

Practice Improvement in Cervical Screening and Management (PICSM): Symposium on Management of Cervical Abnormalities in Adolescents and Young Women

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A symposium with the primary goal of identifying strategies to increase the adoption of evidence based consensus guidelines for cervical cancer screening and the management of abnormal cervical cytology and histology in adolescents and young women was held June 19–20, 2009 in Bethesda, MD at the National Institutes of Health (NIH), under the sponsorship of the American Society for Colposcopy and Cervical Pathology (ASCCP) and in partnership with the American Cancer Society (ACS).

The 2006 ASCCP Guidelines for the Management of Women with Abnormal Cervical Cytology and Cervical Cancer Precursors were developed at a consensus process comprising 146 experts representing 29 organizations and professional societies who met at the NIH. The guidelines contain special recommendations to manage abnormal adolescent cytology results. These recommendations have subsequently been adopted by ACOG. The guidelines identify adolescents, defined as females under the age of 21 years, as a special population requiring interventions based on evidence recognizing the natural history of abnormal cytology is different in adolescents than adults. Anecdotal reports and clinician

surveys verify under usage of the 2002 ACS [1] and 2003 American College of Obstetricians and Gynecologists (ACOG) guidelines [2], on when to initiate screening, and the 2006 ASCCP management guidelines for adolescents [3–5].

PICSM delegates, representing 22 organizations, reviewed the literature on cytologic abnormalities in adolescent and young women to identify where evidence was lacking, assess adherence to existing recommendations; and, based on these findings, addressed strategies to increase guideline usage in adolescents and young women. Consensus recommendations were achieved on key messages that needed to be disseminated and methods to disseminate and implement them were recommended. Supporting information, not available at the time of the symposium, has been added. The following summarizes the 9 presentations.

Guidelines for Screening and Management of Abnormal Cytology in Adolescents

The guidelines for when to begin screening, managing ASC-US/LSIL, ASC-H, and HSIL cytology and CIN 1, CIN 2, CIN 2,3 and CIN 3 histology [3, 4] in adolescents were reviewed. Key messages were: 1) HPV testing is not recommended under any circumstances for screening or management of adolescents; 2) ASC-US and LSIL should be managed similarly by repeat cytology alone

at 12 month intervals without colposcopy or HPV testing; and 3) CIN 1, CIN 2 and CIN 2,3 may be followed with observation rather than invasive therapies, whereas CIN 3 should be treated.

The Natural History of HPV Infections and CIN in Adolescents

HPV infections, ASC-US and LSIL are common in adolescents, appearing shortly after the onset of sexual activity [6–10]. There is good evidence that in adolescents more than 90% of HPV infections, LSIL cytology and CIN 1 lesions regress within 3 years [11–13]. This epidemiologic evidence strongly supports observation over intervention for adolescents with LSIL and CIN 1, but it should be recognized fifty percent of this group that clears an initial HPV infection will have a repeat HPV infection within 3 years [14]. With more than 70% of adolescents with ASC-US are HPV positive [15], making HPV testing not useful for triage in adolescent populations.

There is a high rate of CIN 2 regression in adolescents [16, 17] with 60% showing regression within 3 years. Progression to cancer, even among those with CIN 3, is negligible. There are no published studies in adolescents describing progression from CIN 2,3 to cancer. In woman ages 20–24 years the estimated annual progression rate from CIN3 to cancer in women is 0.5%, increasing throughout life to 10% per year for women 80 years and older [18].

The Burden and Challenges of Cytology, Colposcopy and Histology in Adolescents, and Risks for Cervical Cancer in Adolescents

The literature shows adolescents with ASC-US or LSIL cytology have the highest rate of high risk (HR) HPV but the lowest rate of cervical cancer [19–22]. SEER statistics show that from 1998–2006 an average of 14 cervical cancers occurred annually in girls aged 15–19 year olds, an incidence rate of 0.1 per 100,000 (Table 1) [21]. This rate is unchanged from that reported in 1973–77, which preceded the recommendation to start screening at age 18 or at first intercourse, whichever occurred earlier [23]. Because of this change in the age to begin screening, adolescent populations went from no screening to considerable screening.

