Cervical cancer in pregnancy

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INTRODUCTION

One to 3 percent of women diagnosed with cervical cancer are pregnant or postpartum at the time of diagnosis [1,2]. About one-half of these cases are diagnosed prenatally, and the other half are diagnosed in the 12 months after delivery [3]. Cervical cancer is one of the most common malignancies in pregnancy, with an estimated incidence of 0.8 to 1.5 cases per 10,000 births [3-6].

Most patients are diagnosed at an early stage of disease [7,8]. This is probably a result of routine prenatal screening, but it is also possible that advanced stage disease interferes with conception. Stage for stage, the course of disease and prognosis of cervical cancer in pregnant patients are similar to those of nonpregnant patients [8,9].

There are no data from large randomized trials upon which to base recommendations for the care of pregnant patients with cervical cancer. Therefore, management is based upon evidence from randomized trials in nonpregnant women, findings from observational studies of pregnant women, and the unique medical and ethical considerations underlying each individual case. Treatment should be individualized and based on the stage of cancer, the woman's desire to continue pregnancy, and the risks of modifying or delaying therapy during pregnancy.

CLINICAL PRESENTATION

Cervical cancer is often first suspected when a screening test for the disease is abnormal [6]. While they have not been studied directly, the performance characteristics of the Papanicolaou (Pap) test do not appear to differ significantly between pregnant and nonpregnant women [10]. Overall, the rate of significant cytological abnormalities among obstetrical patients has been reported to be 5 to 8 percent and is similar to that of the nonpregnant population [1,7].

Symptoms and signs of cervical carcinoma in pregnancy are dependent upon the clinical stage and lesion size. In two series, all pregnant patients with stage IA and 50 percent of those with stage IB carcinoma were asymptomatic at the time of diagnosis and had their disease detected by routine cancer

screening (table 1) [6,11]. Patients with symptomatic stage IB disease presented with abnormal vaginal bleeding or discharge; patients with more advanced disease also presented with pelvic pain, sciatica-type leg pain, flank pain, chronic anemia, and shortness of breath. Since many of these symptoms are similar to those associated with a normal pregnancy, the diagnosis of cervical cancer may be delayed in pregnant women.

A gross cervical lesion may be observed or palpated at any gestational age. The ability to detect early neoplasia by physical examination may be limited by normal pregnancy-associated cervical changes such as ectropion, stromal edema, and ripening. In addition, normal decidual reaction of the cervix may resemble carcinoma.

DIAGNOSTIC EVALUATION

Women with clinical findings — Cervical cytology to exclude cervical cancer is part of the diagnostic evaluation of abnormal vaginal bleeding in pregnancy. Management of abnormal cytology is described below. (See 'Women with abnormal cervical cytology' below.)

A gross lesion suspicious for malignancy should be biopsied. Women with pathological confirmation of cervical cancer or preinvasive disease should be referred to a gynecologic oncologist for staging. Referral is also indicated if the suspicious cervical mass is biopsy-negative for invasive carcinoma but the biopsy results are nondiagnostic. (See 'Colposcopy' below.)

Women with abnormal cervical cytology — Management of women with an abnormal cervical cytology in pregnancy should follow the 2012 Bethesda consensus guidelines [12]:

- Women younger than age 20 have a high prevalence of human papillomavirus (HPV) infection and minimally abnormal cytology tests (atypical squamous cells of undetermined significance [ASC-US], low-grade squamous intraepithelial lesions [LSIL]). The spontaneous resolution rate of these abnormalities is 90 percent, and the risk of invasive cancer is very low [13]. Therefore, colposcopy during pregnancy can be omitted, but cytology should be repeated postpartum.

- ASC-US and LSIL in pregnant women over the age of 20 years may be managed as in the nonpregnant patient, with the exception that it is acceptable to defer colposcopy to at least six weeks postpartum. (See "Cervical cytology: Evaluation of atypical squamous cells (ASC-US and ASC-H)" and "Cervical cytology: Evaluation of low-grade squamous intraepithelial lesions (LSIL)".)

- Colposcopy is recommended for all adolescent and non-adolescent women with atypical squamous cells in which a high grade squamous intraepithelial lesion cannot be excluded (ASC-H), high-grade squamous intraepithelial lesions (HSIL), and atypical glandular cells (AGC).

Colposcopy — At colposcopy, lesions suspicious for cervical intraepithelial neoplasia (CIN) II/III or cancer should be biopsied. If colposcopy reveals no CIN II/III or suspicion for cancer, additional cytologic and colposcopic evaluation should be performed postpartum, but no sooner than six weeks after delivery.

Cervical biopsies can be performed during pregnancy without a significantly increased risk of excessive bleeding [14]. Bleeding, if encountered after biopsy, can be controlled with use of Monsel's solution or suturing. Endocervical curettage is not performed in pregnant women because of concern that it may disrupt the pregnancy, although there is no evidence proving an increased risk of pregnancy disruption [7].

If colposcopy in early pregnancy is unsatisfactory, repeating the procedure in 6 to 12 weeks may result in a satisfactory examination because the transformation zone may have "migrated" to the ectocervix, thus allowing a satisfactory examination by 20 weeks of gestation [14].

