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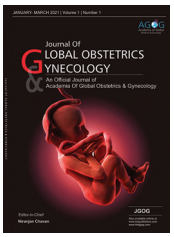

Cervical Cancer in Pregnancy

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ABSTRACT

Cervical cancer is one of the most common gynecological malignancies diagnosed during pregnancy. The incidence of cervical cancer during pregnancy is not high, and the symptoms are often confused with other conditions in pregnancy. The management in pregnancy depends on factors such as tumor size, histological type, lymph node status, patients' desire to continue pregnancy, and period of gestation. It is imperative to maintain balance between effective treatment and maternal and fetal health which requires a multidisciplinary management approach. Chemotherapy is a safe option starting from second trimester to prevent disease progression when pregnancy continuation is desired.

Key words: Pregnancy, Cervical cancer, Chemotherapy, Staging

BACKGROUND

Cancer during pregnancy is an uncommon occurrence, with an estimated incidence of 1 in 1000 pregnancies corresponding to 0.07–0.1% of all malignant tumors.[1] Among the gynecological cancers, cervical cancer is the most common malignancy diagnosed during pregnancy, with an estimated incidence of 0.8–1.5 cases/10,000 births.[2,3] About 1–3% of women are diagnosed during pregnancy or in postpartum period. Approximately one-half of these cases are diagnosed prenatally, and rest are diagnosed in 12 months after delivery.[2]

Women with cervical cancer in pregnancy are usually diagnosed in early stage. This is probably due to the fact that advanced stage interferes with conception. The disease course, presentation, stage, and prognosis are similar to that in non-pregnant patients. However, the management plan needs to be individualized based on the disease stage, patients' preference and the risks associated with modification or delayed treatment during pregnancy.

CLINICAL PRESENTATION

Cervical cancer is often suspected when an abnormality is detected on cervical cytology which are reported in about 5–8% women in pregnancy similar to non-pregnant women.[1,4] Signs and symptoms during pregnancy depends on the size of the lesion and the stage of the disease. Early stage disease mostly has no obvious clinical symptoms during pregnancy. However, patients may present with abnormal bleeding, discharge, or abdominopelvic pain. The diagnosis is often delayed as most of these symptoms are common in a normal pregnant patient also. The pregnancy associated changes limits the ability of physical examination to detect early neoplasia. Although, gross lesions may be visualized or palpated at any gestational age.

Therefore, any women during pregnancy or postpartum period if presents with vaginal bleeding, one should keep in mind the possibility of cervical abnormality and if required a thorough gynecological examination and cervical screening should be conducted for an early diagnosis.

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DIAGNOSTIC EVALUATION

Screening

Cervical screening cytology is an essential component of the diagnostic evaluation to exclude cervical malignancy in case of abnormal vaginal bleeding presentation during pregnancy. However, cervical cytology can be difficult to interpret due to pregnancy related changes such as; ectropion, inflammation, stromal edema, and presence of Arias- Stella reaction with similar accuracy as in non-pregnant women.[5,6] Biopsy should be taken from visible lesions suspicious for malignancy to rule out cervical cancer or pre-invasive disease.

Women with abnormal cervical cytology should be managed similar to that in non-pregnant women. However, expedited

diagnostic excisional treatment should not be done during pregnancy without first performing colposcopy.

Colposcopy

Colposcopic evaluation should be performed by experienced colposcopists as due to pregnancy related changes it can be challenging. Lesions suspicious for CIN 2,3 or cancer should be biopsied[7] and if biopsy confirms findings of CIN 1, repeat cytologic and colposcopic evaluation should be performed 4 weeks after delivery. For CIN 2 and 3 without suspicion of invasive disease, colposcopic evaluation can be performed every 12–24 weeks during pregnancy, or can be deferred until 4 weeks postpartum.

Diagnostic Evaluation

During pregnancy conization procedure is indicated only if diagnosis of invasive cancer will alter the management, otherwise, should be performed in postpartum period to avoid disrupting the pregnancy. If indicated, it is preferably performed between 12 and 20 weeks of gestation and is sufficient enough if patient is diagnosed with stage 1A1 disease. Complications related to conization during pregnancy include hemorrhage, miscarriage, premature rupture of membranes, preterm labor/delivery, and infection.

