

Cervical Cancer in Pregnancy

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ABSTRACT

Cervical cancer is one of the most frequent malignancies diagnosed during pregnancy. Cervical cancer in pregnancy is not fundamentally different from the issue in non pregnant state. But of course, there are challenging points of the pregnant patient. This subject analyses diagnosis, prognosis, and management of cancer during pregnancy, not only the cancer's effect on the pregnancy, but also the pregnancy's effect on the cervical cancer. Because of the lack of randomized controlled trials on cervical cancer during pregnancy, there is not a unique approach in the management strategies. The presence of the fetus and childbearing of the patients makes the topic more complex. So that, a multidisciplinary approach is needed in these cases. Termination of pregnancy does not improve maternal outcomes. During pregnancy, cervical cancer stage mainly based on tumor size, local and nodal spread determines the type of the management. Chemotherapy seems to improve the opportunity of fetal preservation without increased rates of complications and seems to be the major topic of further investigations.

Keyword: Cervical Cancer; Pregnancy; Diagnosis; Treatment; Chemotherapy; Surgery; Radiotherapy

INTRODUCTION

However; it is one of the most frequent malignancies diagnosed during pregnancy, diagnosis of cervical cancer during pregnancy is extremely rare. Reported incidence of cervical cancer ranges between 0.02 to 0.1%. Pregnancies [1,2] and approximately % 3 of newly diagnosed cervical cancer occurs in pregnant women [3]. Data for cervical cancer during pregnancy is based on observational studies of pregnant women. Because of the retrospective manner of these studies and case series, both the incidence and management of disease is uncertain [4].

Managing cervical cancer during pregnancy is still a big challenge because of the presence of the fetus and childbearing of the patients. So that, a multidisciplinary approach is needed, in which a gynecological surgeon, medical oncologist, radiation oncologist, radiologist, pathologist, primatologists, neonatologist, and the patient herself is imperative.

Today; screening for cervical cancer is accepted as an essential part of prenatal care. All of the consensus guidelines recommend that all pregnant women should undergo a Pap test at the initial prenatal visit [5]. The estimated incidence of abnormal cervical cytological findings during pregnancy is approximately 1–5% of all pregnancies [6]. Thus, diagnosis of cervical cancer during pregnancy is generally made at the early stages. Neither pregnancy, nor cervical cancer seems to worsen the prognosis of each other.

Because of the inadequate knowledge and lack of randomized controlled trials on cervical cancer during pregnancy, there is not a unique approach in the management strategies. Thus, the management should be individualized according to the stage of cancer and the woman's desire to continue pregnancy and future fertility [7,8].

DIAGNOSIS

Presentation of cervical carcinoma in pregnancy is related to the clinical stage of the disease and lesion size. At early stages of the disease (stage 1A and some stage 1B); there are no signs and symptoms in most of the cases. Routine cancer screening is generally the way they are detected. Vaginal bleeding is the most common sign in symptomatic early stage disease [9]. With the evolving stages, pelvic pain, flank pain, chronic anemia can be prominent signs.

Related to normal findings of pregnancy such as ectropion and presence of decidual cells that can mimic atypical (Arias-Stella reaction), evaluation of cervical lesions and Pap test can be challenging [10].

Similar diagnostic procedures with non pregnant state are valid in pregnant patients with suspected cervical cancer. Colposcopy is the second step of diagnosis for patients with abnormal cervical screening test results, but end cervical curettage is contraindicated [11].

After confirmation of diagnosis by colposcopic biopsy, patients without invasive cancer can be followed up without any treatment till delivery and the management can be delayed to postpartum period [12].

Approximately, 2.7-9.7% of high grade lesions can progress to invasive cancer. For these cases of suspected progression, repeated colposcopic biopsies in each trimester are recommended [13]. Conisation or Large-Loop Excision Procedure (**LEEP**) should be done as early as possible, when there is a suspicion of micro invasive or invasive disease. Because with the evolving gestational age the complications of procedures such as bleeding, preterm labor and pregnancy loss, increase [14,15].

MANAGEMENT OF INVASIVE CANCER

The most important factors affecting the management of cervical cancer during pregnancy are gestational age, tumor size, stage of disease, nodal metastases and histological subtype. Squamous-cell, adenocarcinoma, and adenosquamous lesions are the frequent subtypes and have better prognosis than rare subtypes like small-cell carcinoma [16].

In traditional management approach, all of the patients with invasive cancer were undergone pregnancy termination and treated definitely. But in current approach, for early-stage disease with no nodal involvement pregnancy preserving should be offered to the patient. But if the patient chooses termination of pregnancy, if the disease progresses during pregnancy or if nodal involvement is present definitive treatment should be done immediately. So, determination of regional lymph-node spread is of great importance [17].

The definite method of evaluating lymph node metastase is histopathological assessment of lymph nodes. If it is performed by skilled surgeons laparoscopic lymphadenectomy seems appropriate up to 20 weeks gestational age [18]. In a study on laparoscopic lymphadenectomy researchers 32 cases, in which the average gestational week was 23 and there is a patient at 31 weeks gestational age.

They found no surgery associated morbidities and they had no conversion to laparotomy. The rate of positive pelvic metastases was also, similar to non-pregnant patients with disease of the same stage [19].