Colposcopic evaluation of the cervix in pregnancy can be challenging; it should be done by a colposcopist experienced in recognizing both pregnancy-related and cancer-related cervical changes [14,15]. As an example, the increased vascularity of the gestational cervix exaggerates the way immature metaplastic epithelium reacts to acetic acid, which may mimic a dysplastic lesion [16]. Conversely, neoplastic cervical lesions early in pregnancy may be mistaken for the normal eversion of the squamocolumnar junction or benign cervical decidualization. The reliability of colposcopy with directed biopsy is not related to the stage of pregnancy when performed by an experienced colposcopist familiar with the changes of the cervix that occur in pregnant women. The reliability of colposcopy and biopsy in pregnancy is illustrated by the following studies:

- In one series of 612 gravid patients with abnormal cytology, no invasive carcinoma was missed, and complications of biopsies were minimal, with only two patients experiencing preterm labor and delivery (both had undergone cone biopsies) [14].
- Similarly, another study found colposcopy to have concordance, overestimation, and underestimation of the final diagnosis in 72.6, 17.6, and 9.8 percent of cases, respectively [15]. The authors also noted that the reliability of colposcopy and directed biopsy was not related to the pregnant state.
- In one multi-institutional study that included over 1000 women who presented with an abnormal Papanicolaou (Pap) smear in pregnancy, colposcopy and subsequent biopsy were performed in 89 patients [17]. Of those with a colposcopic impression that was normal/CIN I (n = 27), the biopsy confirmed this in 22 (81 percent) but found CIN II/III in 5 (19 percent). Of those with a colposcopic impression of CIN II/III (n = 62), the biopsy confirmed these findings in only 34 patients (54.8 percent), with normal/CIN I findings in the 28 remaining cases (45.2 percent).

Repeat evaluation postpartum is essential, as persistent high-grade disease is common [17-19]. As an example, one study reported persistent HSIL postpartum in all 28 patients with antepartum HSIL, three of whom were diagnosed with microinvasive carcinoma [18]. Another study observed that HSIL regressed to normal in 53 percent, 31 percent had persistent high-grade disease, and 16 percent regressed to a lower grade lesion within six months postpartum, but about half the patients in this series were lost to follow-up [17]. (See "Cervical cytology: Evaluation of atypical squamous cells (ASC-US and ASC-H)" and "Cervical cytology: Evaluation of low-grade squamous intraepithelial lesions (LSIL)" and "Cervical cytology: Evaluation of high-grade squamous intraepithelial lesions (HSIL)" and "Cervical intraepithelial neoplasia: Management of low-grade and high-grade lesions".)

Indications for and performance of conization — Traditional indications for cervical conization in the nongravid population are not applicable during pregnancy. Diagnostic conization in nonpregnant patients is performed to exclude invasive cancer when a punch biopsy shows only microinvasive disease or adenocarcinoma in situ (stage IA or microscopic IB, no clinically visible lesion) because the maximum depth of invasion can only be determined by examination of the entire lesion. In contrast, diagnostic conization is only indicated during pregnancy if confirmation of invasive disease will alter the timing or mode of delivery; otherwise, conization is postponed until the postpartum period to avoid potentially disrupting the pregnancy [20,21]. (See "Invasive cervical cancer: Epidemiology, risk factors, clinical manifestations, and diagnosis", section on 'Diagnosis' and "Cervical adenocarcinoma in situ".)

If prepartum conization is performed, the optimal time appears to be the second trimester, preferably between 14 and 20 weeks of gestation. Cervical conization should not be performed within four weeks of the estimated date of delivery because labor may cause the fresh conization wound to hemorrhage or extend [22]. (See "Management of the pregnant patient undergoing nonobstetric surgery".)

Technically, pregnancy-related eversion of the squamocolumnar junction facilitates the conization procedure in pregnant women. Frequently, a limited wedge biopsy is all that is needed to produce an appropriate diagnostic specimen. Some experts suggest excising a "coin"-shaped specimen instead of a "cone"- shaped specimen to limit disruption of the endocervical canal, minimize morbidities associated with blood loss, and avoid disturbing the fetal membranes [23]. If a true conization is required, one option is to perform a cone cerclage whereby a cerclage is placed immediately after the conization [24]. (See "Cervical intraepithelial neoplasia: Procedures for cervical conization" and "Transvaginal cervical cerclage".)

Potential complications of conization during pregnancy include hemorrhage (5 to 15 percent), miscarriage, premature rupture of membranes, preterm labor/delivery, and infection [20,25]. Fetal death is uncommon. It has been reported weeks after the conization procedure and, in some cases, was attributed to chorioamnionitis [26]. The frequency of operative hemorrhage greater than 500 mL correlates with the trimester in which the procedure is performed: the risk is minimal in the first trimester, about 5 percent in the second, and about 10 percent in the third [21,27]. In the largest consecutive series of cone biopsies during pregnancy (n = 180), fetal loss possibly or probably related to the procedure occurred in eight (4.5 percent) pregnancies [27]. Three of the eight fetal losses occurred prior to 14 weeks of gestation and one to four weeks after conization. Thirteen women (7.2 percent) lost greater than 500 mL of blood, 11 of whom were in the third trimester.

DIAGNOSIS

The diagnosis of cervical cancer is based upon histological confirmation of the disease in a cervical biopsy specimen. (See "Invasive cervical cancer: Epidemiology, risk factors, clinical manifestations, and diagnosis", section on 'Histopathology'.)

STAGING

Accurate staging is critical for patient counseling and treatment planning. Cervical cancer staging is clinical and follows the guidelines set forth by the International Federation of Gynecology and Obstetrics (FIGO; (table 1)). (See "Invasive cervical cancer: Staging and evaluation of lymph nodes".)

Physical examination — Physical examination is a key element of the clinical staging process and includes assessment of the primary tumor, uterus, vagina, parametria, groin, right upper quadrant, and supraclavicular nodes. If examination in an ambulatory setting is suboptimal, we suggest performing the examination under anesthesia.

Imaging studies — In the nongravid population, radiologic studies that can be used for FIGO staging include chest and skeletal radiographs, intravenous pyelogram (IVP), and barium enema. Findings on computed tomographic (CT) studies, magnetic resonance imaging (MRI), positron emission tomography (PET), and lymphangiograms cannot be used for staging purposes, with the exception of the urogram portion. However, these studies can be helpful for treatment planning.