Thus, for diagnosis often a wedge biopsy provide an adequate specimen. However, some suggest that rather than removing a cone, a "coin shaped" specimen will avoid disruption of the endocervical canal, thus minimizing the blood loss and preventing disruption of pregnancy.[8] The diagnosis of cervical cancer is confirmed by histopathological examination of cervical biopsy specimen.

STAGING

It is very important to stage the disease accurately for proper counseling and treatment planning of the patient. The staging is mainly clinical. In 2018, the International Federation of Gynaecology and Obstetrics expanded the list of tests and procedures that may be used in assigning stage to include imaging and pathologic findings where available.[9,10] In pregnant women for staging the disease, care must be taken while considering imaging modalities keeping in mind to balance between the information obtained for maternal management with competing need to limit fetal exposure. The preferred modalities of imaging in pregnancy are ultrasound and magnetic resonance imaging (MRI), which are associated with minimal or no increased risk. MRI without contrast can be used safely in all trimesters to calculate the tumor volume and the extent of spread to adjacent organs and lymph nodes, whenever required X-ray with adequate abdominal shielding can be used if necessary for proper staging and management of the patient.

MANAGEMENT

The diagnosis of cervical cancer during pregnancy is challenging not only for the woman but also for her family, and the treating clinician. Management of pregnant women with cervical cancer diagnosis requires a multidisciplinary team approach including obstetrician, gynecologists, pathologists, and pediatrician taking into account the patient and her families preference regarding preservation of the pregnancy.

Once cancer is diagnosed on biopsy, management mainly depends on the histological type, lymph node status, disease progression during pregnancy, period of gestation, and patients' desire for pregnancy continuation [Figure 1].

Pregnancy Continuation Desired

Women who desire to continue pregnancy or where pregnancy could not be terminated owing to advanced gestation the management needs to be individualized based on stage of disease, patients' preferences, available treatment options, and fetal viability.

Gestational age <22–25 Weeks at Diagnosis

Laparoscopic staging lymphadenectomy for lymph node assessment should be performed before conservative surgery. It can be performed in 1st and 2nd trimester up to 22–25 weeks of gestation with no increased risk of complications.

Lymph Node Involvement

If the nodes are negative for malignancy, further management depends on the extent of the disease.

Stage 1A1: Conization procedure appears to be sufficient enough for the management of this stage. In a study by Takushi *et al.* on eight pregnant women with Stage 1A1 cervical cancer diagnosed on conization with negative margins and no lymphovascular space invasion, no disease progression was found during pregnancy when managed expectantly before definitive treatment.[11]

Stage 1A2-1B1: The reported risk of parametrial extension is <1%. A conservative approach such a simple trachelectomy or delayed treatment till delivery can be considered. Radical trachelectomy should be avoided in pregnancy. Several cases in the literature have described radical trachelectomy during pregnancy with a 32% incidence of spontaneous abortion following this procedure.[12] Besides, being technically challenging is associated with significant blood loss and therefore should be avoided if pregnancy conserving approach is needed.

Stage IB2, 1B3: If there is no evidence of lymph node involvement, offers neoadjuvant chemotherapy (NACT). Alternatively, NACT can be considered without prior lymphadenectomy, with surgical staging being performed 6–8 weeks after delivery.

Women have advanced disease, when nodes are found positive on lymphadenectomy specimen or an involvement is suspected based on imaging findings, still, if women desire to continue their pregnancy, they should be counseled regarding the management options which includes NACT during pregnancy or early delivery after fetal lung maturity. Thus, management approach should be individualized based on disease characteristics, patients' desire, fetal viability, and morbidity associated with prematurity.

