# Cervical Intraepithelial Neoplasia in Pregnancy

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There is no evidence that cervical intraepithelial neoplasia (CIN) progresses more rapidly because of pregnancy. Management of CIN in pregnancy, therefore, is conservative. Screening for invasive cancer is done at the first prenatal visit. Colposcopically directed biopsy can then be used to rule out invasive cancer. Postpartum cytology and colposcopy are important follow-up procedures for these women. Cryosurgery for CIN is usually contraindicated in pregnancy. This report includes examples of two pregnant patients with high-grade lesions. A diagnostic and treatment algorithm based on the current "expert opinion" is presented.

*Key words.* Pregnancy; cervical intraepithelial neoplasia; colposcopy; cryosurgery; hysterectomy.
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A Papanicolaou (Pap) smear at the first prenatal visit permits cervical cancer screening of women who might otherwise not present for health care. Performing a Pap smear at this visit is a standard of care,[1] despite evidence that this policy may not be cost-effective.[2]

During pregnancy, approximately 86% of all cervical abnormalities are classified as low-grade squamous intraepithelial lesions (LSIL). Most of these are attributable to the human papillomavirus (HPV),[3] which is among the most common sexually transmitted diseases in the United States and Europe today.[4] The other 14% are high-grade squamous intraepithelial lesions (HSIL).

The incidence of invasive carcinoma in pregnant women ranges from 1:250 to 1:5000.[5] The maternal pregnant state, with hormonal and vascular changes, does not affect the natural history of an invasive cervical cancer even when it is stratified for stage.[3]

Pregnancy is not a risk factor for the development of cervical intraepithelial neoplasia (CIN), which has not been documented to occur more commonly in pregnancy. The progression rate of cervical intraepithelial lesions becoming invasive cancer during pregnancy is very low.[6,7] The rate of regression to normal of low-grade lesions that were untreated but followed sequentially by colposcopy during pregnancy has been found to be as high as 65%.[8] The regression rate to normal of high-grade lesions that were not evaluated by biopsy but were followed sequentially by colposcopy during pregnancy ranged from 20%[8] to 25%.[6] There is no evidence that CIN progresses more rapidly to an invasive cancer in the pregnant state than in the nonpregnant state.

The following two cases included in this review represent examples of the dilemma practicing physicians face when providing obstetrical care. Both women were treated with cryosurgery for HSIL during pregnancy. Patient 1 was treated inadvertently very early in pregnancy, ie, before it was known she was pregnant. Patient 2 was treated intentionally with cryosurgery at 12 weeks' gestation before transferring to our clinic for care.

## Case Reports

### *Patient 1*

A 28-year-old, G3P2A1 white woman presented for colposcopy because her Pap smear showed atypical squamous cells of undetermined significance (ASCUS). She was not known to be pregnant at this time. Colposcopy with biopsy and endocervical curettage (ECC) revealed a flat acetowhite lesion with coarse mosaic pattern, biopsy specimens of which showed moderate dysplasia (CIN-2) with coexistent HPV and no endocervical dysplasia. No vaginal or vulvar condyloma was present. Two weeks later

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after having a negative result on a pregnancy test, she was treated with cryosurgery, which consisted of a 3-minute freeze, thaw, and a 3-minute freeze. The time of this procedure corresponded to 20 days after her last menstrual period. Her urine pregnancy test was positive 17 days after treatment, or 37 days after her last menstrual period. Except for hydrorrhea, which was expected, she had no immediate complications from the cryosurgery. Her pregnancy course was complicated by essential hypertension, depression, and intrauterine growth retardation. She did not have premature labor, spotting or bleeding, or spontaneous rupture of membranes during the course of her pregnancy.

The patient was induced at term for hypertension and intrauterine growth retardation. Her cervix dilated and effaced with appropriate oxytocin-induced contractions following the 1.2 cm per hour curve for multiparous women. At 7-cm dilatation, there was a prolonged fetal deceleration with the fetal heart rate decreasing to 60 beats per minute over a 5-minute period. A viable female infant was delivered by cesarean section with 1- and 5-minute Apgar scores of 8 and 9, respectively. The patient's 6-week postpartum Pap smear revealed LSIL with HPV effect. Colposcopy with biopsy revealed no further progression of the intraepithelial neoplasia. She wished to be treated with an ablative process again.