In pregnant women, we suggest the following approach that balances the need to obtain information for maternal management with the competing need to limit fetal exposure to ionizing radiation. (See "Diagnostic imaging in pregnant and nursing women".)

- A chest x-ray (with abdominal shielding) is warranted for evaluation of pulmonary metastatic disease in all patients with more than microscopic cervical cancer.
- For stage IA and microscopic/very small stage IB (<1 cm) cervical cancer in which extracervical disease is unlikely, routine radiographic imaging of the urinary tract may be omitted.
- For larger stage IB1, bulky stage IB2, or more advanced disease and/or higher-risk histology (adenocarcinoma, small cell carcinoma), the urinary tract should be imaged with ultrasonography or MRI to rule out stage IIIB disease.
- For larger stage IB1, bulky stage IB2, or more advanced disease and/or higher-risk histology (adenocarcinoma, small cell carcinoma), additional imaging of the abdomen and pelvis is extremely helpful for patient counseling and formulation of a management plan.

Ultrasonography and/or MRI can be used to evaluate liver and urinary tract involvement. MRI has the advantage of excellent tissue contrast and depicts pelvic anatomy in three planes; therefore, it can be used to calculate tumor volume and assess spread to adjacent organs and lymph nodes. For the assessment of tumor size in nonpregnant patients, the overall accuracy of MRI is 93 percent and the negative predictive value for parametrial invasion is above 95 percent [28]. For small nodal metastases, the accuracy of conventional MRI in nonpregnant patients is poor; however, once nodal diameter is greater than 1 cm in short axis, the sensitivity and specificity of MRI are 62 to 89 percent and 88 to 91 percent, respectively [28].

Lymphadenectomy — In selected patients who desire to continue their pregnancy but are at significant risk for lymph node metastases, staging lymphadenectomy during pregnancy via extraperitoneal or laparoscopic approach may provide the most definitive information on lymph node status [29-32]. This information is important, as patients diagnosed with high-risk (node-positive) disease should be

counseled about the importance of initiating immediate definitive therapy [33]. Case reports on patients with early-stage cervical cancer who underwent successful laparoscopic lymphadenectomy during pregnancy suggest the feasibility of this approach, although this may be dependent on the surgeon's preference and experience [30-32].

Endoscopy — Endoscopic staging procedures, such as cystoscopy or proctosigmoidoscopy, are rarely indicated, but if required, experts in this area have concluded that endoscopy during pregnancy is generally safe if performed by an experienced operator [34,35].

MANAGEMENT OF PREINVASIVE DISEASE

Treatment of preinvasive disease should be deferred to the postpartum period. Re-evaluation and definitive therapy for preinvasive disease should be completed six to eight weeks following delivery [36]. Even when the preinvasive disease is high-grade, the risk of progression to invasive carcinoma during pregnancy is exceedingly small (0 to 0.4 percent) [37-39]. In addition, regression may occur postpartum, thus obviating the need for excision [18,38]. It is unclear whether route of delivery (vaginal versus cesarean) affects the rate of regression [39]; therefore, route of delivery should be based on standard obstetrical indications. We do not advocate excision during pregnancy because it can be a morbid procedure in this scenario [18,39]. (See 'Indications for and performance of conization' above.)

MANAGEMENT OF INVASIVE DISEASE

A diagnosis of invasive cervical cancer in pregnancy poses major challenges to the patient, her family, and her care providers. A careful multidisciplinary team approach is required and should take into account the desires of the pregnant patient (and her family) regarding preservation of the pregnancy. A process to guide the management of women diagnosed with invasive cervical cancer in pregnancy is given in an algorithm (algorithm 1).

Immediate, definitive treatment, regardless of gestational age, is generally appropriate in the following settings [33]:

- Documented lymph node metastases
- Progression of disease during the pregnancy
- Patient choice to terminate the pregnancy

Pregnancy termination — After a diagnosis of cancer, some patients will choose termination of pregnancy, which is subject to local statutes. For a patient with early-stage disease, we generally recommend radical hysterectomy with the fetus in situ and with preservation of the ovaries whenever possible. (See "Management of early-stage cervical cancer".)

For patients with more advanced disease, definitive treatment should be administered as in the nonpregnant patient. (See "Management of locally advanced cervical cancer".)

Before chemoradiation, we advocate evacuating the uterus, especially if the fetus is more than 20 weeks of gestation, as this will avoid the possibility of nonlethal fetal exposure to potential teratogens. If termination is not performed before chemoradiation and treatment does not result in spontaneous abortion, medical or surgical uterine evacuation can be performed after chemoradiation, guided by the clinical scenario and subject to local statutes. (See "Overview of second-trimester pregnancy termination" and "Second-trimester pregnancy termination: Induction (medication) termination".)

Pregnancies not terminated — Given the complex ethical and medical issues present, management of cervical cancer in women who do not choose or are unable to terminate pregnancy requires individualized consideration of stage of disease, treatment options, patient preferences, and fetal viability. These cases require multidisciplinary collaboration with a gynecologic oncologist, maternal-fetal medicine specialist, and neonatologist, as well as clinical support for the associated psychosocial distress that accompanies this situation.

Data to help guide the management of these patients are limited [33], but radiation therapy (RT) is contraindicated as it can cause fetal demise or serious nonlethal fetal harm. Our approach is based on fetal gestational age and the International Federation of Gynecology and Obstetrics (FIGO) stage of cervical cancer at diagnosis (table 1).

Gestational age less than 22 to 25 weeks at diagnosis — We suggest that patients undergo lymphadenectomy provided it can be performed safely. Limited data indicate that lymphadenectomy can be performed in the first and most of the second trimester with no increased risk of complications [40].

