In The Name of God

Management of preinvasive & invasive Cervical Cancer during pregnancy & postpartum

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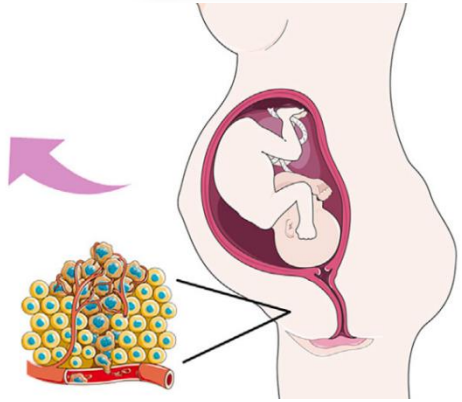


Introduction

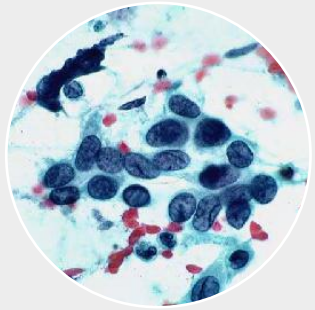
- ● Cervical cancer is one of the most common malignancies in pregnancy, with an estimated incidence of 0.8 to 1.5 cases per 10,000 births.

- ● One to 3 percent of women diagnosed with cervical cancer are pregnant or postpartum at the time of diagnosis.

- ● Approximately one-half of these cases are diagnosed prenatally, and the other half are diagnosed in the 12 months after delivery.

Clinical presentation

- ● Cervical cancer is often first suspected when a screening test for the disease is abnormal.



- ● Overall, the rate of significant cytological abnormalities is:

➢5 to 8 percent & similar to that of the nonpregnant population

➢Characteristics of the (pap) test do not appear to differ significantly.

Clinical presentation of cervical carcinoma in pregnancy

- Symptoms and signs are dependent upon the clinical stage and lesion size.
- Approximately 50% are asymptomatic at the time of diagnosis and detected by routine cancer screening.
- **Abnormal vaginal bleeding or discharge;**
- **Pelvic pain, Flank pain,**
- **Sciatica-type leg 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.

Diagnostic evaluation

- **Women with clinical findings;**
  - Abnormal vaginal bleeding = Cervical cytology to exclude cervical cancer
  - A gross lesion suspicious for malignancy should be biopsied.

- **Women with pathologic confirmation of cervical cancer or preinvasive disease;**
  - Should be referred to a gynecologic oncologist for staging.
  - Referral is also indicated if the cervical mass is suspicious for invasive carcinoma but the biopsy results are nondiagnostic.

Women with abnormal cervical cytology

- The management is the same as nonpregnant women, with the following exceptions:

- Expedited treatment with a diagnostic excisional procedure is unacceptable without having first performed colposcopy.

- For preinvasive disease excision during pregnancy is not advocated because it can be a morbid procedure.

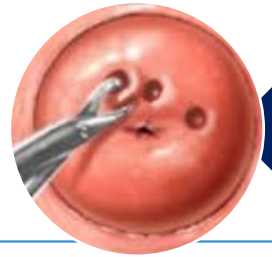
- Endocervical curettage and endometrial biopsy should not be performed as part of the colposcopic evaluation; however, the endocervical canal may be sampled gently with a cytobrush.

Management of preinvasive disease

- **● Re-evaluation and definitive therapy for preinvasive disease should be deferred to the postpartum period & completed six to eight weeks following delivery.**

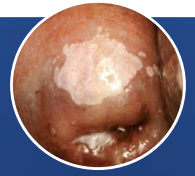
- **● Even when the preinvasive disease is high-grade, the risk of progression to invasive carcinoma during pregnancy is exceedingly small (0 to 0.4 percent).**
- In addition, regression may occur postpartum, thus obviating the need for excision.

- **● It is unclear whether route of delivery (vaginal versus cesarean) affects the rate of regression, therefore, route of delivery should be based on standard obstetrical indications.**



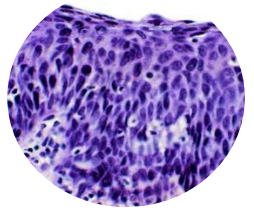
Cervical biopsies

- Cervical biopsies can be performed during pregnancy without a significantly increased risk of excessive bleeding.
- Bleeding, if encountered after biopsy, can be controlled with use of Monsel 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.