### *Patient 2*

A 31-year-old, G3P2, white woman presented for prenatal care at our facility at 24 weeks' gestation. Her initial obstetrical visit was at 8 weeks 3 days in a private physician's office. A Pap smear performed at that time showed HSIL. No vaginal or vulvar lesions were grossly visible. She underwent colposcopy and had three specimens taken at that time for biopsy. Endocervical curettage was not done because of pregnancy. The colposcopic examination revealed a flat, three-quadrant acetowhite lesion with some abnormal vessels. Two of the biopsy specimens showed HPV, and the third showed severe dysplasia (CIN-3). Cryosurgery was performed at 12 weeks' gestation; the exact method used was not recorded. A follow-up Pap smear at our facility at 27 weeks' gestation showed ASCUS. No vaginal or vulvar lesions were grossly visible. The patient refused colposcopy.

She gave birth to a viable male infant with 1- and 5-minute Apgar scores of 8 and 9, respectively, by spontaneous vaginal delivery at term. Her postpartum Pap smear continued to show ASCUS. The patient was able to keep a colposcopy appointment at 20 weeks' postpartum. The biopsy results and ECC at that time showed no evidence of any dysplastic epithelium. The subsequent two Pap smears at 6-month intervals remained normal.

## Discussion

### *The Historical Perspective*

In the 1950s and 1960s, the management of CIN in pregnancy was aggressive, involving diagnostic conization in every woman with class III or IV cytologic results (any degree of CIN) to rule out invasive disease.[8] This type of management resulted in significant morbidity and mortality. Maternal complications from a cone biopsy include hemorrhage requiring transfusion and hospitalization, premature labor, cervical incompetence, hemorrhage at time of delivery, a faster second stage of labor, abortion, infection, and maternal death.[9,10] Hemorrhage occurs up to 14% of the time in pregnant women undergoing a conization.[3] Fetal complications from conization during pregnancy include maternal chorioamnionitis with fetal death[11]; abortion; and fetal, neonatal, or perinatal death occurring in 2% to 18% of the cone procedures.[3]

The next decade provided evidence that colposcopically directed biopsies of all pregnant women with any degree of abnormal cytology was an acceptable tissue-sparing management strategy. The risk of hemorrhage from the colposcopically directed biopsy was extremely low. Maternal complications included bleeding and possible infection, but no reported fetal complications.[6,8,11–15] The endocervical curettage, although never subjected to a clinical trial for efficacy, was never and still is not an appropriate adjunct to colposcopic assessment during pregnancy[3,9,12] for two reasons. First, the cervical ectropion in pregnancy facilitates complete visualization of the squamocolumnar junction, transformation zone, and lesion margins. Second, the risk of fetal disruption is greater than the risk of an intracanal squamous or adenocarcinoma.

More recently, as colposcopic skills and experience have increased, several authors found that biopsy specimens of low-grade lesions were not needed if the patient was serially followed throughout her pregnancy and postpartum period with colposcopic and cytologic examinations.[6,16] Recent literature supports this trend toward conservative management. The incidence of invasive cervical cancer is quite low,[17] and the progression to invasive cancer from a LSIL is undocumented within a 40-week span. It is unlikely that colposcopy of low-grade lesions would ever be dropped from the current conservative management plan because, on antenatal screening, up to 10% of high-grade lesions can be misclassified as low-grade lesions.[9] In 25% of cases, high-grade lesions in a pregnant woman can progress to invasive cancer within as little as 6 months[18] or regress to normal.[6] Biopsy specimens of high-grade lesions are taken under colposcopic

guidance to establish the presence of microinvasive or invasive cancer.[9,13,14]