No evidence of nodal involvement — If nodes are negative for cancer, the treatment approach is based on the extent of cervical disease:

Microinvasive disease (Stage IA1) — For patients with documented (or suspected) stage IA1 cervical cancer (table 1), we perform conization. Although only low-quality data are available, this strategy appears to be sufficient and relatively safe [41,42]. In a report of eight pregnant women with IA1 squamous cell carcinoma (negative margins and no lymphovascular space involvement [LVSI]) diagnosed by cervical conization and managed expectantly for 9 to 25 weeks, no disease progression was documented before definitive therapy [41].

It is important that patients are aware that cervical conization during pregnancy may be associated with significant morbidity and perinatal complications. These include risks of excessive bleeding ranging from 5 to 15 percent and a risk of spontaneous abortion, which is up to 15 percent with cold-knife conization [27,43]. The risk of complications increases with the gestational age at the time of the procedure and the volume of tissue removed. Because of these risks, some have advocated the use of a coin excision, hoping to cause less disruption to the endocervical canal [44].

While the management of stage IA1 adenocarcinoma of the cervix is controversial, a report in pregnant women [42] and a growing body of evidence in studies of nonpregnant women [45] suggest that stage by stage, cervical adenocarcinoma may be treated similarly to its squamous counterpart and has a comparable prognosis.

Stage IA2 to IB1 tumor <2 cm — For patients with stage IA2 and a subset of patients with stage IB1 tumors <2 cm (table 1), the reported risk of parametrial extension is less than 1 percent [46]. Therefore, conservative surgical options, including a simple trachelectomy or large conization, are appropriate. Radical trachelectomy should be avoided if pregnancy preservation is desired. In a 2014 review of the literature that included 19 cases, this procedure was associated with a 32 percent incidence of spontaneous abortion [33].

Stage IB1 (tumor 2 cm or larger) and higher — For patients with stage IB tumors ≥2 cm or higher (table 1), we offer neoadjuvant chemotherapy if they have no evidence of lymph node involvement on lymphadenectomy. Alternatively, neoadjuvant chemotherapy can be administered without prior staging lymphadenectomy, in which case, surgical staging should be performed six to eight weeks after delivery. (See "Management of locally advanced cervical cancer", section on 'Neoadjuvant chemotherapy'.)

In one review of 50 women treated with neoadjuvant chemotherapy, median gestational age at diagnosis was 19 weeks [33]. Chemotherapy was platinum-based and administered at three-week intervals until 33 weeks gestational age on average. The overall response rate was approximately 90 percent (62.5 percent complete response rate). With a median follow-up of two years, survival by stage was reported as (table 1):

- Stage IB1 – 94 percent
- Stage IB2 – 70 percent
- Stage >IB – 70 percent

If neoadjuvant chemotherapy is administered, treatment should continue up to 34 to 35 weeks of gestation with delivery planned three weeks later (ie, term). We would utilize the standard regimen administered to women with metastatic cervical cancer in the nonpregnant patient, which consists of cisplatin plus paclitaxel delivered every three weeks for up to six cycles [47]. However, it should be acknowledged that the literature regarding the use of chemotherapy in pregnancy is based on case reports and small series [48-50]. Still, these series have mostly reported a relatively favorable risk profile for fetal, neonatal, and maternal complications. We agree with the guidance from the Second International Consensus Meeting on Gynecologic Cancers in Pregnancy and suggest not administering gemcitabine, vinorelbine, topotecan, or biologic agents (including antiangiogenesis agents) in the pregnant patient because of the lack of safety data [33]. (See 'Systemic therapy in pregnancy' below and "Management of recurrent or metastatic cervical cancer", section on 'Metastatic disease'.)

Positive nodal involvement — Patients with evidence of nodal involvement, confirmed on lymphadenectomy or suspected based on imaging findings, have advanced cervical cancer. For women who wish to preserve their pregnancies, treatment options include neoadjuvant chemotherapy or early delivery. Given the complex ethical and medical issues present, management requires an individualized approach that considers advanced disease characteristics, patient preferences, fetal viability, and morbidity of prematurity. These cases require multidisciplinary collaboration with a gynecologic oncologist, maternal-fetal medicine specialist, and neonatologist, as well as clinical support for the associated psychosocial distress that accompanies this situation. These women should be counseled

about their poorer prognosis. The approach to these patients is similar to women with advanced disease in whom pregnancy preservation is not desired.

Gestational age 22 to 25 weeks or later — For women who are diagnosed with invasive cervical cancer at a later gestational age (22 weeks or later), lymphadenectomy becomes less of an option due to the increased risks associated with surgery and the size of the pregnant uterus. Therefore, decisions on treatment should be based on the clinical stage of disease at diagnosis.

Stage IA to IB1 tumor <2 cm — For women with a tumor <2 cm, we suggest delaying treatment until six to eight weeks after delivery. (See 'Considerations about delivery' below.)

Several lines of evidence support this approach [51-54]:

- In nonpregnant women, it is common to allow a six-week interval between diagnostic conization and definitive surgery if definitive surgery is not performed within 72 hours of the diagnostic cone biopsy. This delay has not been associated with adverse effects on outcome [53].
- A review of 98 pregnancies in which therapy for cervical cancer was deliberately delayed for 3 to 40 weeks to allow fetal maturation also provided reassuring data [51]. At last follow-up, 93 patients (96 percent) were alive with no evidence of disease. All 98 of the patients had stage I to II disease, and most had very early stage disease (stage IA and small volume IB1), for which there is only a small risk of clinically significant disease progression. An updated summary of these cases is presented in the table (table 2).
- A case-control study compared the outcomes of 45 women with stage I cervical cancer diagnosed during pregnancy or within six months postpartum with those of 44 nonpregnant, matched controls [52]. The mean gestational age of the 23 pregnant women was 22 weeks (range 8 to 39 weeks). In 10 of these women, primary treatment was delayed for up to eight weeks to improve neonatal outcome. The overall five-year survival rate was 80 percent among subjects and 82 percent among controls.

