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# Cervical neoplasia in pregnancy. Part 1: screening and management of preinvasive disease

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Cervical cancer screening is an essential component of prenatal care. The diagnosis and management of cervical intraepithelial neoplasia (CIN) during pregnancy are challenging, and sufficient information does not exist to allow for a definitive evidence-based approach. The American Society for Colposcopy and Cervical Pathology has recently published guidelines regarding the evaluation of abnormal Papanicolaou tests and the treatment of CIN in this setting. Many techniques traditionally recommended in the evaluation of abnormal cervical cytology and the treatment of CIN in the nonpregnant woman, such as colposcopy, cervical biopsy, and electrosurgical excision, can be applied to the pregnant patient with important exceptions. The vascular cervix associated with the gravid condition and the risk of premature pregnancy loss mandates deviation from existing consensus guidelines in screening for cervical cancer in pregnancy and treating associated CIN. In the present review, current guidelines regarding cervical cancer screening are reviewed, and data from studies of pregnant populations are summarized.

**Key words:** cervical cancer, cervical neoplasia, management, pregnancy

One percent of the population of child-bearing women screened annually for cervical cancer will be diagnosed with cervical intraepithelial neoplasia (CIN).[1] Among the 4 million women who become pregnant each year in the United States,[2] between 2% and 7% (ie, 80,000-320,000) will have an abnormal Papanicolaou test during pregnancy.[3-5] Cervical neoplasia (including carcinoma in situ and invasive carcinoma) is estimated to complicate 1.5 to 12 of every 100,000 pregnancies.[6-8] To establish protocols for cervical cancer screening and the treatment of cervical intraepithelial neoplasia in pregnancy, we reviewed recently published guidelines[9-12] and prepared an algorithm specific to the management of CIN in pregnancy. The evaluation and management of invasive cervical cancer in pregnancy will be discussed in a separate article.

## Screening and cervical cytology in pregnancy

Theoretically, patients may present for their first prenatal visit having begun intercourse within the last 3 years, or they may have had several consecutive normal Papanicolaou tests, making them eligible to extend the Papanicolaou test interval. Younger mothers and those with higher parity are known to have higher rates of human papillomavirus (HPV) infection.[13,14] It is therefore the recommendation of the authors that all pregnant patients undergo Papanicolaou test screening at the time of their initial prenatal exam.

Some clinicians may be concerned about the placement of a foreign object, such as the cytobrush, into the cervical canal. In an attempt to evaluate alternatives to this traditional sampling method, 1 randomized trial compared the cytobrush with use of a Dacron swab. They reported an improved yield of endocervical cells for the cytobrush (96% vs 70%) without any difference in complications including bleeding and spontaneous abortion[15]; thus, it is recommended that the cytobrush, or comparable combination broom, be used during the collection of a prenatal Papanicolaou test.

The Papanicolaou test currently has a sensitivity for detecting high-grade cervical neoplasia outside pregnancy of between 70% and 80%.[16] Several factors can complicate the sampling and analysis of cervical cytology in pregnancy, including the presence of a large ectropion, frequent inflammation, and the presence of confusing decidual cells that are often mistaken for atypia.[17-19] The decidual cells, or Arias-Stella reaction, are large, hypervacuolated cells with variably staining cytoplasm and a large nucleus, explaining their association with false-positive results. However, if care is taken to provide the cytologist with a detailed patient history, errors should be minimized. Overall, the Papanicolaou test appears to have demonstrated an accuracy in pregnancy that is equivalent to the nonpregnant patient.[3]

## Normal Papanicolaou test with or without high-risk HPV deoxyribonucleic acid

The follow-up of a normal Papanicolaou test, obtained in the antepartum setting, would not differ from the nonpregnant population. Consistent with the American Cancer Society (ACS) and the American College of Obstetricians and Gynecologists (ACOG) guidelines, patients who have had 3 or more normal Papanicolaou tests and have not had a history of dysplasia, immunodeficiency, or in utero diethylstilbestrol exposure and are above the age of 30 years could potentially forgo the routine postpartum Papanicolaou test, to be repeated at 3 year intervals.