## *Colposcopy During Pregnancy*

The purpose of colposcopy in pregnancy is to examine the cervix for invasive carcinoma. Many expert colposcopists state that the colposcopic presence of invasive carcinoma in pregnancy is difficult to differentiate from the normal changes of pregnancy,[9,13] even when classic acetowhitening, vascular patterns, and borders of lesions are considered. Hormonal changes that occur during pregnancy cause dramatic physiologic effects on the cervix. Estrogen causes hypertrophy of the fibromuscular stroma with increased vascularity of the entire lower genital tract causing the blue hue (Chadwick's sign) common in pregnancy. The endocervical columnar epithelium is usually everted onto the ectocervix, which can be seen very clearly by 20 weeks' gestation. The squamocolumnar junction is readily visible by the second trimester. Islands of immature squamous epithelium occur as the everted columnar epithelium is exposed to the acidic vaginal pH. Usually the metaplasia is physiologic, but it may incorporate or express neoplastic changes. Gland openings become more prominent with a very acetowhite outline. These changes and the increased vascular markings may represent decidualized stroma, a great mimicker of cervical carcinoma. Small, white punctate areas scattered across the entire cervix are perivascular decidual cuff markings, a normal variant of pregnancy. Decidualization of the cervical stroma can give rise to yellowish-white plaque-like areas that may be nodular or ulcerated, also mimicking cancer. Stromal decidualization occurs in approximately 30% of pregnant women.[9] There is usually copious, tenacious mucus covering the entire transformation zone. Vaginal wall laxity is very common, often necessitating ancillary equipment for colposcopic visualization.

## *Management*

The appropriate management for a woman with a low-grade lesion is to follow her with repeat cytologic and colposcopic examinations about every 10 weeks or at 28 weeks' gestation and again postpartum.[9,16] Endocervical curettage is never performed during pregnancy. Definitive diagnosis and treatment is appropriate in the postpartum state. Often, these lesions will have resolved postpartum because of intrapartum tissue loss with labor and because of the return of the maternal immunocompetence. If a high-grade lesion is documented on screening cytologic examination and confirmed by colposcopic impression, a biopsy to rule out invasion must be done. Benedet[16] feels that women older than 30 years are at high risk for a high-grade lesion and should have a biopsy taken during pregnancy to rule out invasion. If the biopsy confirms a high-grade lesion, the patient should be seen at 8- to 10-week intervals with repeat cytologic and colposcopic procedures to monitor for progression to cancer. Cytologic and colposcopic examinations postpartum with biopsy and ECC will confirm the lesion, at which time definitive treatment can be scheduled.

Cryosurgery during pregnancy is contraindicated by most physicians. Documented complications from this procedure include pain, cramping, hydrorrhea,[19,20] a malodorous discharge,[21] acute bilateral salpingitis,[20] local infection with mild endometritis and parametritis, heavy vaginal bleeding and pyometra,[22] mucometra,[23] and vasomotor syncope.[24] Long-term effects can include cervical stenosis in up to 3% of cases, and residual dysplasia if the appropriate cryosurgical method is not used.[25] Possible complications from cryosurgery during pregnancy can include uterine contractions, uterine ischemia, and pain.[26] Uterine contractions could result in a spontaneous abortion or preterm labor. Hydrohematometra can occur when the cervical os is blocked by postcryosurgery cellular debris, and the serosanguinous straw-colored fluid accumulates in the endocervical canal and into the uterus.[23,27] This "plug syndrome" may cause chorioamnionitis and fetal demise.

If microinvasive cancer is detected on biopsy, a larger biopsy, such as a conization or wedge biopsy, must be conducted to rule out invasion. If the disease is confined to microinvasion, prognostic features such as lymph vascular space involvement, confluence of foci of invasion and surface area of the tumor, gestational age, and patient preference must all be taken into the management decision. Mode of delivery is based on obstetrical factors rather than on the basis of microinvasion; vaginal delivery is common in those with low-risk prognostic features. Close cytologic, colposcopic, and histologic follow-up is necessary for 2 years postpartum.

If invasive carcinoma is detected on wedge or cone biopsy, management is again dependent on the prognostic features of the cancer, the fetal gestational age, and the patient's preference. A cesarean section with radical hysterectomy is usually the treatment of choice. Women with stage I (a or b) cervical cancer have the same disease-free survival when definitive therapy is delayed until fetal maturity, as do those who choose immediate radical hysterectomy.[17] The Figure represents the triage algorithm currently used for managing pregnant women with abnormal cytology results.

