Atypical Papanicolaou Smear in Pregnancy

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Atypical glandular cells (AGC) in Papanicolaou (Pap) smears can be associated with premalignant and malignant cervical and endometrial lesions. AGC is difficult to diagnose in pregnancy due to confusion with normal cellular changes that accompany graviditas. While guidelines have been established for management of AGC cases in the non-pregnant patient, special considerations are required when this is discovered during a pregnancy. A routine Pap smear performed on a 29-year-old woman being seen for a history of infertility yielded AGC and a high-grade squamous intraepithelial lesion. The patient achieved pregnancy 1 month later. Satisfactory colposcopic exam was performed with cytobrush sampling of the endocervical canal, in addition to 2 exocervical biopsies at 11 weeks gestation. Positive diagnosis of endocervical adenocarcinoma *in situ* resulted in a risk-informed decision to proceed with a cold knife conization of the cervix. Final pathology showed complete resection of the lesion with negative margins and an additional area of squamous dysplasia (cervical intraepithelial neoplasia, grade II to III). Appropriate follow-up was recommended. AGC found upon Pap smear during a pregnancy can be associated with significant pathology for which an aggressive management approach is warranted.

Keywords: Pregnancy; Cervical intraepithelial neoplasia; Vaginal smear; Squamous cell carcinoma; Precancerous conditions

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Papanicolaou (Pap) smears that contain atypical squamous cells of undetermined significance can be followed up with repeat smears. However, those that contain atypical glandular cells (AGC) are more likely to be associated with severe underlying conditions and, therefore, warrant particular attention.¹ The diagnosis of AGC by pathologists is difficult as there is a high degree of interobserver variation.²⁻⁷ Up to 50% of women with AGC have significant histologic abnormalities, and cancer is present in 19.5% of women with AGC.^{1,3,8-13} In women younger than 35 years of age, cervical adenocarcinomas are increasing.^{1,14,15} The National Cancer Institute, American Society of Colposcopy and Cervical Pathology, American College of Obstetricians and Gynecologists, and Centers for Disease Control recommend immediate diagnostic work-up and treatment in AGC cases.¹⁵⁻²³ However, how to proceed with AGC in pregnancy has received limited discussion.

Case Report

This study was approved by the Institutional Review Board of Marshfield Clinic Research Foundation. A 29-year-old white woman (gravida 2, para 0, abortus 1) had a Pap smear diagnosis of AGC and high-grade squamous intraepithelial lesion (figure 1). The pathologist made a recommendation for colposcopy with endocervical biopsy. One month later the patient had a positive pregnancy test.

The patient denied use of tobacco, alcohol or drugs, and had no history of abnormal Pap smears, gynecologic surgery, or sexually transmissible diseases.

Figure 1. High grade squamous intraepithelial lesion (squamous carcinoma *in situ*) on Pap smear (Papanicolaou stain, x400).

Figure 2. Cervical biopsy showing endocervical adenocarcinoma *in situ* (thick arrow) and adjacent severe squamous dysplasia (CIN III) (thin arrow) (H&E, x200).

She had no family history of breast, colon, or gynecologic cancer. The patient had a 2-year history of infertility (oligomenorrheic with irregular menses).

Sixteen months earlier the patient was evaluated for abdominal pain and discomfort related to menses. Pelvic examination was negative. Abdominal computerized tomography, ultrasound, and Pap were all normal. Five months prior to the current pregnancy, the patient was treated with metronidazole gel for bacterial vaginosis. At the time of abnormal Pap diagnosis, the patient was using vaginal progesterone suppositories for infertility.

Figure 3. Residual endocervical adenocarcinoma *in situ* on the cone biopsy with focal severe squamous dysplasia (CIN III) and negative margins (H&E, x100).

In addition to 2 exocervical biopsies at the transformation zone, a colposcopy was performed with cytobrush sampling of the endocervical canal (figure 2). Biopsies showed dysplastic endocervical epithelium with adenocarcinoma *in situ* (AIS) and areas of severe squamous dysplasia (CIN III). Additional Pap smear review revealed high-grade squamous intraepithelial neoplasia and atypical endocervical cells favoring adenocarcinoma. No features diagnostic of frankly invasive disease were found.

Cold knife conization of the cervix was performed at 11 weeks gestation. Pathology of the conization specimen showed complete excision with AIS involving endocervical glands and focal moderate to severe squamous dysplasia (CIN II to III) (figure 3). Ultrasound showed normal fetal activity and a normal amount of amniotic fluid.

Pap smears at 28 and 36 weeks gestation and postpartum were normal. The patient was advised to avoid another pregnancy until she had at least two normal Pap smears after delivery.

Discussion

Our case showed evidence of both squamous cell abnormalities and AGC. According to the 2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities,²⁴ nearly half the patients with biopsy-confirmed AIS have a coexisting squamous abnormality and, therefore, the presence of a coexisting squamous abnormality does not change the management of women with AGC or AIS.^{21,24-26} AGC is a significant indicator of more serious lesions, such as high-grade preinvasive squamous disease, AIS, and invasive adenocarcinoma.^{1-3,8-16} This case illustrates that AGC found upon Pap smear during

Management of AGC in Pregnancy

* Endocervical curettage (ECC) not possible in pregnancy.