As a non-invasive method Magnetic Resonance Imaging (**MRI**) provides an opportunity for assessment of locoregional spread on lymph nodes. It is accepted as an essential tool for planning of the management and treatment of cervical cancer during pregnancy [20,21]. PET-CT is not recommended during pregnancy. Fetal liver's high uptake of radionuclide seems to be the most important limitation of this issue. Because of the high fetal uptake, safe doses of radionuclide cannot be estimated properly [22].

In approximately %70 of patients, the disease is confined to the uterus, in other words stage1 cervical cancer is present [23]. If there is not nodal involvement, at this stage close follow up of patients clinically and radio logically and delay the treatment after fetal maturity can be an appropriate approach [24].

In patients with micro invasive disease (stage1A1), if the patient accepts the risks of procedure such as bleeding, spontaneous abortion and preterm delivery cold knife conisation can be the choice of treatment. In these group patients with negative margins and no Lymphovascular Space Involvement (**LVS1**) no disease progression was documented [25].

In patients with stage 1A2 and stage1B1 patients with tumor size < 2 cm, a simple trachelectomy or large conization will be an appropriate option, because of the rare parametrial invasion [26].

Neo-adjuvant chemotherapy is the preferred treatment when the tumor size is bigger than 2 cm in stage1B1 patients without lymph node involvement [17]. Platin based chemotherapy including cisplatin and paclitaxel is the recommended regimen, with three weeks interval up to 34 or 35 weeks gestational age and up to 6 cycles. But, it should be kept in the mind that these chemotherapy regimens are based on just a few case series and still have have potential risks to both baby and the mother [27].

If there is evidence of lymph node metastase, the case is accepted as advanced cervical cancer and the treatment should be individualized after this stage of disease, in respect to disease characteristics, patient preferences, fetal viability, and morbidity of prematurity. Neo adjuvant chemotherapy and delivery as soon as possible should be considered.

After the 22nd gestational week, treatment of patients at Stage IA to IB1 tumor <2 cm, can be delayed safely until fetal maturity is carried out [28]. For women at stage IB1 with a larger tumor ≥ 2 cm and positive lymph nodes, neo adjuvant therapy is recommended if the patient does not accept the definitive therapy. Delay of the treatment is not recommended in this group of patients [8].

Follow up of the patients during pregnancy is critical also, because if the disease progresses all of the management approaches should be revised. The route of follow up differs stage by stage.

Patients with micro invasive disease should be revisited each trimester by colposcopy and careful pelvic examination.

The patients with stage 1A2 and 1B1, who are administered chemotherapy or delayed the treatment, should be evaluated with pelvic examination and MRI to rule out the progression of disease.

The route and timing of the delivery should be individualized as well. The preferred method of delivery is cesarean in most of the cases. Only patients with stage1A1 and 1A2 disease can be candidates for vaginal delivery. If vaginal delivery is the route of delivery, episiotomy should be avoided. Tumor cell implantation in the episiotomy site has been reported in some case series. At stage 1B1 disease and higher stages, vaginal delivery is not recommended. At these stages, worse maternal outcomes were reported with vaginal rather than cesarean delivery [29,30].

If a patient, at the stage of 1A1 with negative conisation margin, desires future fertility, only follows up of this patient with pelvic examination and colposcopy will be appropriate. But if the conisation margin is positive, at the sixth postpartum week conisation should be repeated.

Similarly, if a patient with stage IA2 disease or tumor up to 4 cm, desires future fertility, radical trachelectomy (with lymphadenectomy if not already performed) will be the appropriate management.

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.

Extracervical hysterectomy is the recommended treatment modality in a case with micro invasive disease without lenfovascularity involvement, if she does not desire fertility. At the latter stages of disease with no desire for future fertility radical hysterectomy should be the choice of treatment.

If the patient has metastatic disease chemotherapy is the recommended therapy not for cure, for supporting disease control.

Chemotherapy after the first trimester of pregnancy does not seem to increase the rates of complications such as congenital anomalies, preterm deliveries, or growth restriction and chemotherapy helps to increase the chances of fetal preservation. But still, pharmacokinetics and pharmacodynamics of chemotherapy during pregnancy is not well understood and the real effect of these drugs on the long term development of the fetus needs further assessment.

International Federation of Gynecology and Obstetrics Staging of Carcinoma of the Cervix [31].

Stage 0	Carcinoma in situ, intraepithelial carcinoma; Cases of Stage 0 should not be included in any therapeutic statistics of invasive carcinoma.
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
Stage IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5mm and no wider than 7 mm. (The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular; from which it originates. Vascular space involvement, either venous or lymphatic should not alter the staging.)
Stage IA1	Measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm.
Stage IA2	Measured invasion of stroma greater than 3 mm and no greater than 5 mm in depth and no wider 7 mm.
Stage IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA.
Stage IB1	Clinical lesions no greater than 4 cm in size.

Stage IB2	Clinical lesions greater than 4 cm in size.
Stage II	The carcinoma extends beyond the cervix, but has not extended on to the pelvic wall; the carcinoma involves the vagina but not far as the lower third.
Stage IIA	No obvious paramaterial involvement.
Stage IIB	Obvious paramaterial involvement. The carcinoma has extended on to the pelvic wall; on rectal examination there is no cancer-free space between the tumor and the pelvic wall; the tumor involves the lower third of the vagina; all cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to another cause.
Stage III	No extension onto the pelvic wall, but involvement of the lower third of the vagina.
Stage IIIA	Extension onto the pelvic wall or hydronephrosis or nonfunctioning kidney.
Stage IIIB	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
Stage IVA	Spread of the growth to adjacent organs.
Stage IVB	Spread to distant organs.

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