There is no data showing screening women less than 21 years old impacts future rates of CIN 2,3. A recent study in England showed that screening women aged 20–24 years old had no detectable impact on reducing

Table 1. Annual Counts, Age-Adjusted Incidence Rates and Median Age at Diagnosis of Invasive Cervical Carcinoma Age: United States, 1998–2003*y

Age, y	Average Annual	Incidence Count (95% CI) Percent	Incidence Rate	Median age
All ages	10,846	8.9 (8.8–9)	100	47
Age, y				
0–14	0		0.0	
15–19	14	0.2 (0.1–0.2)	0.1	
20–24	123	1.6 (1.5–1.7)	1.1	
25–29	543	6.9 (6.7–7.2)	5.0	
30–34	1045	12.3 (12–12.6)	9.6	
35–39	1350	14.6 (14.3–14.9)	12.5	
40–44	1534	16.3 (15.9–16.6)	14.1	
45–49	1323	15.4 (15–15.7)	12.2	
50–59	1958	14.5 (14.2–14.7)	18.0	
60–69	1352	14.8 (14.5–15.1)	12.5	
70–79	1008	12.9 (12.6–13.3)	9.3	
≥80	595	11.2 (10.9–11.6)	5.5	

From: Watson M, Saraiya M, Benard V, Coughlin S, Flowers L, Cokkinides A, Schwenn M, Huang Y, Giuliano A. Burden of Cervical Cancer in the United States, 1998–2003. *Cancer* 2008;113(10 suppl):2855–64.

cervical cancer rates in women under the age of 30 years [24]. This is consistent with previous studies done in numerous countries following introduction of cervical screening. There was a dramatic reduction noted for all other age groups with regular cervical cytologic screening [25].

Although cervical cancer incidence rates peak at different ages for white, black and Hispanic women, the two studies, between 1995–1999 and 2000–2004, showed decreased rate of cervical cancer in all categories except Hispanic/all races women aged 15–24 years and non-Hispanic/other women aged 25–34 [26]. This suggests cervical cancer in adolescents and young women is uncommon and may not be prevented by early cytology screening. Why screening may be ineffective in the youngest age groups is not clear. One explanation is that cervical precancer arising in adolescents becomes invasive cancer quickly because lesions may be more aggressive. It is possible harm occurs from screening too early with resulting aggressive management of CIN in adolescents and young women. A special advisory committee in England recently recommended that the first invitation to screening not be before age 24.5 with the target for screening to begin at age 25 for just these reasons [18].

The biology of the adolescent cervix was reviewed. Squamous metaplasia is the normal replacement of cervical columnar epithelium with squamous epithelium. This process is most active during adolescence. The process of metaplasia appears to support HPV replication, explaining why adolescents have greater rates of HPV

infection [27]. Metaplasia in adolescents can also be confused with CIN at colposcopy, making this procedure less reliable for diagnosis and triage in this age group [28–31]. Cytology and histology are also more difficult to interpret in adolescents [32–36]. For example CIN 2 in adolescents is often down-graded after review by an expert pathologist. Understanding the natural history of HPV and CIN is important determining guidelines rather than making decision solely base on the abnormal cytology and histology.

The Risks of Over Management and Cervical Treatment of Adolescents

Reliable evidence shows cervical excision procedures can be harmful, increasing the risks of preterm delivery and low birth weight infants [37–40]. The studies of pregnancy outcomes following LEEP demonstrate a 2-3-fold increase in preterm birth [37–40]. In studies measuring excisional depth, the risk of preterm delivery was greater when the depth of excision was greater than 10 mm compared to those where it was less than 10 mm (RR 2.6, 95% CI 1.3–5.3) [39, 41]. There are no data demonstrating increased infertility [41]. Adverse psychological effects related to cervical cancer screening, evaluation of abnormal cytology results and treatment of CIN are reported [42–46], including negative effects on sexual functioning [47].

Data from the ALTS trial show large numbers of women are treated unnecessarily with LEEP for small lesions that may have been biopsied off at colposcopy or regressed by the time women were scheduled for treatment [32, 48–52]. Recent data shows more than 50% of CIN2,3 in women age 20–24 spontaneously regresses by age 25 without treatment [18, 53].

The Impact of HIV on the Natural History of HPV

HPV-induced cancers (including cervical, vulvar, vaginal, and anal) are more common in immunosuppressed individuals than in the general population [54]. HPV infections and persisting disease are also more common. Because of the poorer clearance of HPV, multiple HPV type infections are commonly found in HIV positive women [55], leading to increased rates of CIN 2,3 compared to the general population [56, 57]. Recurrent CIN is common in HIV positive women with few options for treatment except repeat LEEP, resulting in increased risks for adverse events. HAART does not alter the natural history of CIN in women [55]. We recommend slightly different guidelines in HIV positive

adolescents in two situations given the existing evidence [58]: 1) It is not recommended to wait 3 years after the onset of sexual activity for screening. 2) Because of the increased rates of CIN 2,3 and invasive cancer, HIV-infected adolescents with ASC-US or LSIL should have immediate colposcopy.

Similar to adolescents in the general population, HIV-infected adolescents with CIN 1 and CIN 2,3 should be managed with observation, cytology and colposcopy. Because of the high rate of recurrence, it is best to reserve treatment for CIN 3. As with all adolescents, HPV testing should not be used for triage or management in HIV-infected adolescents [3, 58].

