 3 and 5 mm in depth and is no wider than 7 mm. | 
| IB    | Lesion is visible and confined to the cervix or is preclinical but larger than the aforementioned limits of IA stage. | 
| IB1   | Lesion is no greater than 4 cm. | 
| IB2   | Lesion is greater than 4 cm. | 
| II    | Lesion extends into the vagina but no further than the upper two thirds and/or extends into the parametria but not to the pelvic sidewall. | 
| IIA   | Lesion extends into the upper two thirds of the vagina; no parametrial involvement. | 
| IIB   | Obvious parametrial involvement; does not extend to the pelvic sidewall. | 
| III   | Lesion extends into lower one third of vagina or extends to pelvic sidewall; or there is evidence of hydrenephrosis or a nonfunctioning kidney without a noncancerous cause. | 
| IIIA  | Lesion extends into the lower one third of vagina but not to the pelvic sidewall. | 
| IIIB  | Lesion extends to the pelvic sidewall or hydrenephrosis or nonfunctioning kidney. | 
| IV    | Tumor has spread beyond the true pelvis or clinically involves the mucosa of the bladder or rectum. | 
| IVA   | Tumor has spread into adjacent organs. | 
| IVB   | Tumor has spread to distant organs. |
invasive cervical cancer have been established in the pregnant patient, a multidisciplinary meeting should be arranged with representatives from gynecologic oncology, maternal-fetal medicine, neonatology, social work, and radiation oncology. The decision to delay or initiate treatment has religious, ethical, moral, and cultural implications that need to be carefully addressed.

Treatment guidelines for the non-gravid patient with invasive squamous cell carcinoma of the cervix have been developed through a series of well-designed, randomized trials. In such patients, the decision to proceed with either surgical excision or radiation with chemotherapy is based almost exclusively on the clinically determined stage. With the notable exception of very early lesions, the treatment options lead to sterility, either by removal or destruction of the organs responsible for the reproductive function. Naturally, the presence of a live fetus within the uterus complicates the situation to the point at which either the pregnancy must be terminated or there must be a departure from standard treatment modalities. Based on a lower level of evidence, an alternative treatment paradigm can be cautiously constructed.

Stage IA cervical cancer

Although no official definition for microinvasion has been agreed upon, 2 sets of criteria have emerged. Initially, the concept of microinvasion was neglected by the FIGO staging system for squamous cell carcinoma of the cervix. In response, the Society of Gynecologic Oncologists (SGO) divided stage IA lesions at the cut off of 3 mm depth of invasion and 7 mm of horizontal spread, creating stages IA1 and IA2. FIGO has since adopted the division in IA staging (Table 1). They continue to differ, however, in that the SGO system excludes from stage IA1 anyone with evidence of invasion of the lymphovascular spaces.

Regardless of the definition, further controversy persists regarding the management of patients with IA1 squamous cell carcinoma (SCCA) of the cervix. For the nonpregnant patient with no desire for future child-bearing, extrafascial hysterectomy is the treatment of choice. Lymph node dissection is felt to be unnecessary, with less than 1% of such patients having positive lymphatic spread. In the gestational patient who desires immediate treatment of her IA1 lesion, with the intent on ending the pregnancy, her choices include termination followed by hysterectomy or removal of the uterus with the fetus in utero.

With up to 40% of patients with cervical cancer being diagnosed under the age of 45 years, fertility-sparing alternatives to hysterectomy have been explored and debated. Recently, Diakomanolis et al followed up 90 patients with microinvasive disease, treated with CO2 laser conization, and found no recurrence of high-grade or invasive lesions at a mean follow-up of 54 months. Even when the margins were positive, Itsukaichi et al demonstrated no recurrences after a median follow-up of 4 years. In 1 of the largest studies, Okamoto et al performed laser conization on 198 patients with microinvasive disease and again described no recurrences.

