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Cervical Cancer Associated with Pregnancy: A Brief Review

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Abstract

Cervical cancer is one of the most common cancers diagnosed during pregnancy. Abnormal bleeding is the most common symptom followed by abnormal cervicovaginal cytologic tests in asymptomatic patients. Screening for cervical cancer is an important component of prenatal care. Many consensus guidelines recommend that all pregnant women undergo a Pap test at the time of their first prenatal checkup. Most of the patients with cervical cancer diagnosed during pregnancy (approximately 75%) have stage I tumors. Tumor size (stage) and nodal stage are important considerations for management of early stage carcinoma of cervix. Management is individualized based on tumor size and stage, patient age, trimester of pregnancy and desires of the patient (or couple) regarding the pregnancy. This article reviews the challenges and issues pertaining to cervical cancer in pregnancy.

Keywords: Cervix; Pregnancy; Cancer; Radiation.

Introduction

Worldwide, cervical cancer is the third-most common cancer in women, accounting for more than 500,000 new cases and approximately 275,000 deaths. Association of carcinoma *in situ* or invasive carcinoma of the uterine cervix and pregnancy is rare, but it poses a therapeutic dilemma to the oncologists. Incidence of cancer cervix with pregnancy is approximately 1 to 10 per 10,000 pregnancies [1]. The incidence of and mortality rates from invasive cervical cancer have steadily declined in developed countries over the past five decades, in part because of the implementation of screening programs that detect many cancers at a preinvasive stage. Unfortunately, cytologic screening programs have not been implemented effectively in developing countries.

Epidemiologic studies have long demonstrated that patterns of occurrence suggest that disease stems from a sexually transmitted agent. Nearly all cervical cancers contain HPV DNA. There is compelling evidence for a causal relationship between HPV and cervical carcinoma. Infection with HPV during pregnancy is more frequent compared with non pregnant controls [2,3]. Contributing factors may be related to down regulation of cell mediated immunity and active metaplasia of cervical epithelium during pregnancy.

Screening

Screening for cervical cancer is an important component of prenatal care, especially for patients who are not having regular gynaecological follow up. Many consensus guidelines [4,5] recommend that all pregnant women undergo a Pap test at the time of their first prenatal checkup. Analysis of The Pap test can be difficult during pregnancy (because of large ectropion, frequent inflammation, presence of confusing decidual cells that can be mistaken for atypia, also called an Arias-Stella reaction), but has the same accuracy as in nonpregnant women [6]. Approximately 1.3% to 2.2% of pregnant women will have abnormal cytology during pregnancy.

Diagnostic procedure should be same as for non pregnant women if abnormal cytology is detected. Colposcopy with biopsy should be performed, which has a sensitivity of 73% to 95%. During pregnancy endocervical curettage is contraindicated [7]. Regression of low grade lesions occur in 48-62%, remain unchanged in 29-38% of cases. Progression to more severe lesions is very rare. For high grade

lesions regression is low and progression is seen in about 2.7 to 9.7% cases. Pregnancy is continued and no further treatment is needed if there is no sign of invasive cancer. On follow up during trimesters colposcopy with biopsy should be performed. Conisation or loop excision should be performed if micro invasive or invasive disease is suspected during early pregnancy. With increased duration of pregnancy conisation can increase risk and morbidity because of bleeding, premature delivery or premature rupture of membranes.

Signs and Symptoms

Abnormal bleeding is the most common symptom. A large number of asymptomatic patients have an abnormal cervicovaginal cytologic test result or abnormal vaginal examination. Clinical manifestations in patients with advanced disease may include pelvic pain, flank pain, sciatica type leg pain, chronic anemia and shortness of breath. Any pregnant woman presenting with bleeding pervaginum or discharge PV should be evaluated with pelvic examination and pap smear examination.

Staging

Proper staging of the disease is important to tailor the treatment to optimize the oncologic outcome and to know the prognosis. Zemlickis and colleagues in their study found that pregnant women were more likely to present with early disease because of regular, preg-nancy-related obstetric examinations [9]. However, this was not found by Stensheim and colleagues who reported no differ-ences in extent of disease when comparing 80 preg-nant patients with 111 lactating patients and 5865 nonpregnant patients diagnosed with cervical can-cer [10]. The International Federation of Gynecology and Obstetrics (FIGO) staging system for diagnosis and evaluation of cervical cancer is based on clinical examination (inspection, palpation, colposcopy), histologic examination of directed biopsy or conization specimens and radiographic examination of the chest, KUB, Cystescopy and Proctosigmoidoscopy.

MRI can help determine tumour size in three dimensions, stromal invasion, amount of healthy stroma, vaginal and parametrial invasion, and also lymph node infiltration [11]. Kanal et al, have shown in their study that MRI is has no deleterious effects on the developing foetus in any trimester of the pregnancy [12]. Gadolinium can be used if necessary. No adverse effects to the neonate have been found after gadolinium exposure in all three trimesters [13]. However, gadolinium crosses the placenta and is excreted by the foetal kidney into amniotic fluid . MRI for staging during pregnancy has been described for locoregional extent of disease by Zanetta and colleagues in 6 patients [14] and also Balleyguier and col-leagues in 12 patients [15]. MRI features of cervical cancer in pregnant patients were comparable to the nonpregnant patient, and allowed for tailored treatment plan-ning Some prospective studies have shown that Ultrasound is an alternative to MRI during pregnancy [16,17]. X- rays studies expose the fetus to radiation and highest dosages are generated by Computed Tomography. Exposure of fetus to radiation leads to higher life time risk of developing cancers [18]. The risk of childhood cancer is highest after abdomino-pelvic imaging [19-21].