Colposcopy

- **If colposcopy is performed, lesions suspicious for cervical intraepithelial neoplasia (CIN) 2,3 or cancer should be biopsied.**



- If biopsy reveals CIN 1, additional cytologic and colposcopic evaluation should be performed postpartum, but no sooner than four weeks after delivery.
- **If biopsy reveals CIN 2,3, and invasive disease is not suspected, repeat colposcopic evaluation can be performed every 12 to 24 weeks during pregnancy, or deferred until four weeks postpartum.**

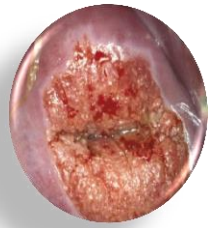
Evaluation of the transformation zone

- If colposcopy in early pregnancy is unsatisfactory;
- ● Repeat the procedure in 6 to 12 weeks

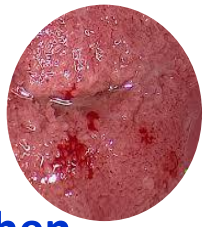
- ● It may result in a satisfactory examination because the transformation zone may have "migrated" to the ectocervix, thus allowing a satisfactory examination by 20 weeks of gestation.

Reliability of colposcopy and biopsies

- Normal physiologic and anatomic changes such as ectropion, stromal edema, , hyperemia, decidual reaction, and ripening may resemble carcinoma and the ability to detect early neoplasia by physical examination may be limited.
- Production of more metaplastic cells, and
- Reactive changes and
- Inflammation
- The increased vascularity of the gestational cervix exaggerates the way immature metaplastic epithelium reacts to acetic acid, which may mimic a dysplastic lesion.



- Conversely, neoplastic cervical lesions early in pregnancy may be mistaken for the normal eversion of the squamocolumnar junction or benign cervical decidualization.

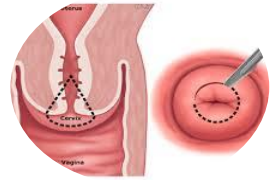


- The reliability of colposcopy with directed biopsy is not related to the stage of pregnancy when performed by an experienced colposcopist familiar with the changes of the cervix that occur in pregnant women.

Conization procedure in pregnant women

- ● 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.

- ● **If a true conization is required, one option is to perform a cone cerclage whereby a cerclage is placed immediately after the conization.**

Indications for and performance of conization during pregnancy

- **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 because the maximum depth of invasion can only be determined by examination of the entire lesion.
- **An excisional procedure does not always remove the entire transformation zone in pregnancy and it is less likely to be complete.**

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.

Patients planning future childbearing, and those in whom the concerns about potential adverse pregnancy outcomes (eg, preterm delivery) after an excisional procedure outweigh concerns about cancer, may reasonably choose colposcopy rather than expedited treatment.

Complications of conization during pregnancy

- **Potential complications include:**
- **Hemorrhage (5 to 15 percent), correlates with the trimester in which the procedure is performed**
- **Miscarriage,**
- **Premature rupture of membranes,**
- **Preterm labor/delivery, and infection.**
- **Fetal death is uncommon (chorioamnionitis)**

Management of preinvasive Cervical Cancer during pregnancy

Management of preinvasive Cervical Cancer during pregnancy

- Pregnant patients are managed similarly to nonpregnant patients with few exceptions:
- The physiologic changes to the cervix during pregnancy (eg, hyperemia) make colposcopy and identifying cancerous lesions more difficult.
- The morbidity associated with cervical conization during pregnancy is substantial .
- During pregnancy colposcopy;
- Is deferred until postpartum for minor abnormalities (CIN 1),
- Is performed during pregnancy for high-grade lesions (CIN 2,3), and treatment is performed only if invasive disease is suspected.