Should disease progression be observed, treatment may become necessary. The approach is similar to patients presenting at an earlier gestational age and with evidence of nodal involvement. (See 'Surveillance during pregnancy' below and 'Positive nodal involvement' above.)

Stage greater than IB1 (Tumor 2 cm or larger) — For women with a larger tumor ≥2 cm, there is a lack of data on treatment delay and outcomes. Some oncologists have suggested that treatment not be postponed for patients with tumors exceeding 4 cm, which also includes patients with positive lymph nodes (confirmed or clinically suspected) [55]. However, if the patient prefers not to deliver early, we would advocate for the administration of neoadjuvant chemotherapy until delivery rather than a delay of treatment. (See 'Systemic therapy in pregnancy' below.)

Surveillance during pregnancy — Women with a diagnosis of cervical cancer who proceed with their pregnancy require follow-up during the pregnancy to ensure that they do not experience disease progression. The surveillance strategy is dependent on the extent of disease:

- Women with stage IA1 disease are followed with clinical examinations and colposcopy each trimester throughout pregnancy.

- For women who elect to delay definitive therapy until after delivery and for those patients who are on neoadjuvant chemotherapy, we recommend proceeding with a pelvic examination every three to four weeks during pregnancy. In addition, repeat imaging using magnetic resonance imaging (MRI) without gadolinium should be performed to rule out disease progression. These women should be followed by a maternal-fetal medicine specialist in order to ensure close maternal surveillance and monitoring of fetal growth and well-being.

Patients who demonstrate evidence of disease progression should undergo definitive treatment as discussed above. (See 'Management of invasive disease' above.)

Considerations about delivery — The timing of delivery must be individualized based on the gestational age of the fetus, the stage of the cervical cancer, and whether the tumor shows evidence of disease progression during the pregnancy. A term delivery at ≥37 weeks and ideally at 39 weeks is optimal; however, if earlier delivery is indicated for medical or obstetrical reasons, steroids may be administered to reduce the morbidity of preterm birth. (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery" and "Short-term complications of the preterm infant".)

No randomized trials evaluating maternal outcome according to mode of delivery are available. Retrospective and case-controlled studies suggest that vaginal delivery through a cervix with microscopic cervical cancer generally does not alter maternal prognosis [1,56]. Therefore, women with stage IA1 and IA2 cervical cancer can proceed with a vaginal delivery, with cesarean delivery reserved for standard obstetrical indications. Episiotomy should be avoided when possible. At least 15 cases of tumor cell implantation in the episiotomy site have been reported after vaginal birth in women with cervical cancer [56]. Five of the 11 patients who had recurrence of cervical cancer in the episiotomy site died of their disease [7]. (See "Approach to episiotomy".)

For women with stage IB1 or greater cervical cancer, vaginal delivery should be avoided. The limited data suggest that maternal cancer outcomes are worse with vaginal rather than cesarean delivery [1,57]. Furthermore, patients with bulky or friable gross tumor and those with barrel-shaped cervical cancer are at risk for significant hemorrhage and obstruction of the birth canal during labor and attempted vaginal delivery [58]. Thus, it is prudent to schedule a cesarean delivery once fetal maturity is likely, ie, at least ≥37 weeks and ideally at 39 weeks.

Definitive treatment for cervical cancer — For women who opted to continue their pregnancy, the definitive treatment of cervical cancer can occur at the time of delivery or postpartum. Our approach is as follows:

- For women who wish to preserve future fertility:

  - No further treatment is warranted if they had stage IA1 disease, provided that they had no further evidence of disease during follow-up. If the conization margin was positive, delivery by

cesarean and repeat conization six to eight weeks postpartum to rule out invasive disease is indicated.

- We proceed with a radical trachelectomy (with lymphadenectomy if not already performed) if they had stage IA2 disease or a tumor up to 4 cm in size. This can be performed six to eight weeks after delivery.

- For women who do not wish to preserve fertility:
  - Those patients with stage IA1 disease without evidence of LVSI are candidates for an extrafascial hysterectomy. This may be done concomitantly with a cesarean delivery if this has been previously arranged. However, the convenience of performing cesarean delivery and hysterectomy in one setting needs to be weighed against the potential added morbidity of this combined procedure.
  - Patients with stage IA1 with LVSI, IA2, or IB1 tumors <2 cm should undergo definitive treatment with radical hysterectomy, which can be done at the time of cesarean delivery or as a second surgical procedure postpartum.
- Patients treated with neoadjuvant chemotherapy during pregnancy for locally advanced disease or node-positive disease should undergo a radical hysterectomy, which can be done at the time of cesarean delivery or as a second surgical procedure.

The definitive treatment for women diagnosed with more advanced disease during pregnancy who delayed treatment until after delivery mirrors that of the nonpregnant patient and is discussed separately. (See "Management of locally advanced cervical cancer" and "Management of early-stage cervical cancer", section on 'Surgical treatment'.)

WOMEN WITH METASTATIC DISEASE

Patients with evidence of disease outside of the cervix involving other organs (eg, liver or lungs) have stage IV cervical cancer. The prognosis associated with metastatic cervical cancer is poor, and pregnancy is expected to make the situation even more psychologically and emotionally difficult for the patient and her family. It is important that the psychosocial needs of women in this situation be actively addressed, even while a treatment plan is developed. For women with metastatic cervical cancer in pregnancy, the management is medical and aimed at disease control, not cure. Therefore, these women should be offered chemotherapy with agents in use for women with metastatic or recurrent cervical cancer who are not pregnant. The chemotherapy agents of choice (cisplatin and paclitaxel) can be initiated during pregnancy. (See 'Systemic therapy in pregnancy' below and "Management of recurrent or metastatic cervical cancer".)