Genital Warts and HPV Induced VIN

Genital warts are common in adolescent and young women and men [59–61]. Genital warts are benign with and commonly regress after 1–3 years [59]. Although it is presumed that treatment with successful lesion resolution decreases transmission, treatment is primarily aesthetic and based on patient preference [62, 63]. Treatment methods can be self-applied or provider applied [64, 65]. Patient ability to understand treatment options, along with patient preference, should be when considered treating adolescents with genital warts. It should be emphasized that the presence of genital warts does not change the natural history of CIN lesions, therefore recommendations on initial, interval screening, and the management of abnormal cytology should not be altered in adolescents with genital warts [3]. VIN in adolescents is seen but vulvar cancer is virtually non-existent [66]. Although there is limited data on VIN in adolescents, anecdotal reports and one study support conservative follow-up [66] or therapy for VIN with topical wart therapies including trichloroacetic acid (TCA) and imiquimod [67].

Barriers to Using Published Cervical Screening and Abnormal Cytology Management Guidelines

The challenges to implementing the guidelines are significant. Data suggest poor adherence to the ACS and ACOG screening guidelines are common [68]. In a provider survey conducted by the CDC, 50% of providers were screening 18-year-old virgins and 80% were screening 18 year olds who had initiated sex within the last month. When women were asked about cervical cancer screening, 60% of women who had initiated sex less than 3 years ago reported that they had had cervical cancer screening [69, 70]. These data clearly show that guidelines for initiating screening are not being widely used.

Obstacles to adherence to guidelines, include industry who has commercial interest in cytology and HPV testing products, government representatives legislating social mores, and a health care system that benefits from limiting spending by rationing care. Health care provider obstacles include a lack of awareness of guidelines, rejecting evidence, care by anecdote (I had a patient who....), loss of pretext for health screening, concern that clinical-patient relations may be altered with extended interval screening, time constraints (“It takes more time to explain why the test is not being done than doing the test.”), guidelines don’t apply to the provider’s population (not my patients...), underestimation of harm secondary to screening too early, low esteem for guidelines (cookbook medicine), medical-legal ramifications if the cancer is missed, marketing (consumers will go elsewhere), and economic benefits/threats (loss of income with decreased numbers of colposcopies).

A review of carrots and sticks have shown promise in improving compliance within medical provider organizations. Carrots to improve compliance include recording performance (provider report cards), positive peer pressure educators (champions), and financial rewards (pay for performance). Sticks include poor report cards, peer pressure, financial penalties, and sanctions. System wide opportunities for change include restricting benefits by age and/or by medical necessity. Prior authorization to vary from guideline recommendations might be required. The barriers to adopting guidelines are multiple, but economics, tradition and fear of change dominate. Change requires multi-level interventions including education, incentives, penalties, and consumer education. Planned Parenthood’s guideline implementation starts at the front desk with staff education. Clinicians need to be engaged through interactive education, clinical reimbursements, physician champions, and outcomes monitoring.

HPV Vaccines

The clinical trials data demonstrate the effectiveness HPV vaccine in non-exposed women [71–74]. There is no preventative or therapeutic benefit for women already infected with HPV vaccine types [75]. Therefore women who are positive by HPV DNA testing or serology for the vaccine’s targeted HPV types do benefit from the vaccine for those HPV types. To overcome this immunization guidelines should focus on pre-sexually active children and adolescents [48, 76]; unfortunately current CDC information shows less than 35% of the

target group have been vaccinated, with less than 25% receiving the recommended three vaccinations [77].

The Potential Impact of Vaccination on Screening Guidelines

By removing the most evident and threatening cytologic, colposcopic, and HPV testing results from cervical cancer prevention programs, vaccination will leave behind more equivocal and less predictive abnormalities, and it will become increasingly expensive to find important lesions [78]. This means that the vaccine will eliminate the 16-18- lesions (most evident and threatening); there by leaving the lesions caused by other high risk types, which have less predictive value for progression.

To be cost-effective an HPV vaccination program will require adjusting existing cervical cancer screening. If current vaccination coverage is suboptimal, screening guidelines are unlikely to change in the foreseeable future since changes in screening would need to be directed towards the fully vaccinated [79, 80]. Additionally, vaccination documentation will be difficult, given the lack of a national health registry. As an increasing proportion of the population becomes vaccinated, the incidence and prevalence of CIN 2,3 and AIS will decrease, resulting in an increase in the negative predictive value of present screening strategies, but a decrease in the positive predictive value [78, 81]. These changes are independent of any changes occurring with the screening test itself and are purely due to the underlying prevalence of CIN 2+. As a result, if the screening intervals are not lengthened, or a more specific test is not used, the number of false positive results will increase and the number of false negative results will decrease [81]. This means that if vaccination gets rid of 16/18 lesions, then an abnormal cytology is even less likely to harbor a CIN 3 lesion. Evidence based modeling studies suggest that high vaccination rates would therefore promote starting screening later, screening less often, and moving towards screening with virologic tests that are more specific for risk [78, 82–84].