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At present, there are no randomized controlled trials from which to establish evidence-based guidelines on the routine use of postpartum Papanicolaou tests. One randomized trial evaluated the use of the postpartum Papanicolaou test at 4, 6, or 8 weeks following delivery.[20] The authors concluded that the longer time interval, or the 8 week interval, was associated with fewer false-positive tests as a result of decreasing inflammation. It should, however, be noted that many women have their only cytological screening during their perinatal visits.[21] As such, the authors recommend following standard guidelines for the interval following a normal Papanicolaou test, unless the follow-up may be compromised by poor patient compliance.

Although many programs have instituted reflex testing, or high-risk human papillomavirus testing only in the presence of atypical squamous cells of undetermined significance (ASC-US), there are some sites that perform high-risk HPV testing at the time of initial cytologic sampling in women over 30 years of age. Thus, some women will fall into the category of having normal cervical cytology with a positive high-risk HPV analysis. Clavel et al[22] followed up such patients and found that only 4% of such women had findings of CIN 2 or higher. This has led to the recommendation, restated in the 2006 consensus guidelines, that women with negative cervical cytology and positive high-risk HPV be followed up with a repeat of both tests at 12 months.[9,11,23] Because most women with such findings have only transient HPV infections, it is recommended that pregnant women with negative cervical cytology and positive high-risk HPV results undergo a repeat of both tests at the 6 week postpartum visit.

Furthermore, many women may also be found to have the result of a negative Papanicolaou test and negative high-risk HPV. For pregnant patients 30 years old and older who demonstrate this double-negative finding, joint guidelines by the National Cancer Institute, the American Society of Colposcopy and Cervical Pathology (ASCCP), and the ACS recommend that they undergo repeat screening at an interval no shorter than 3 years from the negative result.[9,11,23]

## Absence of endocervical cells

With the expansion of the transformation zone in early pregnancy, it should be easier to sample endocervical cells during pregnancy. Papanicolaou tests lacking endocervical cells during pregnancy should be repeated.[24,25]

## Diagnostic procedures in pregnancy

Although the timing and the indications for cervical screening do not differ appreciably between pregnant and nonpregnant patients, the management of cytologic abnormalities can be widely divergent. Such differences lie primarily in the reluctance of most physicians to perform the necessary interventions for both the proper diagnosis and the treatment of cervical neoplasia.

### Colposcopy during pregnancy

Increasing pelvic congestion during pregnancy may make the procedural aspects of colposcopy more difficult. An increase in vaginal wall protrusion and wall redundancy may obscure a direct line of visualization between the colposcope and the cervix. The use of a vaginal sidewall retractor, in combination with a Graves speculum, may improve cervical access. Alternatively, a condom with the tip removed can be slipped over the speculum to retain the vaginal side walls. Overall, changes associated with the visual findings of the pregnant cervix may significantly confuse the interpretation of colposcopic results. As such, only those with advanced training and/or extensive experience should perform colposcopy on the pregnant patient who presents with an abnormal Papanicolaou smear.

The adequacy of a colposcopic examination in pregnancy can be further compromised by the common finding of an enlarged cervix. The presence of such may prompt the need for multiple manipulations of both the speculum and the colposcope to obtain a complete examination of all 4 cervical quadrants. As in the nonpregnant state, it is necessary to have complete visualization of the transformation zone. Fortunately, there is a gradual eversion of the endocervix as the pregnancy progresses.[26] Economos et al[27] reported that most patients have such an eversion, as to render virtually all colposcopies adequate by 20 weeks of gestation.