SYSTEMIC THERAPY IN PREGNANCY

Our approach to chemotherapy for the pregnant patient with cervical cancer, when indicated, is summarized below:

- The regimen of choice is the combination of cisplatin plus paclitaxel administered every three weeks for a maximum of six cycles. There is some evidence that cisplatin is filtered by the placenta. In a study of 21 pregnant women with cervical cancer who received cisplatin during pregnancy, platinum concentrations in the amniotic fluid at delivery were only 11 to 42 percent of those in the maternal blood [59]. However, low albumin levels in pregnancy result in higher levels of free cisplatin in the mother and fetus and may increase the risk of toxicity, including ototoxicity [60]. Transient neutropenia in the newborn has also been reported after intrauterine exposure to cisplatin and is a known side effect of this drug.

- Ideally, there should be three weeks between completion of chemotherapy and delivery, so the bone marrow can recover and to allow the placenta to metabolize and eliminate cytotoxic drugs from the fetus. Additionally, since the potential for spontaneous labor increases towards the end of pregnancy, it is prudent to avoid administering chemotherapy in the late third trimester [61].

- To avoid additional toxicity, we do not utilize bevacizumab because of risk of fetal harm based on the drug's mechanism of action and findings from animal studies [62].

Data regarding the safety of chemotherapy in pregnancy are limited. The effects of chemotherapy on the fetus depend upon the gestational age, agent(s) used, and dose [63]. A 2013 systematic review of 48 human pregnancy exposures to platinum derivatives for treatment of cervical cancer at 17 to 33 weeks of gestation reported 67.4 percent of neonates were healthy at birth, and the problems in most of the remainder were associated with prematurity (eg, respiratory distress) [64].

OUTCOME

The majority of studies do not suggest a difference in the oncologic prognosis of women with invasive cervical cancer diagnosed during pregnancy compared with nonpregnant women with invasive cervical cancer when adjusted for stage; however, data are limited [8,9,54,65-68]. As an example, a retrospective study compared 40 women with pregnancy-associated cervical cancer with 89 nonpregnant women with cervical cancer [8]. Maternal survival was not significantly different in both groups after 30 years of follow-up. Another study evaluated 53 women with stage IB disease diagnosed in pregnancy [9]. Five-year survival was similar to that of nonpregnant controls and was not affected by the time of initiation of therapy during the pregnancy. A large, long-term series of pregnant women with invasive cervical cancer reported 5.5 percent developed a second primary, which is similar to the second primary rate in all women under 50 years of age [69].

The effect of cervical cancer on pregnancy outcome is less clear. Three small retrospective studies reported that the diagnosis of a cervical cancer did not adversely affect pregnancy outcome, assuming that the pregnancy was not terminated [8,65,68]. In two of these studies, mean gestational age at delivery and rates of preterm birth, intrauterine growth restriction, and stillbirth were similar for pregnant

women with and without cervical cancer [8,65]; in the third, the mean gestational age at delivery was 36.1 weeks, largely because of iatrogenic preterm birth [68].

In contrast, a large study that linked infant birth/death certificates, discharge records, and cancer registry files in California identified 434 cases of cervical cancer in pregnant and postpartum women over an eight-year period; 136 cases were diagnosed prenatally [66]. Compared with women without cancer, women diagnosed with cervical cancer during pregnancy or postpartum had higher rates of both spontaneous and iatrogenic prematurity, with correspondingly higher rates of low birth weight and very low birth weight infants. These relationships held even in patients diagnosed with cervical cancer up to 12 months following delivery.

Of note, only one case of cervical squamous cell carcinoma with placental metastases has been published [70].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Treatment of cervical cancer".)

SUMMARY AND RECOMMENDATIONS

- Cervical cancer is one of the most common malignancies in pregnancy, with an estimated incidence of 0.8 to 1.5 cases per 10,000 births. Most cases are identified as a result of cervical cancer screening programs. (See 'Introduction' above and 'Clinical presentation' above.)
- Colposcopic evaluation of the cervix in pregnancy with biopsies should be performed by colposcopists with experience in pregnancy-related changes in cervical appearance. Endocervical curettage should not be performed. (See 'Women with abnormal cervical cytology' above.)
- Diagnostic conization is only indicated during pregnancy if confirmation of invasive disease will alter the timing or mode of delivery; otherwise, conization is postponed until the postpartum period to avoid potentially disrupting the pregnancy. (See 'Indications for and performance of conization' above.)
- Staging examinations are modified in pregnant women to limit fetal exposure to ionizing radiation. (See 'Staging' above.)
- A multidisciplinary team approach is crucial to address the complex care issues confronting a pregnant patient with cervical cancer such as termination versus continuation of pregnancy, delay of definitive treatment, mode of therapy during pregnancy, or timing and route of delivery. (See 'Management of invasive disease' above.)
- For patients in whom preinvasive cervical cancer is diagnosed, definitive treatment should be deferred to the postpartum period. (See 'Management of preinvasive disease' above.)

- Immediate, definitive treatment with termination of pregnancy, regardless of gestational age, is generally indicated if there is evidence of pathologic lymph node involvement or documented progression of disease during the pregnancy. (See 'Management of invasive disease' above.)

- Our approach to the management of women with invasive cervical cancer takes into account the wishes of the patient and her family regarding preservation of the pregnancy, the gestational age of the fetus, and the clinical stage of disease in the mother:

  - For women who do not desire continuation of the pregnancy after the diagnosis of invasive cervical cancer, the management is similar to that of nonpregnant women. (See 'Pregnancy termination' above.)

  - For women who desire pregnancy preservation with a fetus at an early gestational age (see 'Gestational age less than 22 to 25 weeks at diagnosis' above):

    – For patients in whom microscopic invasive disease is identified (or suspected), we perform a diagnostic conization. No further treatment is warranted if they had stage IA1 disease, provided that they had no further evidence of disease during follow-up. If the conization margin was positive, delivery by cesarean and repeat conization six to eight weeks postpartum to rule out invasive disease is indicated. (See 'Gestational age less than 22 to 25 weeks at diagnosis' above.)

