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Management of Cervical Intraepithelial Neoplasia 2 in Adolescent and Young Women

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Abstract

Study Objective—To evaluate regression rates among adolescents (aged ≤ 21) with CIN 2 managed expectantly and to determine factors associated with disease regression.

Design—Cohort study using a colposcopic database of 2,996 women seen between August 1999 and November 2005

Setting—Colposcopy clinic in urban, tertiary care medical center

Participants—Adolescents with CIN 2. Routine management consisted of two options: immediate treatment or repeat colposcopic evaluation in 6 months.

Main Outcome Measures—For those managed conservatively, regression was defined either as a subsequent normal colposcopy and/or biopsy and at least 2 smears read as negative for epithelial abnormality or at least 3 consecutive negative smears if repeat colposcopy was not performed. Demographic information, including age, was assessed to determine possible associations with disease regression.

Results—Of the 93 adolescents, 53 (57%) elected to undergo immediate treatment with a diagnostic excisional procedure, and 40 (43%) chose management with colposcopic follow-up. Of those treated, high-grade disease (CIN 2+) was found in 40 (75%). Of the 36 young women followed conservatively (4 were lost to follow-up), regression after a median follow-up time of 378 days was documented in 14 (39%). Of the 22 adolescents not fulfilling our criteria for regression, only 3 had evidence of CIN 2 or worse during follow-up. The remaining 19 had either CIN 1 or mildly abnormal cytologic results. Kaplan-Meier survival estimates indicated younger age (≤ 16 years) tended to be associated with decreased time to regression.

Conclusion—Based on significant regression of CIN 2 among adolescent women, primary management in this population should consist of cytologic and colposcopic follow-up.

Keywords

CIN 2; adolescent; management

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Introduction

Cervical cytology has become a well-established screening tool for cervical neoplasia and cancer (1), and recent changes in the cytologic classification system and recommendations for management of those found to have abnormalities should reduce the number of abnormal smears as well as unnecessary procedures. At present, consensus guidelines call for colposcopic examination of the cervix for women with certain cytologic squamous abnormalities. These abnormalities include atypical squamous cells of undetermined significance (ASC-US) with evidence of high-risk human papillomavirus (HPV) infection, low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL) (2). For specific populations, however, the recommendation for immediate colposcopy in the context of mild cytologic abnormalities does not apply. For example, postmenopausal women with ASC-US or LSIL and evidence of atrophy may undergo a trial of vaginal estrogen therapy with repeat cytology in lieu of immediate colposcopy. Less invasive management (repeat cytology or HPV testing) is also an option for adolescents with *ASC-US and LSIL* (2,3).

Treatment guidelines, however, have remained largely unchanged. The current recommendation is for all patients with high-grade cervical intraepithelial neoplasia (CIN 2 or 3) to undergo *treatment with either ablative or excisional procedures* (the choice depending on the adequacy of the colposcopic examination) to reduce the potential risk of cervical cancer (4). However, CIN 2, and to a lesser extent, CIN 3, can clearly regress. In fact, while approximately 20% of adult women with CIN 2 will eventually progress to CIN 3 or cancer, nearly half will resolve if left untreated (5). Moreover, treatment is not without complication and the possibility of long-term negative health outcomes. Given the potential morbidity of treatment and the possible regression of moderate neoplasia, alternative management strategies have been advocated for the adolescent population. Recent recommendations call for conservative management, and not immediate treatment, for adolescents with high-grade intraepithelial lesions (HSIL) not confirmed with biopsy (2), while others have suggested a similar management scheme for adolescents with biopsy-proven CIN 2 (3,4,6). The purpose of this study, then, was to determine the regression rate of CIN 2 among adolescents managed expectantly, to evaluate potential factors associated with regression in this population and to document the rates of high-grade disease among those treated surgically.

Materials and Methods

Beginning in 1999, women seen in the Colposcopy Clinic at Women and Infants' Hospital in Providence, Rhode Island have been entered into a colposcopic database. This database of 2,996 patients was searched for cases of adolescent and young women (defined as those aged 21 or younger) referred for colposcopy between August 1999 and November 2005. Patients were included in the study if they met the age criteria at the time of their initial qualifying histologic abnormality. Inclusion required CIN 1/2 or CIN 2 on biopsy after any squamous abnormality (ASC-US, ASC-H, LSIL or HSIL). Any adolescent with CIN 2/3, CIN 3 or worse was excluded from this analysis. Pregnant adolescents were included in the study population. Women and Infants' Institutional Review Board approved the use of the database, and the medical record and computerized record review, for this study in October 2004 with annual renewal allowing for update of the database obtained in December 2005.