Each presentation summarized key issues to be addressed. These are summarized in Table 2.

CONCLUSIONS

In summary, data does not support cervical screening girls and young women under 21 age years. The incidence of cervical cancer in this age group has not changed with the increased screening of the group that has occurred over time. Present adolescent management

Table 2. Key Research Gaps for Adolescents With Abnormal Cytology

Cytology guidelines	<ul style="list-style-type: none"> • Randomized trials of ASC, LSIL and CIN 2 management in adolescents. • Randomized trials of ASC-H and AGC in adolescents.
Natural history of HPV	<ul style="list-style-type: none"> • Randomized trial of HSIL management in adolescents. • Epidemiology studies of CIN 2 and CIN 2,3 and CIN 3 in adolescents. • Biomarkers of progression of CIN 2. • Utility of HPV 16/18 in triage of CIN 2.
Burdens & challenges: colposcopy, cytology, and histology in adolescents	<ul style="list-style-type: none"> • Management in regards to age of onset of intercourse rather than age? • Registries to document changes in prevalence of lesions identified on colposcopy, cytology, histology with increasing penetration of HPV vaccine(s) and to document changes in Pap test characteristics (sensitivity, specificity, PPV, NPV, etc). • Epidemiology of studies in AGC in adolescents.
Risks of overmanagement and over treatment of adolescents	<ul style="list-style-type: none"> • Additional biomarkers and other diagnostic tests for screening. • Randomized trials using HPV 16/18 to manage CIN 2/3 in adolescents. • Cone effect (volume or tissue removed) on obstetrical outcome. • Identify appropriate treatments for CIN 2/3 in “unreliable” adolescents. • Determine what is a “reliable” patient. • Identify interventions that can reliably reduce outcome and procedure related anxiety (across multiple populations).
HPV-associated cancers and HIV	<ul style="list-style-type: none"> • Vaccine efficacy in HIV+: both prevention of initial and latent infections • Identify rates of HPV in perinatal studies (longitudinal follow-up of children exposed to HPV at birth). • Identify better options for treatment.
Genital warts and HPV-induced VIN in adolescents	<ul style="list-style-type: none"> • The natural history of EGW in adolescents—is it different than adults? • Randomized treatment trials of external genital warts including efficacy and acceptability. • Treatment options external genital lesions (VIN);

guidelines for cervical cytology screening were made to increase observation watchful waiting by repeat cytology rather than with colposcopy and treatment of detected CIN; therefore the reasons for screening anyone in this age group come into question. Adolescent guidelines have been confusing and uptake slow because these guidelines are so different from recommendations for the management of abnormal cervical cytology in adult women. As a result the workshop members promote these key messages:

- 1) Adolescent cervical cancer prevention programs should focus on prevention of HPV infection through universal HPV vaccination.
- 2) Screening should start at age 21 years: Screening of adolescents (age 20 and under) is potentially harmful, because it can lead to unnecessary evaluation and treatment.
- 3) Some adolescents will continue to be screened outside the recommendation. Protecting these women from unnecessary procedures requires education about the importance of following the recommended guidelines for the management of adolescents with abnormal cervical cytology and cervical cancer precursors.
- 4) It is important for adolescents to have access to family planning and to prevention of acquisition and harmful sequelae of STIs other than HPV. It is important to educate consumers and providers that Pap smears do not equate with the only need for regular reproductive health care and that in the absence of

pap smear screening it is important for adolescents to have access to these other needs.

Each organization will disseminate these key messages and outline their own approach. The ASCCP will design a website devoted to the meeting goals. The website will include a library of PDFs of the most important articles related to HPV, cervical screening and cervical disease management of adolescents and young women. It will include ongoing projects from each of the organizations associated with the dissemination of the key messages, educational CME lectures on this topic, and a Toolbox that is being developed which could be used to address incentives for organizations to implement the guidelines.

It was also agreed among the participants that implementation strategies needed to be organization specific. Several research gaps were identified and are summarized in Table 2.

Acknowledgments

We would like to acknowledge the Adolescent Workshop working Committee members: Tom Cox, Anna-Barbara Moscicki, Heidi Bauer, Richard Guido, Teresa Darragh, and the speakers Richard Guido, Teresa Darragh, and Mark Spitzer. Michael Policar, Jeff Waldman, Mona Saraiya, Philip Castle, Thomas Wright, Tom Cox, Anna-Barbara Moscicki, and all the delegates who attended.

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