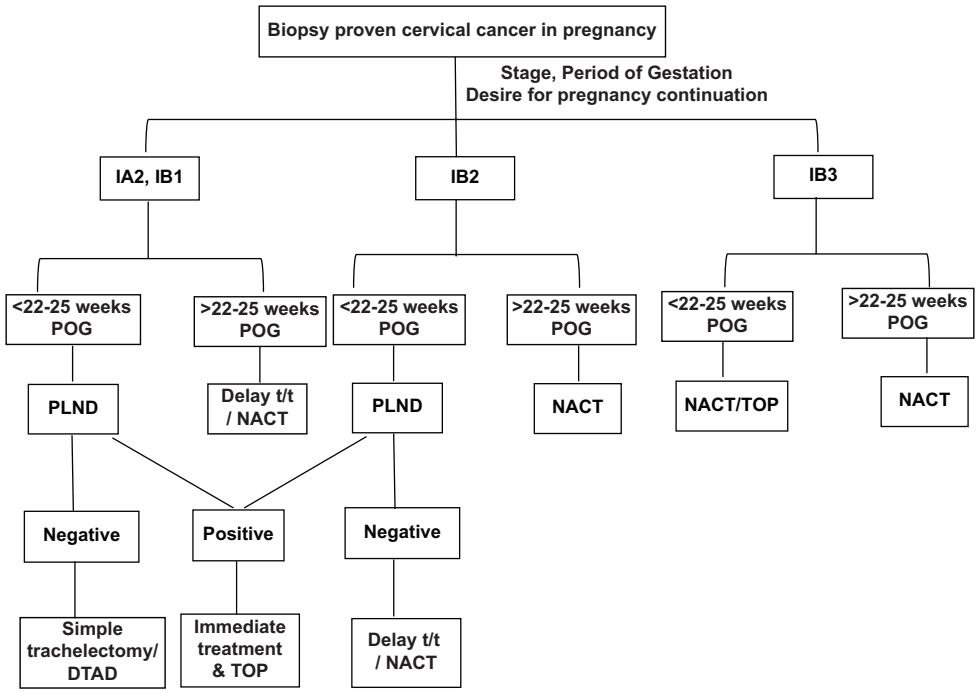

Figure 1: Flow chart of management of cervical cancer in pregnancy . *PLND: Pelvic lymphadenectomy, NACT: Neoadjuvant chemotherapy, t/t: Treatment, TOP: Termination of pregnancy

Gestational Age >22–25 Weeks at Diagnosis

When invasive cervical cancer is diagnosed at a later gestation, lymphadenectomy is associated with increased risk related to surgery *per se* and can be technically difficult, due to the enlarged uterus. Therefore, further plan of management depends on the disease stage at the time of diagnosis.

Stage 1A-1B1: In women with <2 cm tumor, treatment can be delayed for 6–8 weeks till fetal lung maturity is achieved.

Stage 1B2 and more: Treatment with NACT with or without lymphadenectomy is a feasible option, if pregnancy continuation is desired to prevent disease progression until delivery.

SYSTEMIC THERAPY IN PREGNANCY

Chemotherapy regimen is same as given to non-pregnant patients. It is relatively safe in 2nd trimester, though risk of preterm delivery and intrauterine growth restriction is higher. Most commonly used regime consists of cisplatin plus paclitaxel given every 3 weekly for a maximum of six cycles. A gap of at least 3 weeks should be there between last therapy and delivery, so that the fetal bone marrow can recover and also the placenta metabolizes and eliminates the cytotoxic drugs from the fetal circulation before delivery. Since, there is always a chance of going into the spontaneous labor in late third trimester, it is prudent to avoid chemotherapy beyond 34–35 weeks of gestation.[13]

The effect of chemotherapy on fetus depends on gestational age, agent used and drug dose transferred to the fetus. In a systematic review by Zagouri *et al.*,[14] on 48 pregnancies between 17 and 33 weeks exposed to platinum derivatives for the treatment of cervical cancer found that 67% of neonates at birth were healthy and in rest the problems were mostly associated with prematurity. In another retrospective study by Song *et al.*,[15] on 83 pregnant women who received cisplatin-based chemotherapy, they reported higher incidence of low birth babies. Both studies have shown that NACT during antenatal period may lead to low birth weight in babies.

