

Management of Adenocarcinoma In Situ of Cervix in Pregnancy

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Abstract

Adenocarcinoma in situ is one of the premalignant lesions of the cervix and its incidence is believed to be increasing while the pathogenesis of the disease is not clearly understood. Management of Adenocarcinoma in situ (AIS) unlike carcinoma in situ (CIS) has not been clearly described in the current literature.

Here we describe conservative management and serial colposcopy of two pregnant women with adenocarcinoma in situ of the cervix. Both of the cases were diagnosed initially with abnormal Pap smears and were confirmed by colposcopic directed biopsy. None of the patients agreed with any invasive procedure during pregnancy and both of them were followed with serial colposcopy. None of the lesions showed any evidence of progression. All cases underwent cold knife cone biopsies in their postpartum period. Hysterectomy as the final treatment has been done in both cases with no evidence of progression of the disease during pregnancy. We concluded that adenocarcinoma in situ of the cervix during pregnancy could be managed conservatively with definite treatment postponed till after delivery.

Keywords: AIS, CIS, Pregnancy

Introduction

Hepler et al first described adenocarcinoma in situ (AIS) of the cervix in 1952 when reviewing invasive adenocarcinoma of the cervix (1). One year later Friedell and McKay reported two cases of squamous cervical lesion with concomitant cervical AIS (2). The prevalence of the disease has been reported to be between 1/8000 and 1/475,000 in the different literatures (3-6).

Some sources have stated that adenocarcinoma in situ of the cervix is an under-diagnosed lesion based

on the fact that the ratio of invasive adenocarcinoma of the cervix to adenocarcinoma in situ of cervix is 10 to 1 (7). As a result of the difficulty in distinguishing adenocarcinoma in situ from invasive adenocarcinoma, AIS can be over diagnosed as invasive adenocarcinoma. Also, under diagnosis of AIS of the cervix is common in lesions high in the cervical canal or those involving only the deep endocervical cleft glands, which are missed by Pap smears (6,7).

Pathologic results suggesting adenocarcinoma in situ require further evaluation with an excisional cone biopsy extending deep into the canal to confirm the diagnosis and exclude the presence of invasive adenocarcinoma (8). Treatment for positive endocervical margins is less controversial. Due to their risk of residual disease and a higher chance of invasive adenocarcinoma, definitive therapy with hysterectomy should be strongly recommended. Patients who desire

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future fertility should have repeated cones until negative margins are seen and should then be followed closely.

With negative margins and negative endocervical curettage results on the cone biopsies, conservative management can be acceptable with close follow-ups (repeated Pap smears and endocervical curettages every 3 to 6 months for at least 1 to 2 years) (9). Management of AIS in pregnancy has been addressed by a few reports before, however CIS and progression of different stages of CIN have been reviewed. To our knowledge, the total number of AIS cases reported in pregnancy comes to 11 (including ours) although the clinical information during pregnancy is available only in 7 cases and management of AIS is reviewed in only four cases (10). The present data supports the view that if the invasive carcinoma can be excluded, definitive therapy can safely be deferred until after delivery.

CASE 1

A 37-year-old G7P1-1-4-1 (one term delivery – one preterm – four abortions - one live child) visited her OB GYN on 23.7.2002 at 12 weeks gestational age (GA) for her regular Pap smear which was consistent with high grade squamous intraepithelial lesion (HGSIL) with atypical endocervical cells suggested carcinoma in situ (CIS) and adenocarcinoma in situ (AIS) respectively. Her past obstetrical history was significant for one previous term normal vaginal delivery and a preterm vaginal delivery secondary to incompetent cervix. Patient underwent a colposcopy with biopsy of microscopic lesions at 6 and 9 o'clock on 17.9.2002, which were consistent with endocervical adenocarcinoma in situ. Pelvic MRI did not reveal any cervical lesions. A cerclage was placed at 14 weeks. The Patient refused conization and was followed by repeated colposcopies and a second biopsy of the cervix on 17.1.2003 reconfirmed AIS.

She delivered on 21.1.2003 at 38 weeks by cesarean section and the cerclage was removed. The cold knife cone biopsy on 25.2.2003 was consistent with invasive adenocarcinoma with 2.5mm depth extending to endocervical margins and horizontal spread of 15mm. The Patient did not desire future fertility and underwent a type III radical hysterectomy on 18.3.2003. Final pathology revealed minute foci of residual adenocarcinoma in situ with no evidence of invasion and negative lymph nodes.

The patient has been followed-up with serial Pap

smears since and has not developed any abnormality or sign of recurrence.