Given the aforementioned cervical changes associated with pregnancy, it is imperative that the visual impression have a proven and reliable correlation with histology. Some authors have suggested that the changes associated with pregnancy inherently cause an artificial overestimation of lesion severity.[28] However, 1 retrospective investigation reported on the evaluation of 612 cytologic abnormalities in pregnancy.[27] Four hundred forty-nine patients underwent colposcopically directed biopsy, with a correlation of 95% to within 1 degree of the visual impression. Colposcopic impression appears be well correlated with antepartum biopsy, with only 1 of 867 patients demonstrating an invasive lesion in which the colposcopic impression was preinvasive (CIN 3).[27-30]

### Cervical biopsy

Concerns over excess bleeding, resulting from a pregnant and presumably hyperemic cervix, prevent many physicians from performing biopsies, in which they would otherwise be indicated. Such concerns have not been definitively confirmed, although they have been propagated in the literature.[19,31] Conversely, several studies have reported the liberal use of colposcopically directed biopsies in pregnancy.[27,32-34] Although these studies were not designed to investigate the use of cervical biopsy in pregnancy specifically, they do not report significant bleeding complications or adverse pregnancy outcomes associated with the procedure.

Although bleeding is considerably less during the first trimester, some authors advocate waiting until the second trimester before a biopsy is performed to avoid the association of the procedure with a spontaneous, and likely unrelated, miscarriage. Others still advocate the use of a stiff brush as a biopsy substitute for a less invasive diagnosis.[35] This technique employs the use of a spiral brush with thickened bristles, which, when used to brush a suspected cervical lesion, can provide a specimen that is comparable

with that of a punch biopsy.[36] Beyond the first trimester, cervical biopsy or stiff brush procedure should be performed in any patient for whom invasive cancer cannot be reliably excluded.

### Endocervical curettage

Although there have been no randomized trials to evaluate the risk of endocervical curettage (ECC) in pregnancy, many authors feel that ECC is not appropriate when a woman is pregnant.[27,37,38] One retrospective study described the use of ECC in the diagnosis of carcinoma in situ in 33 pregnant patients.[39] They found that 97% delivered at term, with no significant difference in either the rate of preterm delivery or the incidence of low birthweight, when compared with the general population. Nonetheless, with an absence of well-designed trials, ECC in the pregnant patient is unacceptable.[33]

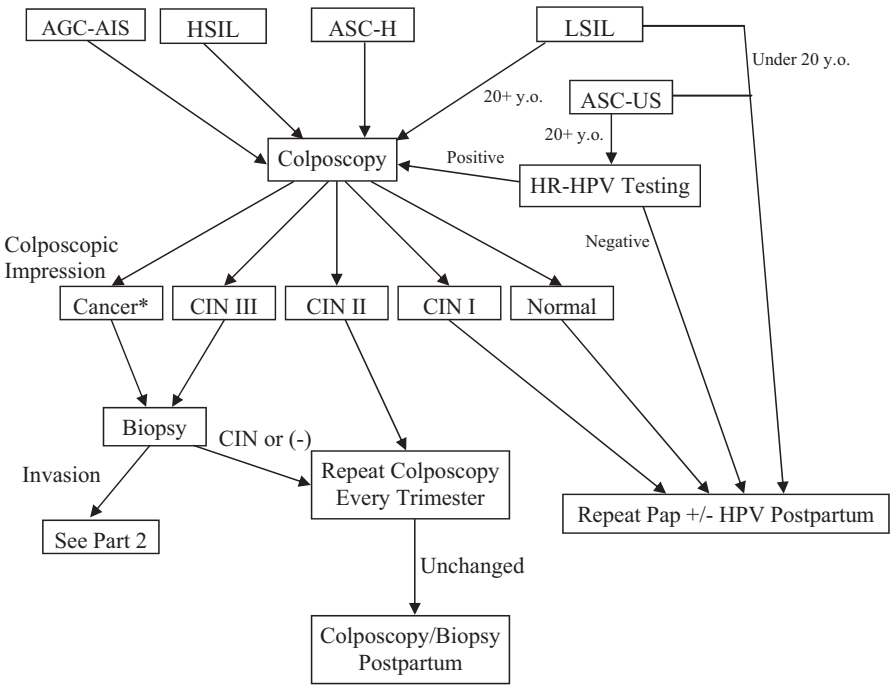
## Management of cytologic abnormalities