Management of preinvasive Cervical Cancer during pregnancy

CIN 1 :

- **Pregnant patients with CIN 1 should not undergo cervical excision or ablation, regardless of the duration of the abnormality and irrespective of whether the preceding tests were high grade (high-grade squamous intraepithelial lesion [HSIL] or atypical squamous cells cannot exclude HSIL [ASC-H]).**

- **The patient should be reevaluated four weeks postpartum and managed based on those results.**

Management of preinvasive Cervical Cancer during pregnancy
CIN 2,3

- **Treatment of CIN 2 or 3 is not recommended.**
- **Pregnant patients with CIN 2 or 3 in whom invasive disease is not suspected are managed accordingly:**

➢ **Observation with colposcopy and cytology (with [HPV] if age appropriate) every 12 to 24 weeks during the pregnancy is preferred.**

➢ **A biopsy may be repeated only if the appearance of the lesion worsens or if cytology suggests invasive disease.**

➢ **Deferring colposcopy until four weeks postpartum is an acceptable alternative.**

Invasive disease suspected

- ● Diagnostic conization is only indicated during pregnancy if confirmation of invasive disease will alter the timing or mode of delivery.

- ● In the case of a gross lesion suspicious for cancer, all that may be needed is a cervical biopsy to confirm the diagnosis, and conization of a gross lesion would and should be avoided.

Frozen section?

- ● Interpretation of frozen sections may be less accurate in patients who are pregnant or have adenocarcinoma or adenosquamous carcinoma.

- ● Surgical therapy of these patients should be based upon results of permanent sections until data showing accuracy become available.

The time for performing of conization

- ● 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.
- ● Technically, pregnancy-related eversion of the squamocolumnar junction facilitates the conization procedure in pregnant women.

Performance of conization

- **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.
- **If a true conization is required, one option is to perform a cone cerclage whereby a cerclage is placed immediately after the conization.**

Management of cervical cancer in pregnancy

Stage for stage, the course of disease and prognosis of cervical cancer in pregnant patients are similar to those of nonpregnant patients

Cervical Cancer & Pregnancy

- Decisions regarding timing of treatment of cervical cancer and delivery require careful consideration of;

- The stage of disease,
- The trimester in which the diagnosis is made, and
- The preferences of the affected patient regarding the pregnancy.

Management of invasive disease

- A careful multidisciplinary team approach is required and should take into account the desires of the pregnant patient (and her family) regarding:
- Termination versus continuation of pregnancy,
- Delay of definitive treatment,
- Mode of therapy during pregnancy, or
- Timing and route of delivery.
- Immediate, definitive treatment, regardless of gestational age, is generally appropriate in the following settings:
  - Documented lymph node metastases
  - Progression of disease during the pregnancy
  - Patient choice to terminate the pregnancy

Key element of the clinical staging process in pregnancy

- **Physical examination —** Physical examination is a key element of the clinical staging process and includes assessment of the primary tumor, uterine size, vagina, parametria, groin, right upper quadrant, and supraclavicular nodes.

- **If examination in an ambulatory setting is suboptimal, performing the examination under anesthesia is suggested.**

Imaging studies —are modified in pregnant women to limit fetal exposure to ionizing radiation.

Key element of the clinical staging process in pregnancy

- ●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 extra cervical disease is unlikely, routine radiographic imaging of the urinary tract may be omitted.

Key element of the clinical staging process in pregnancy

- For larger stage IB1, bulky stage IB2, or more advanced disease and/or higher-risk histology (adenocarcinoma, small cell carcinoma):

- Do imaging of the urinary tract, the abdomen and pelvis with ultrasonography or MRI to rule out stage IIIB disease.

Lymphadenectomy during pregnancy

- ● 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.

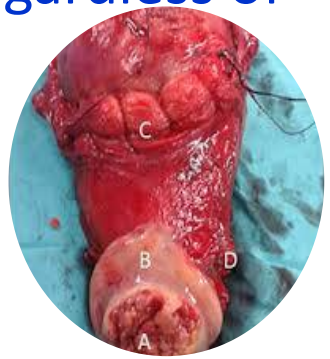
- ● **This information is important, as patients diagnosed with high-risk (node-positive) disease should be counseled about the importance of initiating immediate definitive therapy.**

Endoscopy during pregnancy

- 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.