CASE 2

A 34-year-old white female G1P0 presented on November 1998 at 17 weeks GA with an abnormal Pap smear which was consistent with HGSIL. Colposcopy was performed on 02.1999 and revealed lesions at 11-12 O'clock and 4-7 O'clock which were biopsied. Biopsies were consistent with adenocarcinoma in situ of the cervix with no evidence of invasion which was confirmed with pelvic MRI. Treatment options were discussed with the patient and she refused conization and decided to be followed-up with serial colposcopies every 4-6 weeks. Multiple colposcopies did not reveal any signs of progression. She delivered via cesarean section and postpartum exam revealed the lesion to be unchanged. A cold knife cone on 09.1999 was consistent with AIS with focal intestinal metaplasia and negative margins with concurrent cervical intraepithelial neoplasia II (CIN II) and negative endocervical curettage.

The patient desired future fertility and was followed-up with Pap smears every 3 months. Three consecutive pap smears were negative. The fourth one on 09.2000 was consistent with atypical glandular cells of undetermined significance (AGUS). Colposcopy was negative and endocervical curettage was inadequate for evaluation. Laser conization on 10.2000 was consistent with CIN II and negative margins. Patient was followed-up with serial pap smears until 22.4.2003 when her Pap smear which was consistent with low grade squamous intraepithelial lesion (LGSIL) could not rule out high grade squamous intraepithelial lesion (HGSIL). Colposcopy was inadequate at this time and since there was no cervical tissue left for conization and due to her request, patient underwent a total abdominal hysterectomy on 2.6.2003. The hysterectomy specimen did not show any evidence of residual disease. The patient has been followed-up with serial Pap smears and has not shown any evidence of recurrence.

Discussion

The incidence of cervical AIS has been reported by multiple studies to be increasing. Pathologists' awareness of the lesion, increased prevalence of HPV 18 and/or an increase in the use of oral contraceptives has been considered as the causes for increase of incidence (5, 6). Improved sampling of the transfor-

Table 1: Residual disease and cone biopsy margin status

Author	Residual Disease	
	Negative Margins	Positive Margins
Poynor et al.	4/10 (40%)	3/8 (38%)
Hopkins et al.	1/7 (14%)	4/5 (80%)
Widrich et al.	0/3 (0%)	9/14 (64%)
Denehy et al.	2/7 (29%)	7/10 (70%)
Wolf et al.	7/19 (37%)	10/21 (48%)
Goldstein et al.	13/43 (30%)	8/18 (44%)
Bertrand et al.	0/4 (0%)	0/3 (0%)
Im et al.	4/9 (44%)	5/6 (83%)
Anderson and Arffmann.	0/4 (0%)	2/4 (50%)
Nicklin et al.	2/11 (18%)	5/11 (46%)
Ostor et al.	2/8 (25%)	9/12 (75%)
Azodi et al.	5/16 (31%)	9/16 (56%)
Cullimore et al.	-	1/8 (13%)
Shin et al.	1/16 (6%)	13/21 (61%)
Poynor et al.	41/157 (26%)	85/157 (54%)

* Negative endocervical margin patients were managed with cone biopsy (With permission of Dr. Krivak).

mation zone, endocervix with the cytobrush and improved cytological characterization of AIS of the cervix make the diagnosis easier (11). Based on cytoplasmic characteristics various subtypes of AIS have been described, including endocervical, intestinal, endometrioid, and mixed adenosquamous.

The pathogenesis of cervical AIS is not clearly understood. The progression of squamous cell carcinoma in situ from dysplasia to invasive disease is well-defined (3, 4) however, the infrequency of AIS has made it difficult to delineate the natural history of glandular dysplasia. Specific clinicopathologic characteristics of AIS have suggested that there may be parallel patterns of development between invasive adenocarcinoma and its squamous counterpart.

Adjacent foci of adenocarcinoma in situ have been identified in many cases of early cervical adenocarcinoma, and progression to invasive adenocarcinoma has been reported after conservative treatment for AIS (2, 8, 12) but the existence and progression of glandular dysplasia similar to squamous intraepithelial lesions of the cervix has yet not been identified due to insufficient data.

Any pathologic result suggesting AIS requires further evaluation with an excisional cone biopsy extending deep into the canal. Cold knife cone, laser excisional cone, and large loop electrode excision procedure (LEEP), large loop excision of the transformation zone (LLETZ) are all acceptable methods for excisional biopsy of the cervix. Comparison of cold knife cone with LEEP in four studies has suggested that Cold Knife Cone is a better diagnostic

and therapeutic method for AIS and has a lower positive endocervical surgical margins rate (5, 7, 13, 14).