### Atypical squamous cells

The likelihood of finding an invasive lesion following either antepartum or postpartum biopsy is less than 1% when the high-risk HPV test is positive after an ASC-US Papanicolaou test. However, high-grade lesions may be diagnosed in up to 1 in 5 patients with ASC-US Papanicolaou tests. Because there is no current evidence that either the natural history or the prevalence of HPV infection is altered in the pregnant state,[40] the ASCCP recommendation of managing ASC-US using HPV triage is acceptable, whereas colposcopy should be performed for all pregnant patients with atypical squamous cells favoring high-grade lesions.

Because serial cytology has been shown to have a lower sensitivity than HPV testing[41] and because repeating a Papanicolaou test in the third trimester may be impractical, it is not recommended for antepartum management. ASCCP 2006 guidelines recommend against the use of HPV triage in patients with ASC-US younger than 20 years of age. The guidelines allow for pregnant women older than 20 years with ASC-US to be managed as the nonpregnant woman (ie, HPV testing by either reflex or at a return office visit), with the exception that colposcopy may be deferred until at least 6 weeks postpartum.[9,11] Patients who are high-risk HPV negative can be followed up with a Papanicolaou test at 6 weeks postpartum. Figure 1 describes specific recommendations for the assessment and follow-up of the abnormal Papanicolaou test in pregnancy.

**FIGURE 1**
**Algorithm for the management of the abnormal Pap smear and CIN in pregnancy**




*AGC*, atypical glandular cells; *AIS*, adenocarcinoma-in-situ; *ASC-H*, favor high grade; *ASC-US*, atypical squamous intraepithelial lesion of undetermined significance; *CIN*, cervical intraepithelial neoplasia; *HR-HPV*, high risk human papillomavirus testing; *HSIL*, high grade squamous intraepithelial lesion; *LSIL*, low grade SIL.

*Hunter. Cervical neoplasia in pregnancy. Am J Obstet Gynecol 2008.*

## Atypical glandular cells (AGCs) and adenocarcinoma in situ (AIS)

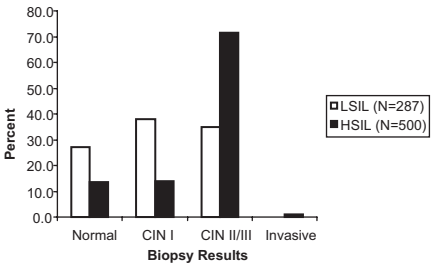
In the pregnant patient, the Arias-Stella reaction can often be misinterpreted as a glandular atypia.[42,43] The Arias-Stella reaction was found to involve the endocervical canal in 9% of hysterectomy specimens obtained perigestationally.[44] Consequently, Kim et al[45] found only 1 carcinoma in situ in 21 patients followed up conservatively for atypical glandular cells in pregnancy. Furthermore, Chhieng et al[46] followed up 30 pregnant patients and 5 postpartum patients with AGCs. Of those who underwent colposcopy and biopsy, 18% had high-grade squamous intraepithelial lesions (HSIL) and 12% had low-grade squamous intraepithelial lesions (LSIL). No adenocarcinoma or AIS was diagnosed. On follow-up, only 2 patients were found to have persistent cellular atypia, 1 of which was glandular and the other squamous.

According to the 2006 ASCCP guidelines, the evaluation of AGCs in pregnant women should be identical to that recurrent for nonpregnant women, except that endocervical curettage, cold-knife cone biopsy, and endometrial biopsy are unacceptable.[10,12]

## Squamous intraepithelial lesions

Although pregnancy can cause physiologic and visual changes in the cervix that may be misinterpreted as dysplasia, it may be presumptive to assume that cytology consistent with an intraepithelial

**FIGURE 2**
**Antepartum biopsy results following low-grade and high-grade squamous intraepithelial lesions[30,31,49,59,69-71]**