Definitive treatment with termination of pregnancy

- ● 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.**

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, it is generally recommended radical hysterectomy with the fetus in situ and with preservation of the ovaries whenever possible.
- ● **For patients with more advanced disease, definitive treatment should be administered as in the nonpregnant patient.**

Pregnancy termination

- ● Before chemoradiation, evacuating the uterus, especially if the fetus is more than 20 weeks of gestation is advocated , 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.**

The approach to the management of women with invasive cervical cancer

- ● The approach takes into account:

➢● **The wishes of the patient and her family regarding preservation of the pregnancy**

➢● **The gestational age of the fetus**

➢● **The clinical stage of disease in the mother**

- For women who do not desire continuation of the pregnancy, the management is similar to that of nonpregnant women.

For women who desire pregnancy preservation with a fetus at an early gestational age:

- **For patients in whom stage IAI disease is identified (or suspected), a diagnostic conization is performed** (conization of a gross lesion would and should be avoided).

- 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.**

Management of cervical cancer in pregnancy

- • **For patients with stage IA2 and IB1 tumors, surgical treatment with a simple trachelectomy (not radical) or large conization are suggested.**
- • For patients with a tumor ≥2 cm, neoadjuvant chemotherapy is suggested.
- • **The combination of cisplatin plus paclitaxel administered every three weeks until 3 weeks to delivery.**

Management of cervical cancer in pregnancy (Grade 2C)

- **For women who desire pregnancy preservation and whose fetus is at a later gestational age:**

➢ Treatment delay is suggested until after delivery, provided that their tumor is <2 cm in size (IB1).

➢ **Neoadjuvant chemotherapy (**not radiation therapy **) is suggested if their tumor is ≥2 cm (IB2).**

Management of cervical cancer in pregnancy (Grade 2C)

- Other oncologists prefer termination of pregnancy and initiation of definitive treatment for these patients because of the high risk of recurrence.

- **Patients who demonstrate evidence of disease progression should undergo definitive treatment.**

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.

Considerations about delivery

- ● 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.
- ● For women with stage IB1 or greater cervical cancer, vaginal delivery should be avoided.
- ● 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.

Vertical transmission

- ● **Maternal transmission of cervical cancer cells to the placenta and/or fetus is rare, but has been reported; the mechanism of spread is presumed to be either transplacental (hematologic) and/or aspiration of tumor-contaminated fluids into the fetal lungs during vaginal delivery.**

- ● **However, as vertical transmission is rare, cesarean delivery for standard obstetric indications in most patients with early-stage cervical cancer is recommended.**

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.
- 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.

Systemic therapy in pregnancy

- 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.
- The problems in most of the remainder were associated with prematurity (eg, respiratory distress).

Systemic therapy in pregnancy

- ● 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.

- ● Since the potential for spontaneous labor increases towards the end of pregnancy, it is prudent to avoid administering chemotherapy in the late third trimester.

- ●To avoid additional toxicity, bevacizumab does not utilized because of risk of fetal harm.

Management of cervical cancer (Postpartum)(Grade 2C)

- ● For women who wish to preserve fertility:
- ● **No further treatment is warranted for stage IA1 disease.**
- ● For women with stage IA2 disease or a tumor up to 4 cm in size: radical trachelectomy six to eight weeks after delivery.
- ● **A lymphadenectomy should also be performed if not done previously.**

Management of cervical cancer (Postpartum)(Grade 2C)

- ● For women who do not wish to preserve fertility:

➢● **An extrafascial hysterectomy for women with stage IA1 disease (**rather than a radical hysterectomy**), provided there is no evidence of LVSI.**

➢● For patients with stage IA1 disease with LVSI, IA2, or IB1 tumors, a radical hysterectomy (**rather than chemoradiation is suggested**).

- ● **For patients treated with neoadjuvant chemotherapy during pregnancy (for locally advanced disease or node-positive disease):**