The database includes information on a number of demographic variables (including age, race/ethnicity, parity, smoking history, HIV status, age at first coitus, number of lifetime sexual partners as well as histories of prior abnormal cytologic smears or biopsies). In addition to all cytologic and histologic results, colposcopic data also recorded includes the adequacy of the examination, specific colposcopic findings (e.g., acetowhite epithelium, abnormal vasculature) and overall colposcopic impression. The dates and results from all subsequent evaluations and

from any excisional procedures were also extracted from the database. If pertinent data was not available from the database, study authors pulled patient records and reviewed computerized pathology records to complete the data collection process. All such results were entered into the database prior to final analysis.

Cervical cytologic smears were obtained using fluid-based thin-layer cytology and were generated from PreservCyt (Cytoc Corporation, Marlborough, MA) samples by use of a semiautomated processor (ThinPrep 3000; Cytoc Corporation). Colposcopic examinations were performed by resident physicians and nurse colposcopists under the guidance of attending physicians, and all histologic specimens were placed in formalin prior to transport to pathology. Women and Infants' Hospital cytotechnicians and pathologists evaluated all specimens and classified them according to 2001 Bethesda terminology or the CIN histologic grading system as appropriate.

For adolescents and young women found to have CIN 1/2 or CIN 2 on biopsy, providers routinely discussed two possible options, expectant management or immediate treatment, with each patient and parent or guardian where appropriate. Following counseling with the provider, the final decision rested with the patient. Recommended follow-up in the latter group consisted of repeat colposcopy in 4-6 months. The primary outcome for the expectant management group was the regression of disease following the initial diagnosis of CIN 1/2 or CIN 2. Regression was defined either as subsequent normal colposcopy (and normal biopsies if such were performed) and at least 2 smears read as negative for epithelial abnormality or at least 3 consecutive negative smears if repeat colposcopy was not performed. Progression was defined as CIN 3 or cancer on biopsy. Women who did not meet the criteria for regression or progression were considered to have persistent disease. In the analysis, women fulfilling the criteria for regression were compared to those with progressive or persistent disease. For patients undergoing immediate treatment with either loop electrosurgical excision procedure (LEEP) or the Fischer Cone Biopsy Excisor, final specimens were evaluated for the presence and severity of neoplasia.

Data were analyzed using descriptive statistics. Differences in characteristics, indications for colposcopy and treatment method for cervical disease by age were compared by Student's t-test for continuous variables and chi-square or Fisher's exact test for categorical variables. The cumulative probability of a CIN 2 lesion regressing among adolescents who were followed with repeat colposcopy was estimated using Kaplan-Meier survival curves as a function of the length of follow-up for the group as a whole and then stratified by age (≤ 16 years, 17-19 years, 20-21 years) and initial histologic diagnosis (CIN 2 versus CIN 1/2), with the log-rank test being used to compare the equality of the survivor functions of the respective groups. Relative rates of regression and 95% confidence intervals were estimated comparing age, race/ethnicity, smoking status and parity. All analyses were performed using STATA 8.0 (College Station, TX).

Results

Ninety-three (10%) of the 947 adolescents in the colposcopy database were found to have CIN 2 on biopsy (cervical lesions classified as CIN 1/2 were found in 28 of the 93 (30%)). Of the 93 young women, 53 (57%) chose to undergo immediate treatment, while the remaining 40 (43%) were scheduled for colposcopic follow-up in 4-6 months. Of the 40 adolescents in the expectant management group, 4 (10%) did not return for a repeat evaluation at Women and Infants. In Table 1, characteristics of the 93 young women, in aggregate and stratified by age (≤ 16 , 17-19 and 20-21), are presented. In general, the population was racially/ethnically diverse and approximately half (41/93 or 45%) were current smokers. Compared to their older counterparts, those aged 16 and under were significantly more likely to have been younger at

the time of sexual initiation (mean age 13.1 versus 15.1 for those aged 17-19 and 16 for women aged 20-21; $p<.01$) and to have had fewer sexual partners (mean number of partners was 3.9 for those aged 16 and younger compared to 6.9 for women aged 20-21; $p=.03$). Of the 36 adolescents in the expectant management group, 5 were pregnant at the time of detection of CIN 2. Three subsequently showed regression, and two had limited follow-up without evidence of persistence or progression.