Management

In patients with invasive carcinoma, the lesion is usually clinically apparent. Multiple punch biopsies are necessary to confirm the diagnosis. of the patient Management is individualized based on tumor size and stage, patient age, and desires (or couple) regarding the pregnancy. Most of the patients with cervical cancer diagnosed during pregnancy (approximately 75%) have stage I tumors [22,23].

Conventional subtypes such as squamous-cell, adenocarcinoma, and adenosquamous carcinoma have same prognosis and therefore similar management as opposed to rare subtypes such as small-cell carcinoma, which has a poor prognosis. In such subtypes, pregnancy termination is mandatory and patients should be treated immediately to deliver optimum therapy. In the past women with tumors diagnosed early in pregnancy were often recommended to abort the fetus. Currently, the trend is to preserve the pregnancy, particularly in patients with early-stage disease and no nodal involvement. Determination of regional lymph-node spread must be done appropriately. MRI is the best imaging procedure for the assessment of locoregional spread. It can be done without a paramagnetic agent in cervical cancer [14].

The gold standard to determine lymph nodal status is histopathological assessment of lymph nodes. Studies have shown laparoscopic lymphadenectomy is feasible upto 20 weeks of pregnancy [24,25]. Thus, pelvic lymphadenectomy seems to be a valid diagnostic procedure during the first or second trimester for patients with early-stage cervical cancer. The rate of positive pelvic metastases is similar to that recorded in non-pregnant patients with disease of the same stage [24,26]. In the absence of nodal spread, two treatment approaches are feasible at this

stage. The most common approach is to carefully follow up patients clinically and radiologically (to rule out tumour progression) and to postpone treatment of the cervical tumour until fetal maturity. Therapy is administered after delivery.

The other option is conservative surgical treatment with a radical trachelectomy to preserve the uterus and the pregnancy. A radical trachelectomy is used in nonpregnant women with early-stage disease and cervical lesions measuring less than 2 cm without nodal involvement and who want to preserve their fertility. Trachelectomy consists of a laparoscopic pelvic lymphadenectomy followed by the removal of the cervix together with the surrounding parametria with preservation of the uterine corpus and the ovaries [27]. For early stage IA1 lesions conization alone is adequate treatment.

Stages IB1, tumour size >2 cm and higher stages. When conservative surgical treatment during pregnancy is not possible, neoadjuvant chemotherapy (NACT) is an option to achieve disease control until foetal maturation, followed by radical hysterectomy postpartum [28]. In patients where conservation is not possible, an abortion is done before initiation of treatment. The whole pelvis is irradiated with external beam radiation followed by brachytherapy in standard doses. If a radical hysterectomy is performed and positive pelvic lymph nodes are found, postoperative irradiation, including external beam with or without intracavitary brachytherapy should be performed.

If the patient refuses abortion, serial MRI scans at 2- to 3-month intervals to ensure no growth or spread to lymph nodes is recommended. In selected patients Neoadjuvant chemotherapy is feasible till maturation of fetus [29,30,31]. NACT can be used to down stage or stabilize while awaiting foetal maturation. . Cisplatin 50–100 mg/m2 every 3 weeks has been used most often during pregnancy [32, 33].

Locally advanced disease can be managed with either neoadjuvant chemotherapy or chemotherapy and radiotherapy. Treatment recommendations for non pregnant women with tumor size 4cm (stage IB2) or greater is concurrent chemoradiotherapy [34,35]. In pregnant patients, this approach means that the pregnancy must be ended before the initiation of therapy. NACT can be used to preserve the preserve the pregnancy till fetal maturation. After delivery Surgery or Chemotherapy with Radiotherapy can be instituted.

Jones et al evaluated the management of invasive cervical carcinoma in 161 pregnant patients. Approximately one-third of patients were diagnosed in each trimester. 86 were treated with surgery alone, 30 with radiation therapy alone, and 45 with a combination of the two modalities. The 5-year survival was 94.6%, 76.9%, and 68.9% for patients diagnosed in the first, second and third trimester respectively. The prognosis of patients with invasive carcinoma of the cervix associated with pregnancy was similar to that of nonpregnant patients [36].

Conclusion

Carcinoma cervix during pregnancy is relatively rare. Carcinoma cervix during pregnancy remains a therapeutic challenge for physician. There are no clear guidelines for management. Screening with pap smear test is recommended during initial pregnancy. Management is individualized based on tumor size and stage, patient age, and desires of the patient (or couple) regarding the pregnancy. Currently, the trend is to preserve the pregnancy, particularly in patients with early-stage disease and no nodal involvement. Termination of pregnancy and Surgery or Radiation therapy is an alternative for node positive disease. Management of locally disease is controversial and varies from case to case.

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