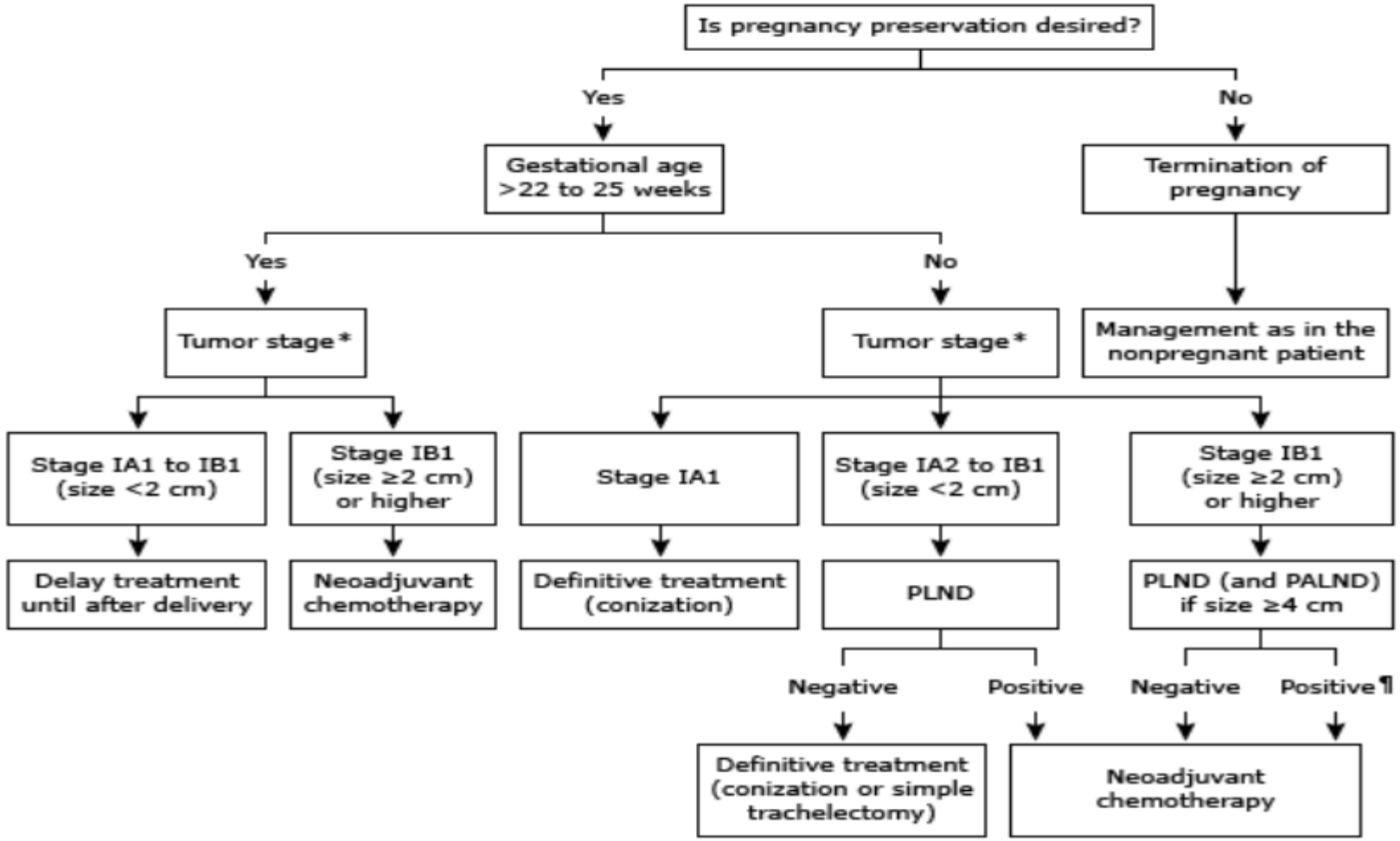
➢● Do a radical hysterectomy, which can be done at the time of cesarean delivery or as a second surgical procedure.

Management of more advanced cervical cancer in postpartum (Grade 2C)

- ● **The definitive treatment for women diagnosed with more advanced disease during pregnancy who delayed treatment until after delivery mirrors that of the nonpregnant patient.**

- ● 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.

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.

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Post treatment surveillance for cervical cancer in 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, proceeding with a pelvic examination every three to four weeks during pregnancy is recommend .

Post treatment surveillance for cervical cancer in 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.

Post treatment surveillance for cervical cancer in pregnancy

- ● Careful clinical evaluation is the most important component

➢ A review of systems.

➢ Physical examination with particular attention to the supraclavicular and inguinal lymph nodes

➢ Rectovaginal examinations

➢ Abdominal examinations

- ● For those treated with hysterectomy for very early disease, annual cervical cytology should be performed until 25 years.


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