Excisional procedures are reserved for those patients in whom occult malignancy cannot be ruled out. However, in the pregnant patient, delaying the treatment of an occult lesion may have no impact on survival. Given that these procedures can be associated with significant blood loss and that they may be associated, coincident or otherwise, with a se-
rious pregnancy complication, it is not recommended that excisional procedures be performed during a desired pregnancy except in rare circumstances.

Conservative treatment regimens for patients with stage IA1 cervical cancer should be applied only to patients with squamous cell pathology. Tumors of the cervix demonstrating invasive adenocarcinoma are more frequently multifocal, with “skip” lesions inviting misleading interpretations of margin status. As such, some would suggest that patients with adenocarcinoma should not undergo fertility-sparing surgery and should be treated as though they are a stage IB or greater.

Similarly, patients who are diagnosed with stage IA2 cervical cancer are, in general, not eligible for the same fertility-sparing, excisional procedures as those with stage IA1 disease and, outside pregnancy, should be treated with radical hysterectomy. Such patients have similar options as those with stage IB1 lesions as detailed below, with regard to a purposeful delay in treatment or a termination of the pregnancy followed by immediate treatment. However, patients with stage IA2 lesions may be better candidates for the fertility-sparing radical trachelectomy than patients with visible IB1 lesions. The first case of a successful vaginal radical trachelectomy during pregnancy was recently reported by van Niewenhol et al.

**Stage IB1**

Some would argue that prior to reaching 20 weeks’ gestation, pregnant women with invasive cervical cancer should be treated without fetal-sparing intentions. This approach, however, does not take into account the complex social, religious, and emotional factors that can influence such a decision. Nevertheless, at these progressive stages of disease, urgent treatment is indicated to arrest further cancer progression and to prevent maternal mortality.

Treatment options for patients with stage IB1 or IIA disease with lesions less than 4 cm include external beam irradiation and brachytherapy generally with concomitant systemic cisplatin or radical hysterectomy with bilateral pelvic lymphadenectomy followed by tailored postoperative therapy, depending on the pathological findings. The survival rates for these patients following either surgery or irradiation therapy have been shown to be 74-93%. In younger women, such as those who might be coincidentally pregnant, surgical management may be preferred to irradiation because the ovaries can be retained to preserve both hormonal and surrogate-assisted reproductive function.

Should surgery be chosen, certain risk factors may necessitate the addition of adjuvant therapy. Patients with lymph nodes positive for metastatic disease may benefit from adjuvant chemoradiation. Parametrial invasion, lymphovascular space invasion, and deep stromal invasion have been shown to be independent factors in predicting recurrence and death. These patients may also benefit from adjuvant therapy.

Radical hysterectomy can be performed either following an elective termination or while the fetus remains in utero (Figure 3). Sivanesaratnam et al reported on 14 type III radical hysterectomies performed during pregnancy. Although they described a mean blood loss of 1.4 L, they cited no major complications and no increase in the incidence of nodal metastases. Those patients presenting in pregnancy had a 5-year survival of 93%. Similarly, Monk and Montz reported on 13 patients undergoing radical hysterectomy with fetus in situ and 8 patients undergoing cesarean section followed up by radical hysterectomy. Although, for patients not undergoing a cesarean section, they reported a mean blood loss of less than 800 mL, they did have 1 vesicovaginal fistula, 1 pulmonary embolism, and 2 wound seromas. Disease-free survival was noted to be 95% at a mean follow-up of 40 months. Other authors have reported similar results with the use of either radical hysterectomy with fetus in situ or following cesarean section. Figure 4 illustrates 1 proposed algorithm for the treatment of such patients.

**Stage IB2 to stage IVA**

Although some patients with stage IB2 and IIA disease may be surgical candidates, such treatment courses have found an increasingly limited role in recent years. Pelvic radiation, including external beam and brachytherapy, has been the standard of care for the treatment of advanced cervical cancer for
many years. However, a number of well-designed studies have recently demonstrated an improved disease-free and overall survival for patients who also receive radiosensitizing chemotherapy, and the practice of chemosensitization has become the standard of care.