The relationship between cone biopsy margins status and residual or recurrent disease has been shown to be different for cervical AIS than Squamous CIS. Although the different rates of residual disease after conization have been reported, all authors have stated significant higher residual rates with LEEPs compare to cold knife cone as can be seen in Table 1 (9).

In all of the studies, residual disease rate was significantly higher once endocervical and even exocervical margins were positive. All authors have suggested either cold knife cone or hysterectomy as an additional therapy for patients with positive margins. The occurrence of persistent disease after a negative cone margin may be explained by the multifocal character of the lesion resulting in “skip” lesion or by inadequate histopathologic study of the cone specimen (9).

Previous studies by Im et al. (14) and Anderson and Arffmann (7) had earlier shown a high rate of residual disease even with negative endocervical margins. Poynor et al. (11) and Wolf et al. (13) confirmed these rates. Azodi et al. (15) reported residual rates of 35% in their series from Yale. They all suggested hysterectomy as the optimal treatment for AIS due to high residual rates, inadequate techniques for detecting residual AIS after cone biopsy, and unknown preinvasive lead time to develop invasive cervical adenocarcinoma. Hysterectomy is probably the most acceptable treatment of choice for cervical

Table 2: Disease recurrence after conservative management

Author	No. of patients treated conservatively	Disease Recurrence
Bertrand et al.	5	0
Poynor et al.	15	7
Hopkins et al.	3	0
Widrich et al.	38	6
Denehy et al.	19	1
Wolf et al.	6	2
Anderson & Arffmann.	23	0
Im et al.	2	0
Ostor et al.	53	0
Nicklin et al.	12	0
Luesley et al.	7	1
Houghton et al.	11	0
Azodi et al.	8	1
Shin et al.	95	9
Total	297	27 (9%)

(With permission of Dr. Krivak)

AIS unless preservation of fertility is a strong concern.

With reference to Table 2, which shows a review of 14 studies, additional surgery was required in 27 of 297 patients (9%), with the disease recurrence rate found in each study ranging from 0% to 46% (9).

Shin et al (16) followed 95 patients treated with conservative therapy for 6 to 137 months. Ostor et al. (17) studied 53 patients who elected conservative management and followed clinically from 1 to 16 years, no patient developed recurrent disease. In their studies they concluded:

1) In patients who desire to preserve future fertility conservative therapy should have an excellent outcome if they have negative cone biopsy margins.

2) Patients with positive margins should undergo a second excisional procedure to exclude residual and/or invasive adenocarcinoma due to their higher risk for residual AIS.

3) Patients who undergo conservative management should be followed closely for disease recurrence.

Griffin et al. (10) reported 3 patients with AIS of the cervix in pregnancy. They performed cold knife conization during pregnancy and postpartum hysterectomy in 2 patients. In the third patient because of the advanced gestational age, conservative management was preferred. No progression or residual disease was reported overall.

Krivak et al. (8) reported a case of recurrence in vaginal cuff after hysterectomy on a patient with positive margins but no residual disease in hysterectomy specimen.

Treatment for the disease recurrence included radical upper vaginectomy with parametrectomy and postoperative pelvic radiotherapy.

In our cases of AIS in pregnancy, both of the cases were diagnosed initially with abnormal Pap smears and were confirmed by colposcopic-directed biopsy. None of the patients agreed with any invasive procedure during the pregnancy and both of them were followed with serial colposcopy. None of the lesions showed any evidence of progression. Both cases underwent cold knife cone biopsies in their postpartum period.

Although our first case was diagnosed with invasive adenocarcinoma and was treated accordingly, we had no evidence suggesting that the progression from AIS to invasive adenocarcinoma occurred during pregnancy due to lack of conization during pregnancy. Our second case was treated with cold knife cone with negative margins. The attempt was made to manage her conservatively but once she had recurrent dysplasia, hysterectomy was performed based on her request.

In conclusion we believe that AIS in pregnancy can be managed conservatively and similar to CIS if diagnosed after second trimester. According to Griffin et al. and our study, there was no sign or evidence of progression. It seems that postponing the treatment to the postpartum period does not worsen the outcome of the disease. We suggest a thorough discussion of risk and benefits with the patient and conization of the cervix in any evidence of invasive disease. Due to the invasive character of the disease a cold knife

conization of the cervix is the procedure of choice during the postpartum period.

We still recommend hysterectomy as the best treatment option for the patients not desiring future fertility but conservative management in the patients who desire future fertility and have negative margins is an acceptable option with close follow-up and Pap smears every three months for at least one year. We also acknowledge the limitations of our conclusions due to the small amount of cases and hope that future studies provide more definite suggestions based on retrospective or prospective studies.

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