Of those undergoing immediate treatment, CIN 2+ was confirmed in 40 (75%). Seven women (13%) had negative final pathologic specimens. The finding of CIN2+ on the cone specimen did not differ by the histologic indication for treatment (7/9 or 78% of those with CIN 1/2 had CIN 2+ on LEEP versus 33/44 or 75% with CIN 2) or by the cytologic indication for the initial colposcopy (full data not presented). In the group electing to undergo repeat evaluation, the median length of follow-up was 378 days. Regression was documented in 14/36 (39%), with the youngest adolescents experiencing the greatest rates of regression (60% compared to 29% of those aged 20-21). This observation, however, was not statistically significant (RR 1.94, 95% CI (0.3-11.5)). Other factors potentially associated with regression, such as lesion type (regression decreased for CIN 2 as compared to CIN 1/2: RR 0.60 (0.17-1.49)) and number of lifetime sexual partners (regression decreases with each additional partner: RR 0.93 (0.81-1.06)) were not found to be significant. Of the 22 patients who did not experience regression by our study definitions, 19 had evidence of mild cytologic (ASCUS, LSIL) or histologic changes (CIN 1) or they did not fulfill the study criteria (for example, although the repeat colposcopic impression and Pap smear were normal, a second evaluation had not taken place at Women and Infants' Hospital). Persistent CIN 2 or progression to CIN 3 was rarely encountered in this expectant management arm, occurring in only 3 young women (8%).

Overall, nearly 50% of women conservatively managed experienced regression within 2 years of follow up, and over 75% had regressed within 3 years of diagnosis with CIN 2 (Figure 1). The youngest adolescents (≤ 16 years) experienced disease regression at a faster rate than did adolescents aged 17 and older (Figure 2). Over 75% of the youngest adolescents had regressed within 2 years of follow up, while less than 50% of the 17-19 and 20-21 year olds had regressed at that point. However, the time to regression curves between age groups were not significantly different ($p=.38$). Regression rates after 2 years of follow up were similar when comparing women who had CIN 2 to those with CIN 1/2 at diagnosis (Figure 3). However, nearly all adolescent and young women with CIN 1/2 experienced disease regression within 3 years of initial diagnosis, while approximately 25% with CIN 2 at diagnosis did not experience regression by the end of the same follow up period. Nonetheless, differences in the Kaplan-Meier curves for the 2 groups were not statistically significant ($p=0.28$).

Discussion

Infection with oncogenic human papillomavirus is extremely common in adolescent women. Approximately 70% of sexually active young women and adolescents will be infected at some point during this period (7), and nearly a quarter will develop LSIL (8). The majority of HPV infections in the adolescent population, however, are transient (7,9,10). Furthermore, rates of regression among those with clinically evident and mild manifestations of infection (LSIL) are high and progression is rare (11). In a population of young women with LSIL, Moscicki found that over 60% experienced regression of their mildly abnormal cytology within 12 months, a proportion which increased to over 90% by three years (12). Based on the accumulating data, then, routine colposcopy for adolescents with LSIL, although currently recommended as an option, is most likely unnecessary, and less invasive management schemes, including serial repeat cytology or oncogenic HPV DNA testing, appear preferable.

The management of high-grade disease is less clear. Although adolescents with HSIL and non-confirmatory biopsies can be managed expectantly according to recent guidelines (2), treatment is generally recommended for cytologic-histologic discrepancy. Cervical conization, however, is not without significant risk and has been associated with cervical stenosis (13), as well as poor obstetric outcomes. Subsequent pregnancies are at risk of second-trimester pregnancy loss and incompetent cervix (14,15), preterm labor (14), PPROM (16), and preterm delivery (14,17-20). Despite the common use of less radical excision procedures, the risk of adverse pregnancy outcomes has been linked, in a number of studies, to LEEP procedures (16,19,21). Such risks are of particular concern for adolescents, many of whom have neither begun nor completed childbearing.

The significant rate of regression seen in our population of adolescents with CIN 2 adds to the growing body of evidence that suggests that expectant management for young women with CIN 2 is indeed a reasonable option, particularly in the younger adolescents. Although the majority of the adolescents treated for CIN 2 in fact had high-grade disease ($\geq$ CIN2) on final pathologic specimens, approximately 40% of the adolescents with the same diagnosis experienced complete regression when managed with colposcopic or cytologic follow-up. Furthermore, evidence of persistent CIN 2 or progressive disease was seen in only 8% of the study population. The remaining 22 women or 52% of the cohort either had no evidence of disease (normal cytology, normal colposcopy) but had not completed a second follow up visit, or had evidence of mild cytologic and/or histologic abnormalities. Given such findings, regression would be expected to occur in the majority of these 22 young women. Even a conservative assumption that only half of women still in follow-up will fully regress to normal (i.e., 11 of the 22) would increase the current observed regression of 40% to nearly 70%. High rates of regression, coupled with potential adverse pregnancy outcomes associated with therapy for cervical neoplasia, should lead to reconsideration of the role of immediate treatment for biopsy-proven CIN 2 in adolescents and young women.