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lesion was falsely positive. Patients with the cervical cytology of LSIL are unlikely to have an invasive lesion on antepartum biopsy, with none of 287 patients demonstrating such pathology.[33] Some authors have even suggested that it is neither cost effective nor necessary to perform colposcopy on every person with LSIL cytology.[33]

According to the 2006 ASCCP guidelines, colposcopy is preferred for the nonadolescent pregnant woman with LSIL, but deferring this procedure until at least 6 weeks postpartum is also an option. For those whose initial colposcopy is performed antenatally, provided there is no cytological, histological, or colposcopically suspected CIN 2, CIN 3, or invasive cancer, postpartum follow-up is recommended. In other words, the recommended management of pregnant women with a histological diagnosis of CIN 1 is follow-up without any treatment. For such women, additional colposcopic and cytological examinations during pregnancy are unacceptable.

There is little debate in regard to the need for patients with an HSIL Papanicolaou test to undergo colposcopy. Figure 2 illustrates that the majority of these patients will have high-grade lesions on antepartum biopsy and that 1 in 100 will have an invasive lesion.[30,31,49,59,69-71] Murta et al[47] reported on 53 patients with biopsy proven high-grade lesions in pregnancy. Most of these patients were managed conservatively, and approximately 75% of them had persistence of their high-grade lesion on postpartum biopsy. None of them had progression to invasive disease. Similarly, Vlahos et al[48] followed up 78 biopsy-proven high-grade lesions through pregnancy, with cytology and colposcopy at 8-10 week intervals. They reported regression to CIN I in 62% of patients, with no progression to invasive disease.

The 2006 ASCCP guidelines advise all pregnant women with HSIL to undergo colposcopy, preferably by clinicians who are experienced in the evaluation of colposcopic changes induced by pregnancy. Although the expertise of providers may differ based on formal training and clinical interests, it is reasonable to expect that members of the ASCCP and/or those gynecologists and gynecologic oncologists who have a special interest in clinical colposcopy will have accumulated significant experience in the evaluation and management of abnormal Papanicolaou tests in pregnancy.

Biopsy of lesions suspicious for CIN 2, CIN 3, or invasive cancer is recommended. Patients with a histological diagnosis of CIN 2 or CIN 3 may undergo additional colposcopic and cytologic examinations at intervals no more frequent than every 12 weeks during pregnancy. Repeat biopsy during pregnancy is advisable only if the appearance of the lesion worsens or if cytology suggests invasive cancer. Pregnant women with HSIL who are not diagnosed with CIN 2 or CIN 3 should undergo reevaluation with cytology and colposcopy no sooner than 6 weeks postpartum.

Figure 1 depicts modifications to the ASCCP, ACOG, and ACS guidelines for the treatment of LSIL and HSIL, respectively, in the special situation of pregnancy. In summary, all pregnant patients with an HSIL Papanicolaou test should undergo colposcopic evaluation, as would be recommended for the nonpregnant patient. For the gravid cervix, however, biopsies can be associated with an abnormally large amount of bleeding, and colposcopic impressions can be misleading, artificially suggesting a higher grade lesion. Furthermore, a poorly timed cervical procedure could be erroneously associated with a coincident miscarriage, preterm labor, or other complication.

## Excisional biopsy in pregnancy

Because the risk of progression of CIN 2 or CIN 3 to microinvasive or frankly invasive cervical carcinoma is minimal and the rate of spontaneous regression postpartum is relatively high, treatment of CIN during pregnancy should be avoided. In point of fact, as will be discussed in the companion article on invasive cervical cancer in pregnancy, many oncologists follow early-stage cervical cancer in pregnancy until fetal pulmonary maturation has been achieved. Not only is treatment of CIN during pregnancy associated with significant perinatal morbidity (including catastrophic intraoperative hemorrhage), but there is also a high rate of incomplete excision, which results in the persistence of CIN as well as a recurrence rate which is significant.[49]

If the referral cytology, colposcopic appearance, and/or cervical biopsy is/are suspicious for invasive cancer, the 2006 ASCCP guidelines recommend that diagnostic excision be considered. Unless invasive cancer is identified, treatment is unacceptable, with reevaluation with cytology and colposcopy being recommended no sooner than 6 weeks postpartum.