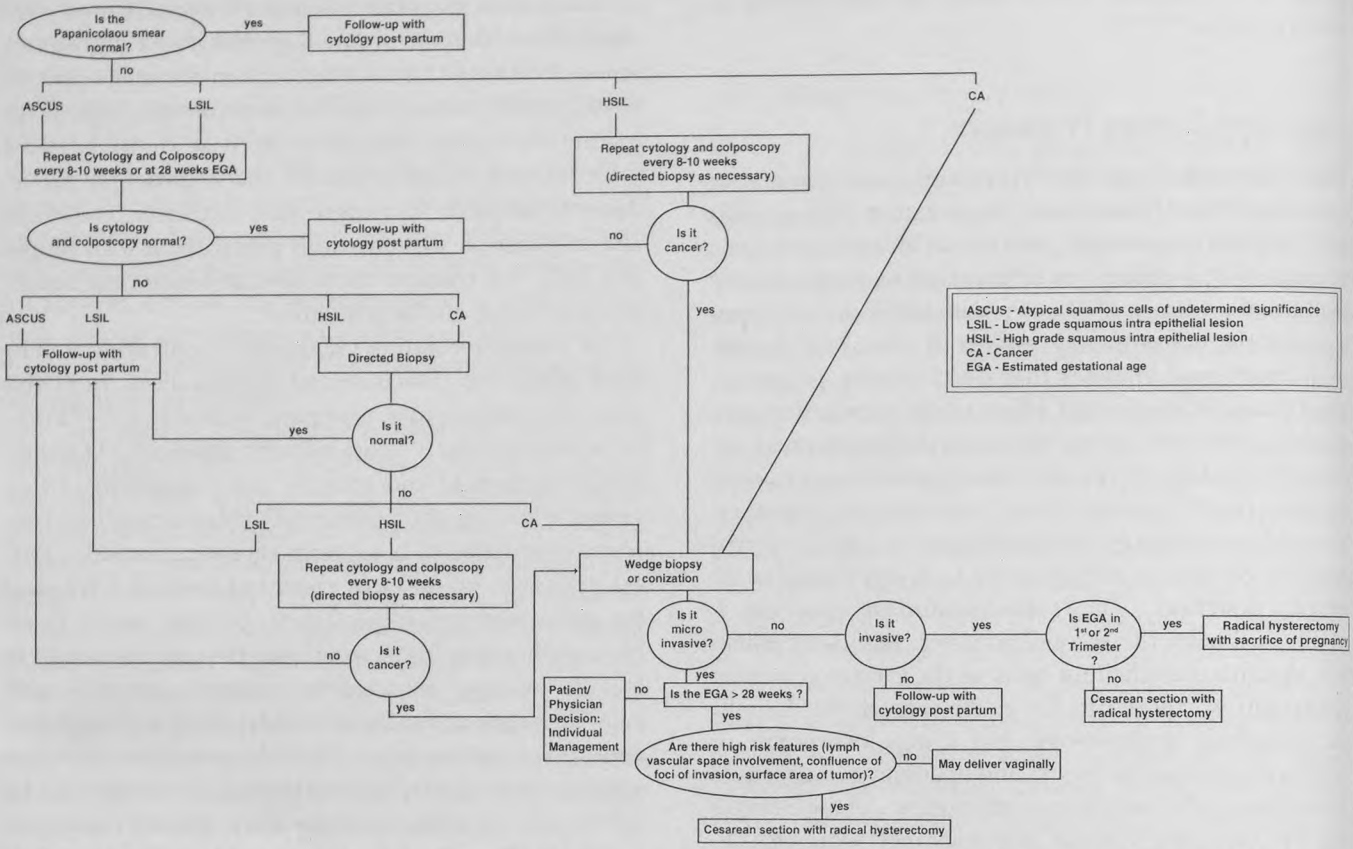


Figure. Triage algorithm used for managing pregnant women with abnormal cervical cytologic findings. Colposcopy of a pregnant cervix can be challenging even for an experienced colposcopist. Second opinions from gynecologic oncologists are often requested in these cases. This algorithm is based, in part, on textual information authored by Campion and Sedlacek.[9]

## Conclusions

In general, treatment of CIN in pregnancy is postponed until after the postpartum cytologic and colposcopic evaluation.[15] Only microinvasive and invasive squamous cervical carcinoma need to be aggressively treated during pregnancy, in which case a large wedge biopsy or conization or hysterectomy is appropriate. The type of hysterectomy depends on the gestational age of the fetus. Cryosurgery, as was done in the two cases presented in this paper, is not recommended during pregnancy.

An appropriate clinical protocol that would help ensure that cryosurgery does not inadvertently occur is to schedule cryosurgical treatment immediately after a woman's menstrual flow. The treatment would usually occur prior to ovulation, making pregnancy unlikely. A more costly method would be to institute routine urine pregnancy tests on the day of treatment just prior to cryosurgery. This method has a small false-negative rate.

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