Rose et al.\(^4\) in a 526-patient study, showed that patients with stage IIB, III, or IVA cervical cancer had an improved overall and disease-free survival after receiving cisplatin with or without 5-fluorouracil, when compared with patients who did not receive platinum-based chemosensitization. Similarly, Morris et al.\(^4\) reported a significantly improved overall and disease-free survival as well as fewer distant and locoregional recurrences in patients receiving platinum-based chemosensitization in concurrence with radiotherapy. Cisplatin is most frequently given at a dose of 40 mg/m\(^2\), weekly for a total of 6 weeks.\(^4\) Treatment is started when the radiation therapy is initiated. Several other regimens and treatment combinations have been investigated.\(^3,4\)

Although the use of chemoradiation in pregnancy has not been specifically studied, several investigators have reported on the use of radiation alone in pregnancy. Sood et al.\(^4\) reported a series of 26 women with cervical cancer who were treated with radiation during or shortly after pregnancy. Patients were treated with both external beam and intracavitary radiation in all 3 trimesters. Of 17 patients diagnosed in the third trimester, 2 patients with stage IA2 disease had intentional delays of treatment for 3 weeks, followed by amniocentesis-confirmed maturity and delivery. Of the remaining 15 patients, 2 infants died because of complications related to prematurity at 27 and 29 weeks. The remaining infants did well and radiation therapy was initiated either with the fetus in situ or within 2 weeks postpartum. All 6 patients diagnosed in the second trimester underwent hysterotomy, with no infant survival. Overall, survival among this peripartum cohort did not differ significantly from a group of matched controls.

The use of radiation in early pregnancy has been associated with rapid spontaneous abortion. Sood et al.\(^4\) reported on 3 patients in whom radiation therapy was initiated with fetus in situ or within 2 weeks postpartum. All 6 patients diagnosed in the second trimester underwent hysterotomy, with no infant survival. Overall, survival among this peripartum cohort did not differ significantly from a group of matched controls.

More recently authors have advocated the use of misoprostol to promote expulsion of the fetus that does not spontaneously abort following radiotherapy.\(^5\) Certainly the irradiated pregnancy that has not spontaneously aborted must be removed from the uterus, either medically or surgically, to prevent the onset of infection and disseminated intravascular coagulation.

Management of cervical cancer in the third trimester may depend on what gestational age reached at the time of diagnosis. Significant gains in fetal outcome can be achieved in the gestational weeks between 28 and 32. Delays of up to 4 weeks in this situation may not have a significant impact on the mother’s prognosis. However, with advances in the outcome of premature infants, it is not recommended that treatment be delayed beyond 32-34 weeks. Furthermore, some authors have suggested that delays between diagnosis and the initiation of radiation therapy should average no more than 2 weeks and should not exceed 4 weeks.\(^5,2\)

There are some data, discussed in the following text, that suggest that patients delivering vaginally have a poorer prognosis than those who are delivered by cesarean section. Many have extrapolated this to suggest that patients in the first and second trimester should be prevented from delivering spontaneously. These patients are instead advocated to undergo hysterotomy for removal of the
fetus. \(^{48,49}\) Given the absence of any data comparing spontaneous miscarriage and hysterotomy in the first and second trimester, others have not advocated the use of routine abdominal delivery for the previable fetus. \(^{55}\) Furthermore, delivery of the previable fetus often requires a vertical uterine incision, in the absence of a well-developed lower uterine segment. Blood loss can be extensive and pteryx has been reported. \(^{48}\) Figure 3 illustrates 1 possible algorithm for the treatment of these more advanced cases.