    – For patients with stage IA2 and a subset of patients with stage IB1 tumors <2 cm, we suggest surgical treatment with a simple trachelectomy or large conization (**Grade 2C**). We suggest not performing a radical trachelectomy (**Grade 2C**). (See 'Gestational age less than 22 to 25 weeks at diagnosis' above.)

    – For patients with a tumor ≥2 cm, we suggest neoadjuvant chemotherapy (**Grade 2C**). We suggest the combination of cisplatin plus paclitaxel administered every three weeks until delivery (**Grade 2C**).

  - For women who desire pregnancy preservation and whose fetus is at a later gestational age (see 'Gestational age 22 to 25 weeks or later' above):

    – We suggest treatment delay until after delivery, provided that their tumor is <2 cm in size (**Grade 2C**). (See 'Stage IA to IB1 tumor <2 cm' above.)

    – We suggest neoadjuvant chemotherapy if their tumor is ≥2 cm (**Grade 2C**). However, other oncologists prefer termination of pregnancy and initiation of definitive treatment for these patients because of the high risk of recurrence. (See 'Stage greater than IB1 (Tumor 2 cm or larger)' above.)

- Radiation therapy should not be administered to women with invasive cervical cancer who desire preservation of their pregnancy because it results in fetal loss or other harm. (See 'Pregnancies not terminated' above.)

- Patients who are diagnosed with cervical cancer and continue their pregnancy should be closely followed until delivery. Patients who demonstrate evidence of disease progression should undergo definitive treatment. (See 'Surveillance during pregnancy' above.)

- For women with stage IA cervical cancer, vaginal delivery is acceptable provided that they had negative margins at the time of their diagnostic conization. However, cesarean delivery should be performed for women with higher stages of disease. (See 'Considerations about delivery' above.)

- Women diagnosed with invasive cervical cancer during pregnancy should undergo definitive treatment of their disease following completion of the pregnancy. (See 'Definitive treatment for cervical cancer' above.)

  - No further treatment is warranted for stage IA1 disease if they desire to preserve fertility.

  - For women with stage IA2 disease or a tumor up to 4 cm in size and who desire to preserve their fertility, we proceed with a radical trachelectomy six to eight weeks after delivery. A lymphadenectomy should also be performed if not done previously.

  - For women who do not wish to preserve fertility:

    – We suggest an extrafascial hysterectomy for women with stage IA1 disease rather than a radical hysterectomy, provided there is no evidence of lymphovascular space invasion (LVSI) (**Grade 2C**).

    – For patients with stage IA1 disease with LVSI, IA2, or IB1 tumors <2 cm, we suggest a radical hysterectomy rather than chemoradiation (**Grade 2C**).

    – For patients treated with neoadjuvant chemotherapy during pregnancy for locally advanced disease or node-positive disease, we proceed with a radical hysterectomy, which can be done at the time of cesarean delivery or as a second surgical procedure.

- The definitive treatment for women diagnosed with more advanced disease during pregnancy who delayed treatment until after delivery mirrors that of the nonpregnant patient. (See "Management of locally advanced cervical cancer" and "Management of early-stage cervical cancer", section on 'Surgical treatment'.)

- When controlled for stage of cervical cancer, the course of disease and prognosis of cervical cancer in pregnant women are similar to those of nonpregnant women. (See 'Outcome' above.)

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Topic 4805 Version 35.0

GRAPHICS

Cervix uteri TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Cervical carcinoma confined to the uterus (extension to corpus should be disregarded)
T1a	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
T1b	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2. Includes all macroscopically visible lesions, even those with superficial invasion.
T1b1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	Tumor without parametrial invasion
T2a1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	Tumor with parametrial invasion
T3	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)
* The pelvic sidewall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N0(i+)	Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	Regional lymph node metastasis
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis

M1	Distant metastasis (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant lymph nodes; lung; liver; or bone)

Prognostic stage groups

When T is...	And M is...	Then the stage group is...
T1	M0	I
T1a	M0	IA
T1a1	M0	IA1
T1a2	M0	IA2
T1b	M0	IB
T1b1	M0	IB1
T1b2	M0	IB2
T2	M0	II
T2a	M0	IIA
T2a1	M0	IIA1
T2a2	M0	IIA2
T2b	M0	IIB
T3	M0	III
T3a	M0	IIIA
T3b	M0	IIIB
T4	M0	IVA
Any T	M1	IVB