Follow-up

Surveillance during pregnancy is required to ensure that the disease does not progress and the follow-up strategy depends on the extent of the disease:

Woman with Stage IA1

It should be followed with clinical examinations and colposcopy in each trimester.

Women with Stage 1B

Whether definitive treatment is delayed until after delivery or patient is started on NACT, follow-up should be done with pelvic examination every 3–4 weeks till delivery. These women should be followed up closely to ensure maternal and fetal well-being and growth. MRI without contrast helps to rule out disease progression and if during follow-up there is evidence of disease progression definitive treatment should be done irrespective of period of gestation.

TIMING OF DELIVERY

Delivery time is individualized based on the stage of disease, gestational age, and progression of the disease. Optimal timing

of delivery is 37 completed weeks; however, early delivery can be considered if indicated for medical or obstetrical reasons. In case, early delivery is anticipated steroids may be administered to achieve lung maturity to reduce the morbidity associated with preterm birth.

CHOICE OF DELIVERY

Women with Stage IA cervical cancer can undergo vaginal delivery, and cesarean section should be considered depending on the obstetrical indications. However, care should be taken to avoid episiotomy when possible as studies have shown recurrence at episiotomy site. There are no randomized trial data available on maternal outcome based on the mode of delivery, but few retrospective studies have shown that vaginal delivery in Stage 1A does not alter maternal prognosis.[16,17]

In Stage IB, vaginal delivery should be avoided. Data suggest that maternal outcomes following vaginal delivery were worse compared to cesarean delivery.[16,18] The risk of significant bleeding and obstruction during vaginal delivery increases with bulky or friable growths. Thus, a cesarean delivery should be planned once fetal maturity or at least ≥37 weeks in women with Stage 1B or more.

However, in locally advanced tumors lower section cesarean should be avoided as there is risk of cutting or extension into the tumor. Thus, a classical vertical incision can be made as it avoids injury to blood vessels supplying tumor and can reduce bleeding. Post-delivery placenta should be sent for histopathological examination to rule out any metastasis.

PSYCHOLOGICAL EFFECT OF CANCER

Cancer diagnosis during pregnancy can lead to both psychological and emotional trauma to the mother. Even there is dilemma for the clinician given that the treatment should be directed to save two lives: Maternal and fetal. Multidisciplinary team approach and counseling can reduce the distress of patient and her family. During pregnancy stress and anxiety can lead to adverse delivery outcomes and developmental and/or cognitive impairments in the neonate. A recent study by de Haan *et al.*[19] reported that educating the patient about necessary treatment steps and the implication of the treatment on the pregnancy outcome and long-term effects on physical and cognitive health of the offspring might alleviate the fear of harming the child, thus reducing guilt and anxiety among pregnant women.

Pregnant patients diagnosed with cancer deserve careful and continuous psychosocial assessment and support for their psychological wellbeing with follow-up in the postpartum period.

Most crucial point in cancer management is breaking the bad news to the woman and her family members. The patient should be counseled along with her family about the disease and should be provided with the information about the effect of cancer on ongoing pregnancy and on mother and fetus.

CONCLUSION

The clinical presentation of cervical cancer is atypical and easily confused with pregnancy changes and diagnosis is often delayed. But once diagnosed, a multidisciplinary team approach is needed to tackle this infrequent medical problem during pregnancy. It is important to promptly assess the ongoing pregnancy status, the gestational age, fetal growth, and viability and weighing the maternal benefits and risks. MRI (non-contrast) and ultrasound are the preferred imaging modalities during pregnancy in terms of fetal radiation exposure. Evidence of lymph node involvement on histopathology or disease progression during the pregnancy warrants pregnancy termination along with definitive treatment, irrespective of the gestational age. Surgical management can be safely performed during pregnancy and should not delay if indicated. Chemotherapy adds to the therapeutic armamentarium during pregnancy and helps in pregnancy continuation and prevention of prematurity.

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