**Treatment delays**

It cannot be known, definitively, how a planned delay in the treatment of cervical cancer during pregnancy will affect the survival of either the mother or the infant. Certainly, for the severely premature infant, even a brief increase in the length of the gestation can have a profound effect on infant survival. Duggan et al\(^{56}\) reported on 8 patients with stage IA or IB cervical cancer who elected to delay treatment to optimize fetal outcome. They reported a diagnosis-to-treatment interval that ranged between 53 and 212 days. None of the 8 patients had recurred by a median follow-up of 23 months. Sorosky et al\(^{52}\) also reported on 8 patients with stage I disease diagnosed during pregnancy. Diagnosis-to-treatment interval ranged between 21 and 282 days, and all patients were alive and disease free, with follow-up ranging between 13 and 68 months. Other researchers have also reported delays of up to 32 weeks in patients with early-stage lesions without an obvious compromise in their overall survival (Table 2).

For patients who choose to delay treatment, close tumor surveillance is warranted. Regular pelvic examinations, including visual inspection and colposcopic evaluation, may assist in the detection of tumor progression during the period of planned delay. Some authors have advocated the use of serial MRI in the assessment of tumor size and spread. \(^{56}\)

**Neoadjuvant chemotherapy**

In patients with more advanced disease, no planned delay in treatment is recommended. Reports of patients insisting on delays have been published with less than optimal outcomes. \(^{14}\) One option for pregnant patients who strongly desire a delay in the treatment of an advanced cervical cancer is the use of neoadjuvant chemotherapy. We reported on 2 patients with locally advanced cervical cancer diagnosed and treated in the second trimester. \(^{57}\) Both patients had significant reductions in tumor volume, allowing them to undergo radical hysterectomy following completion of the pregnancy. One patient had a recurrence 5 months after surgery, and the other was 2 years from surgery with no evidence of disease. No abnormalities have been demonstrated in either baby.

Marana et al\(^{58}\) also reported on the administration of cisplatin (50 mg/m\(^2\), days 2 and 3) and bleomycin (30 mg, day 1) in a patient diagnosed with cervical

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**Table 2: Delay of definitive treatment of cervical cancer in pregnancy**

| Study                  | Year | Stage    | Number of patients | Treatment delay (wks) | Outcome (mean or median follow-up) |
|------------------------|------|----------|--------------------|-----------------------|-----------------------------------|
| Prem et al\(^{37}\)    | 1966 | I        | 5                  | 11-17                 | No adverse effects                |
| Thompson et al\(^{71}\)| 1975 | IA       | 7                  | 5-28                  | No adverse effects                |
| Lee et al\(^{11}\)     | 1981 | IA       | 1                  |                       |                                   |
|                        |      | IB       | 2                  |                       |                                   |
|                        |      | II       | 5                  |                       |                                   |
| Nisker and Shubat\(^{72}\) | 1983 | IB       | 1                  | 24                    | Recurrence and death               |
| Greer et al\(^{73}\)   | 1989 | IB       | 5                  | 6-17                  | No adverse effects                |
| Monk and Montz\(^{35}\)  | 1992 | I        | 8                  | 10-16                 | All alive (40 months)             |
| Duggan et al\(^{56}\)  | 1993 | IA-IB    | 8                  | 8-30                  | All alive (23 months)             |
| Sivanesaratnam et al\(^{37}\) | 1993 | I        | 3?                 | 2-14                  | ?                                 |
| Allen et al\(^{44}\)   | 1995 | IBI      | 2                  | 18-19                 | Both alive (66 months)            |
| Sorosky et al\(^{52}\)  | 1995 | IB       | 7                  | 3-40                  | All alive (37 months)             |
| Sood et al\(^{13}\)    | 1996 | IA1-IB1  | 11                 | 3-32                  | All alive (118 months)            |
| van Vliet et al\(^{59}\) | 1998 | IB-IIA   | 6                  | 2-10                  | One recurrence and death (82 months) |
| Tewari et al\(^{67}\)  | 1998 | IB-IIA   | 2                  | 11-29                 | One recurrence (14 months)        |
| Takushi et al\(^{69}\) | 2002 | IA1      | 8                  | 9-25                  | All alive (120 months)            |
|                        |      | IA2-IIA  | 5                  | 6-13                  | All alive (103 months)            |
|                        |      | II-IIIB  | 5                  | 1-2                   | One death 4 months after diagnosis |