** Long-term surveillance: repeat Pap smear every 4-6 mo until 4 normals obtained, then annually.

Figure 4. Algorithm for management of atypical glandular cells (AGC) in pregnancy.

a pregnancy can be associated with significant pathology for which an aggressive management approach is warranted.

The Bethesda system classifies AGC as “glandular cells that demonstrate nuclear atypia appearing to exceed reactive or reparative changes but lacking unequivocal features of adenocarcinoma.”²⁷ AGC interpretations span from benign, originating in endometrial, endocervical or unqualified sources, to *favor neoplasia* indicating suspicion for AIS or adenocarcinoma.²⁸

Identifying AGC in pregnancy is particularly difficult.^{10,29,30} Cytologic changes associated with pregnancy and the postpartum period, endocervical gland hyperplasia, and/or Arias–Stella reaction, are benign findings that may be misidentified as *in situ* or invasive endocervical adenocarcinoma. Use of the cytobrush may falsely increase reports of AGC, but the ability to provide a rapid initial interpretation is an advantage.³¹ If known, the pathologist must be informed of the pregnancy status of the patient. The Arias-Stella reaction has been described as early as 22 days after the last menstrual period.

Following a confirmatory reading of AGC on the cervical smear, colposcopy with directed biopsy and endocervical curettage (ECC) are indicated in standard guidelines.^{14,16} Colposcopically directed biopsy is safe and reliable in evaluating pregnant patients with AGC,³² but ECC cannot be performed in pregnancy. Alternatively, the cytobrush can be used (figure 4).

If the colposcopy with directed biopsy is negative with an initial Pap reading of AGC not otherwise specified, a Pap smear must be repeated every 4 to 6 months until four normals have been obtained, and then annually. If there is persistent, unexplained AGC or biopsy positive for AIS, adenocarcinoma, or microinvasive SCC, a cone biopsy is necessary.

A conization is required, unless cancer is diagnosed, if the colposcopy is negative and the initial Pap smear favors neoplasia. The rate of positive margins or recurrence for cervical AIS is significantly less when a cold knife conization is performed as opposed to a large loop excision

of the transformation zone.²¹ A narrow cone incorporating the entire endocervical canal (2.0 cm to 2.5 cm) should be carefully performed to avoid disrupting the endometrium or fetal membranes.^{1,9,12,14,16,33,34}

For conization under either spinal or general anesthesia, tocolytic therapy with nonsteroidal anti-inflammatory agents should be used to prevent contractions. Risks of cone biopsy specific to pregnancy include preterm labor, miscarriage, bleeding, premature rupture of membranes, and chorioamnionitis. A large biopsy could result in cervical stenosis or cervical incompetence.³⁵

Squamous intraepithelial neoplasia and microinvasive squamous cell carcinoma can often be treated with cervical conization. Endocervical curettage should not be performed during pregnancy. Treatment for any grade CIN should be delayed until after pregnancy. If biopsy-proven CIN II or III are seen in early pregnancy, repeat colposcopy should be considered later in pregnancy to rule out lesion progression.³⁶⁻⁴⁰ Multifocal adenocarcinoma is more challenging. Microinvasive adenocarcinoma may involve lymph node metastases and deeper invasion. Treatment involves radical hysterectomy with bilateral pelvic lymphadenectomies. In the pregnant patient, a radical hysterectomy with the fetus *in situ*, or pregnancy termination prior to the radical hysterectomy is recommended. After 24 weeks gestational age, steroids should be administered for fetal lung maturity followed by a Caesarean section and radical hysterectomy.

If only AIS is identified on a cone specimen and completely excised, close follow-up with regular Pap smears for the remainder of the pregnancy and then, every 4 months for 2 years and annually afterwards, is required. Where no evidence of invasion exists, no further treatment is needed.^{14,16,33,41} For patients with positive margins, no evidence exists that would indicate an advantage of repeat conization during pregnancy in an attempt to obtain clear margins. Negative margins, while promising in young women and if a 10 mm clear margin can be obtained,^{42,43} are no assurance of freedom from disease.⁴⁴⁻⁴⁷ Conversely, positive margins are not universally indicative of residual AIS.⁴³ Some warn against a potential risk of overtreatment and causing unnecessary stress in the patient if further treatment is based solely on the status of the cone margins.⁴⁸ Repeat conization might be warranted only if microinvasive disease or invasive carcinoma that would alter the timing of delivery were highly suspected.⁴⁹ With clear, unevaluable, or positive margins, long-term surveillance is warranted for cervical AIS.⁵⁰ In our case, the added presence of high grade squamous intraepithelial neoplasia (CIN III) is further reason for continuing surveillance in this patient.⁵¹

Women with AIS of the cervix treated with conization inconsistently have residual disease in the uterus, regardless of positive or negative margins.^{35,52-54} Ironically, many have residual disease that will remain clinically insignificant.¹

Conclusion

Despite broad diagnostic parameters and low AGC incidence, significant disease can be found and treated early, and successfully, in both pregnant and non-pregnant patients.^{6,16} With the incidence of this diagnosis increasing, the potential for continued impact on women's health is significant. While AGC subclassifications and treatment outcomes are studied, an aggressive management and surveillance approach is warranted in both pregnant and non-pregnant patients.¹

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