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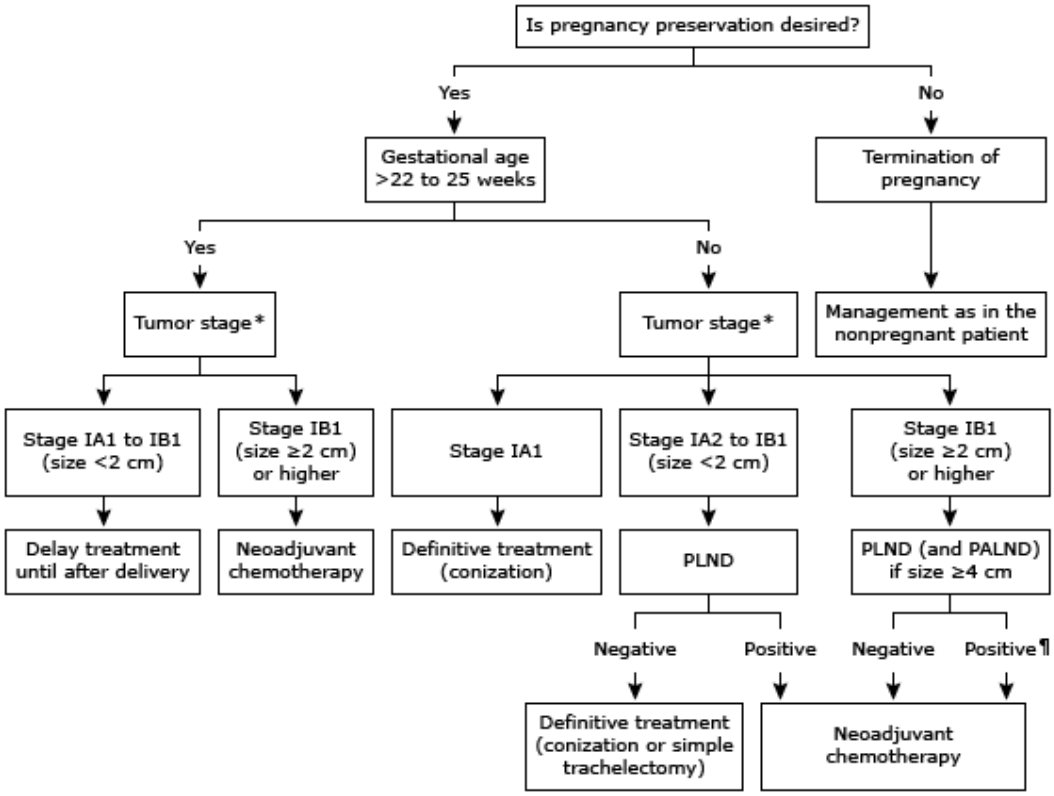
Graphic 113542 Version 5.0

Approach to invasive cervical cancer diagnosed in pregnancy



* Stage based on International Federation of Gynecologic Oncology (FIGO) system.
¶ Due to the risks associated with disease progression, patients should be offered termination of pregnancy and definitive treatment as an alternative option to neoadjuvant chemotherapy.

Graphic 95038 Version 3.0

Reported experience with deliberate delay of therapy for patients with invasive cervical cancer to allow for time for fetal maturity

Author, year	N	Stage	EGA at diagnosis	EGA at delivery	Delay in treatment (weeks)	Disease progression	Follow-up (month; mean/range)	Maternal outcome
Prem, 1966	4	I	≥28	35-36	6 (average)	-	All >60 months	All NED
Prem, 1966	5	I	20-34	34-38	11-17	-	34-64	All NED
Boutselis, 1972	5	IA1	8-24	3rd trimester	-	-	72-180	All NED
Dudan, 1973	2	IB	-	-	8-24	2	-	≥1 DOD
Thompson, 1975	7	IA	-	3rd trimester	5-28	-	50 (3-120)	All NED
Lee, 1981	9	IA-II	≥24	3rd trimester	<12	No	-	All NED
Nisker, 1983	1	IB	-	3rd trimester	24	1	-	DOD
Greer, 1989	5	IB	20-24	28-37	6-17	No	23 (13-35)	4 NED 1 DOD
Monk, 1992	4	IA2-IB	10-23	3rd trimester	10-23	No	40 (2-228)	All NED
Duggan, 1993	8	IA1-IB1	11-31	31-40	8-30	No	33 (3-124)	All NED
Sorosky, 1995	8	IB1	0-34*	33-38	3-40	No	33 (13-68)	All NED
Sorosky, 1996	4[¶]	IB1-IB2	18-32	35-36	4-15	-	51 (12-120)	3 NED 1 DOD
Sood, 1996	11	IA1-IB1	-	3rd trimester	3-32	-	118 (12-360)	All NED
Van Vliet, 1998	4	IB	23-32	32-35	3-10	-	67 (16-106)	All NED
Takushi, 2002	12	IA1-IB2	12-27	30 - term	6-25	No	70-156	All NED
Taen, 2006	1	IB1	14	31	17	No	17	NED
Germann, 2005	9	IB1	1st and 2nd trimester	3rd trimester	4-24 (16)	No	63 (2-168)	All NED
Lee, 2007	11	IA1-IIA	6-31	-	4-34	-	-	9 NED 2 DOD
Yahata, 2008	4	IA1[Δ]	16-23	37-41	>16-25	No	24-155	All NED
TOTAL	**98**	**IA1-II**	**0-34**	**3rd trimester**	**3-40**	**3**	**2-360**	**93 NED 4 DOD**

In some cases treatment delay was greater than the time difference of diagnosis to delivery as post-delivery irradiation may not have started for several weeks postpartum.

EGA: estimated gestational age; NED: no evidence of disease; DOD: dead of disease.
* One patient was diagnosed in the cycle prior to conception and followed through pregnancy.
¶ Excluded 3 cases that were doubly reported in Sorosky's 1995 and 1996 series.
Δ All adenocarcinoma.

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Contributor Disclosures

Amer Karam, MD Speaker's Bureau: Clovis Oncology [Gynecologic malignancies (Rucaparib)]. **Barbara Goff, MD** Employment (Spouse): Lilly [General oncology (Gemcitabine, pemetrexed)] - No relevant conflict on topics. **Vincenzo Berghella, MD** Nothing to disclose **Don S Dizon, MD, FACP** Grant/Research/Clinical Trial Support: Bristol-Myers Squibb [Ovarian cancer, cervical cancer (Nivolumab, ipilimumab)]; Kazia [Ovarian cancer (Cantrixil)]. Consultant/Advisory Boards: AstraZeneca [Ovarian cancer (Olaparib, durvalumab)]; Clovis Oncology [Ovarian cancer (Rucaparib)]; Regeneron Pharmaceuticals [Squamous cell carcinoma (Cemiplimab)]. **Sadhna R Vora, MD** Nothing to disclose **Vanessa A Barss, MD, FACOG** Nothing to disclose

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