## Large loop excision of the transformation zone (LLETZ)

Certainly there are cases in which invasion cannot be definitively ruled out without the use of an excision procedure. LLETZ is used for such diagnostic purposes but may also be useful for therapeutic purposes. The ASCCP recommends LLETZ in the nonpregnant patient under the following circumstances: biopsy-proven CIN 2, CIN 3, and AIS; AGC-favor neoplasia or AIS cytology (if colposcopy and ECC are negative); and normal or CIN I histology in the setting of HSIL cytology.

Naturally physicians are reluctant to perform such an invasive procedure during pregnancy, with the fear that even a coincidental complication could be associated with the LLETZ. As such, it is necessary to examine the indications for LLETZ carefully and to determine when cervical neoplasia must be treated in

pregnancy and when it can be delayed until the postpartum period.

Several studies, over the last few decades, have attempted to evaluate the effects on future child-bearing of large loop excision of the cervix, performed outside pregnancy. Despite a measurable shortening of the cervical length,[50] several studies concluded that LLETZ does not appear to appreciably predispose patients to complications in a subsequent pregnancy, including preterm delivery.[51-55]

A recent metaanalysis by Kyrgiou et al,[56] however, does provide evidence that LLETZ (and cold-knife conization) does increase the risk of preterm birth, low birthweight infants, and cesarean sections. A recent report by Samson et al[57] demonstrated a significant increase in the risk of delivery before 37 weeks in patients who had a prior loop excision of the cervix. Although they also demonstrated an increased risk of low birthweight, they did not find a significant difference in the risk of delivery before 34 weeks. Other investigators have also found LLETZ to be significantly associated with lower birthweights.[58]

In the same way that LLETZ outside pregnancy has demonstrated inconsistent effects on future gestations, investigators performing the procedure during pregnancy have also demonstrated mixed results. Robinson et al[49] reported on a series of 20 loop excisions performed for intraepithelial neoplasia between 8 and 34 weeks' gestation. Two patients required blood transfusions acutely, and 3 patients had a preterm delivery. Of note, only patients who underwent LLETZ between 27 and 34 weeks of gestational age were associated with such complications.

Conversely, Matsuhashi et al[59] performed 9 loop excisions at a gestational age, ranging from 4 to 14 weeks. He noted no significant intraoperative or postoperative complications, and all patients delivered at term. One patient did have a cerclage placed at 28 weeks, although she, too, delivered at term. Similarly, Dunn et al[21] reported on 13 patients undergoing loop excision in pregnancy, all of whom were followed up immediately by the placement of a cerclage. The patients ranged in gestational age from 13 to 32 weeks. All patients delivered at term, although 2 had a blood loss of at least 250 milliliters.

Given the aforementioned reports, it may be suggested that LLETZ can be performed in pregnancy with a reasonable degree of maternal safety. However, this procedure should be performed only in a well-staffed and properly equipped operating room. Furthermore, LLETZ should be reserved for patients who are previable and in whom invasive disease is strongly suspected or confirmed with biopsy. Alternatively, LLETZ can be performed prior to a planned pregnancy termination for patients in whom such a course is desired.

## Cold knife cervical conization

Several earlier studies investigated the use of cold-knife conization for the treatment of suspected or proven severe dysplasia or microinvasive disease during pregnancy. Similar to the findings for LLETZ, cold-knife conization has been associated with heavy vaginal bleeding in 5-15% of pregnant patients.[60,61] Furthermore, the rate of spontaneous abortion was noted to be as high as 25%. Again, in parallel to the findings for LLETZ, approximately 50% of patients will have recurrent CIN following an antepartum conization, presumably secondary to smaller-than-usual excisions.[61,62] Because of the high complication rate attributed to the performance of a cold-knife cervical conization during pregnancy, the authors do not recommend this procedure to rule out microinvasive or frankly invasive disease.