Hunter. Cervical neoplasia in pregnancy. Am J Obstet Gynecol 2008.
cancer at 14 weeks. The chemotherapy was administered at 17 weeks' and again at 20 weeks' gestation. The patient then refused any further treatment, either during or after the pregnancy. The baby is now 3 years old with no evidence of neurodevelopmental sequelae. Unfortunately, the patient died approximately 1 year after delivery. Several case reports have cited the use of a platinum in combination with paclitaxel in the second and third trimester, with no fetal toxicity or long-term sequelae reported.59,60

Data regarding the use of chemotherapy in pregnancy have been largely limited to case studies, such as those mentioned in previous text. Peres et al61 compared 14 pregnancies treated with chemotherapy with 15 pregnancies in which chemotherapy was not used. They reported an increased risk of prematurity and fetal death, although no fetal deformities were noted. Chemotherapeutic agents more commonly associated with fetal malformations include methotrexate, 5-fluorouracil, cyclophosphamide, and chlorambucil.62

Mode of delivery
In assessing the optimal mode of delivery for patients with cervical cancer, Sood et al63 evaluated 56 women diagnosed during pregnancy, of whom 24 delivered viable infants. Although such a report lacks the proper design and the power to draw definitive conclusions, the authors did find a 14% recurrence rate among the 7 patients who were delivered by cesarean section and a 56% recurrence among those patients who were delivered vaginally. Other authors have confirmed such an association between cesarean delivery and improved outcome,64,65 whereas still others have found no difference.11,66 It should be noted that during cesarean section, a high vertical uterine incision should be performed, with the intention of leaving the lower uterine segment intact for optimal pathologic review.

In a separate consideration, Cliby et al67 reported on 4 patients treated for recurrence of their cervical cancer at an episiotomy site. The prognosis with such a recurrence has not been favorable, with 3 deaths among the 4 patients reported by Cliby et al. Other authors have reported similar recurrences.68 Although the evidence is not strong, it certainly suggests that it may be more appropriate to deliver these infants by cesarean section. Naturally, patients in whom radical hysterectomy is the treatment of choice should be delivered by cesarean section concomitant with their cancer surgery.

Prognosis
Given the limited number of systematic case series in the literature comparing the treatment of cervical cancer in both pregnant and nonpregnant women, it is difficult to draw definitive conclusions about how the overall prognosis differs. It does, however, appear that these women have a survival profile that closely approximates the nonpregnant population. Takushi et al69 reported only 1 recurrence and death among 28 patients treated either immediately or with treatment delays of up to 25 weeks. In contrast, Sood et al46 reported a 5-year survival of only 62% for their series of 26 patients diagnosed in pregnancy. Eighteen of the 26 patients reported in the latter were of stage IB2 or greater, compared with only 9 of 28 in the former study. Such a comparison further illustrates that, as in the nonpregnant population, FIGO staging is the most important factor in determining the overall prognosis.

Conclusion
Pregnancy represents 1 of the few circumstances during which young, healthy women, who are not otherwise under the care of a doctor, seek regular and consistent medical attention. It therefore poses an opportunity for cervical cancer screening that cannot be missed. Consequently, the coincident diagnosis of pregnancy and cervical cancer is not uncommon, and it poses unique medical, emotional, and ethical dilemmas. Just as no 2 patients have the same reproductive history, social situation, and position on the controversial topic of pregnancy termination, no specific treatment algorithm should be considered as inflexible.

This is particularly true in light of the fact that such algorithms are not based on randomized, controlled trials but, instead, are extrapolations of well-designed studies in the nonpregnant population, coupled with a body of case series in the pregnant population. Overall, it is the primary goal of the physician treating cervical cancer in pregnancy to balance the health and safety of both the mother and the fetus, with a close adherence to nonpregnant, evidence-based approaches.73

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