Although 2001 Consensus Guidelines recommend either excision or ablation of biopsy-proven CIN 2 and 3, the authors also suggested that observation may in fact be an acceptable management strategy for appropriately counseled adolescents with biopsy proven CIN 2 given the prevalence of HPV-related lesions and the rarity of invasive carcinoma in this population (3). This study demonstrates a significant rate of regression, defined by strict criteria requiring evidence of repetitively normal findings, in a cohort of expectantly-managed adolescents with biopsy-proven CIN 2 and offers evidence to support the practice of conservative management for CIN 2 in adolescent and young women. In addition to the size of the study population, the excellent compliance with expectant management allowed us to demonstrate the high rate of regression in this cohort of young women.

Given accumulating evidence that CIN 2 represents a heterogeneous collection of lesions (22), we attempted to isolate potential predictive factors (e.g., very young age at diagnosis) associated with increased risk of regression. We were, however, limited in drawing conclusions when attempting to *further stratify the relatively small group of women undergoing conservative management* by age or by histologic diagnosis (CIN 1/2 versus CIN 2). Certain characteristics of the population may also limit the study's generalizability to all populations of similarly aged women. The retrospective nature of this study also imposes inherent limitations, such as inconsistent collecting and recording of patient characteristics. In general, the latter was rarely encountered, as the same data collection form was consistently used for all colposcopy patients. In addition, the high rates of compliance with follow-up observed in this study may differ in other populations of adolescents and young women. If compliance rates are poor, the ability of providers to confidently follow young women with CIN 2 may be limited, and expectant management may not be a viable alternative to treatment.

Based on the evidence of significant regression of CIN 2 in adolescents as well as the potential for complications in future childbearing, the practice of immediate treatment of CIN 2 should be reconsidered. Specifically, this study suggests that management with repeat colposcopy for adolescents and young women with biopsy-proven CIN 2 is feasible and should replace immediate treatment as the initial management option in this population. Further validation with sufficiently powered longitudinal studies is clearly warranted.

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Figure 1.
Time to disease regression for adolescents and young women with CIN 2 managed expectantly (n=36)

Figure 2.

Time to disease regression for adolescents and young women with CIN 2 by age category (n=36)

p-value for test of equality of survivor curves=0.38

Figure 3.

Time to disease regression for adolescents and young women with CIN1/2 versus CIN 2
p-value for test of equality of survivor curves = 0.28

Table 1

Sample Characteristics by Age

	Total (n=93)	<=16 N=12	17-19 N=38	20-21 N=43	p-value
Race/Ethnicity (n=91)					
Non-Hispanic White	47 (52%)	4 (36%)	20 (54%)	23 (53%)	
Non-Hispanic Black	18 (20%)	4 (36%)	5 (14%)	9 (21%)	
Hispanic	20 (22%)	2 (18%)	10 (27%)	8 (19%)	0.66
Other	6 (7%)	1 (9%)	2 (5%)	3 (7%)	
Current Smoker	41 (45%)	6 (50%)	19 (50%)	16 (37%)	0.46
Parity (n=91)					
Nulliparous	53 (57%)	10 (84%)	21 (58%)	22 (51%)	
1	25 (37%)	1 (8%)	13 (36%)	11 (26%)	
≥2	13 (14%)	1 (8%)	2 (6%)	10 (23%)	0.07
Mean age at first coitus (SD)	15.3 (2.0)	13.1 (1.5)	15.1 (1.4)	16 (2.1)	<0.01
Mean number of lifetime partners (SD)	5.2 (5.8)	3.9 (3.0)	3.9 (2.8)	6.9 (7.6)	0.03
Indication for colposcopy					
ASC-US	20 (22%)	2 (16%)	6 (16%)	12 (29%)	
ASC-H	4 (4%)	0	1 (3%)	3 (7%)	
LSIL	40 (43%)	5 (42%)	19 (53%)	16 (39%)	0.64
HSIL	25 (27%)	5 (42%)	10 (28%)	10 (25%)	
CIN 1/2	26 (28%)	5 (42%)	14 (37%)	9 (21%)	
CIN 2	67 (72%)	7 (58%)	24 (63%)	34 (79%)	0.19
Treatment					
LEEP	53 (57%)	6 (50%)	20 (53%)	27 (63%)	
Follow up	40 (43%)	6 (50%)	18 (47%)	16 (37%)	0.57