## Coin biopsy

Because pregnancy causes a relative eversion of the squamocolumnar junction, high sampling of the endocervix may not be necessary. Some have advocated the excision of a coin-shaped specimen instead of a cone shape in which the specimen is wedged out in the shape of a pie. Such a shallow excision will cause less disruption to the endocervical canal and may decrease both bleeding and preterm labor complications.[63] In contrast to a typical cone procedure on the nonpregnant cervix, a total of 6 hemostatic sutures should be placed prior to performing the coin procedure in the pregnant patient.

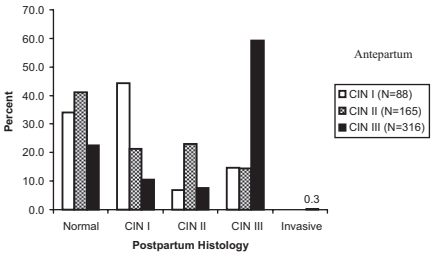
This procedure should be performed only in the operating room, in which adequate exposure, blood products, and proper anesthesia can be secured. Lastly, the size of the specimen should be limited only to the area under question and should in no way attempt to encompass the entire transformation zone. The purpose of such an excision is to diagnose invasion and not to treat intraepithelial neoplasia, the management of which will be discussed in the following text.

## Natural history of CIN in pregnancy

It is clear from the aforementioned detailed investigations that the finding of biopsy-proven CIN in pregnancy does not warrant interruption of the gestation. In fact, CIN 1, 2, and 3 have all been associated with acceptably low rates of progression. Although Figure 3 demonstrates that it is possible for CIN 1 or CIN 2 to progress to CIN 3,[30,31,35,67,69,71,72] this may represent a subpopulation of patients with less than optimal immunocompetence, or alternatively, sampling error during the antepartum biopsies. In either case, the significance of such a progression is of little concern.

Colposcopic surveillance of CIN during pregnancy (Figure 3) is performed exclusively for the purpose of detecting progression to invasive disease. Persistent CIN 3, and therefore progression to the same, can be managed expectantly. Figure 3 demonstrates that the progression from CIN 3 to invasive disease between the antepartum and the postpartum period is an unlikely event. Furthermore, there is no evidence that cytologic, histologic, or colposcopic surveillance of a CIN 3 lesion during the antepartum period has any effect on the overall prognosis of such a progression. In summary, all patients with biopsy-proven CIN 2 or 3 should undergo colposcopic evaluation with directed biopsies at the 6 week postpartum visit. Colposcopic surveillance during the antepartum period is at the discretion of the provider.

**FIGURE 3**
**Correlation between antepartum and postpartum histology**[30,31,35,67,69,71,72]

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### Mode of delivery

With regard to intraepithelial lesions, the local inflammatory reaction initiated secondary to cervical trauma during vaginal delivery may actually improve regression rates.[64] Indeed, 1 study compared regression rates for patients with HSIL delivering both vaginally and by cesarean section and found regression in 67% and 13%, respectively.[65] Other studies have not demonstrated a relationship between delivery mode and rate of regression.[66,67] Patients with intraepithelial disease should have a mode of delivery that is based only on obstetric factors as well as maternal factors not related to CIN.

## Summary

With more than 3 million deliveries in the United States and improving prenatal cervical screening programs, a significant number of pregnant women present with cervical neoplasia each year. Despite the large size of this population, there are relatively few studies on which to formulate evidence-based management guidelines.

As such, recommendations must be proposed on the basis of data that are extrapolated from the nonpregnant population, with modifications sensitive to the unique situation of pregnancy. Fortunately, progression from preinvasive to invasive disease during the time frame of 1 or 2 trimesters is rare. Furthermore, it is well established that, especially in the younger patient population, the rate of spontaneous regression of cervical intraepithelial lesions is high.[68]

This affords the opportunity for most women with preinvasive disease to be managed conservatively until the completion of pregnancy. In the second part of this series, recommendations will be made regarding the treatment of invasive cervical cancer discovered during pregnancy. ■

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