Published in final edited form as:

Obstet Gynecol Clin North Am. 2013 June ; 40(2): 257–268. doi:10.1016/j.ogc.2013.02.007.

Screening Adolescents and Young Women

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Synopsis

Recent guidelines from multiple organizations, including the USPSTF, ACS/ASCCP/ASCP, ACOG and most recently the 2013 Update to the 2006 ASCCP Consensus Guidelines, all stress screening initiation no sooner than the age of 21 years and increased screening intervals for women aged 21 to 29 years. Primary prevention with HPV vaccination has the potential to significantly impact the development of high-grade cervical lesions, including cancer, and will likely affect screening guidelines in the future.

Keywords

Cervical cancer screening; Adolescents; Young women; Abnormal cytology; HPV testing; HPV vaccination

Introduction

In 2009 and again in 2012, recommendations changed for both the age at which to begin cervical cancer screening and the optimal screening intervals for young women (1–5). In late 2012, the 2006 American Society for Colposcopy and Cervical Pathology (ASCCP)

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Disclosures:

Funding sources:

Dr. Boardman None

Dr. Robison Brown/Women and Infants' Women's Reproductive Health Research (WRHR) Career Development Program

Conflict of Interest:

Dr. Boardman None

Dr. Robison None

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Consensus Guidelines were also revised and recommendations regarding the management of abnormal cervical cytology and histology in young women, and particularly for those in their early 20s, have been recently published (6). The impetus for these changes included data showing an exceedingly low risk of cervical cancer in these populations (7), evidence that screening is less effective in young women under the age of 25 as well as the potential for increased risk of harm including not only anxiety but adverse pregnancy outcomes for those young women undergoing excisional procedures (8,9).

Adolescents, defined as women aged 20 years and younger, represent a unique population of patients. Incident oncogenic HPV infection and mild cytologic abnormalities are commonly seen in this age group. Rates of sexually transmitted infections, including HPV, are highest in younger women. In a recent meta-analysis of women with normal cytology, 23% of those under the age of 25 years compared to 9% of those aged 25–34 years and less than 5% of those aged 35 years and older were found to be HPV positive (10). Although acquisition of HPV is often associated with risk factors such as a higher number of new sexual partners and younger age at first intercourse, young age remains a significant risk even following adjustment for other known behavioral factors. The biological vulnerability of young women to HPV and other STIs has often been attributed to the extent of cervical ectopy in younger women. Recent prospective data, however, showed that the key factor involved in HPV 16 acquisition and the development of a clinical cervical lesion was not amount of ectopy, but rather the rate of observed metaplastic change (11).

Although at risk to develop high-grade disease, many adolescents will experience regression of both cytologic and histologic disease. Despite the high incidence of HPV infection among newly sexually active women, such infections in adolescents and young women are often transient. In numerous studies, approximately 50% of HPV infections in young women persist in the short term, but fewer than 10% remain at 24 months (12–15).

HPV-related low-grade cytologic abnormalities, in particular, are frequently detected in sexually active adolescents (16). For example, in a cohort of 1,075 sexually active teens between 15 to 19 years of age with normal cytology and negative HPV tests at recruitment, 407 (38%) became HPV positive over the 3-year study period, and 246 (23%) developed abnormal cervical cytology (17). Similar rates of incident HPV infection were documented in a longitudinal cohort study of more than 500 college-aged women in Washington State (18). Here, the 36-month cumulative incidence of squamous intraepithelial lesions in this population was 47%. Of the 112 women who developed incident low grade squamous intraepithelial lesions (LSIL), 96 (87%) became cytologically normal while enrolled in the study (19). Moscicki et al similarly demonstrated very high rates of resolution of LSIL among teens and young women, with regression rates over 60% at 12 months of follow-up and 91% at 36 months (20).

Regression has also been noted in young women with high-grade squamous intraepithelial lesions (HSIL), as well as biopsy-proven cervical intraepithelial neoplasia (CIN) 2. Over a median follow-up period of 18 months, Moore found regression in 65% of a cohort of young women aged 20 years and younger with CIN 2 (21). In another retrospective study of expectantly managed adolescents and young women (aged 21 years and younger) with CIN 2, Fuchs demonstrated that 50% of CIN 2 lesions regressed within 2 years, and 75% regressed within 3 years. Progression to CIN 3 occurred in 8% of this cohort (22). Moscicki documented similar rates of regression of CIN 2 (68% by 3 years) among a cohort of 95 adolescents and women aged 13 to 24 years. In none of the above studies was invasive cancer detected (23).

Similar to adolescents, women in their early 20s commonly present with mild cytologic abnormalities, the optimal management of which has remained unclear. Data in adolescent populations has clearly demonstrated that cervical cancer is rare, and rates of high-grade neoplasia in teens and in young women under the age of 25 years with ASC-US and LSIL appear to be lower than what has been seen in adult populations (24, 25). Women in their late 20s, on the other hand, have been found to have significantly higher rates of CIN2+ compared to their younger counterparts, and thus immediate colposcopy remains the standard of care for this population. For these reasons, recommendations for conservative management of mildly abnormal cervical cytology and histology (including CIN2) in women in their early 20s have recently been made (6).

Screening of Women Aged 20 and Younger

Recommendation

Cervical cancer screening should begin at age 21 years. Factors such as age of sexual initiation or number of sexual partners should not be used to initiate screening prior to age 21 (3–5). This recommendation does not apply to HIV-seropositive young women, women with known immunocompromise or young women previously treated for CIN2, CIN3 or cancer.

In the past

Over the past two decades, guidelines have steadily moved away from screening young women under the age of 21. In 2002, the American Cancer Society (ACS) recommended initiating cervical cancer screening at age 21 or at 3 years following sexual debut (whichever came first) (26). This recommendation, however, was difficult to follow and raised concern about doing harm with little evidence of benefit. Beginning in the late 2000s, multiple organizations, including the American College of Obstetricians and Gynecologists (ACOG) (1) and ASCCP (2), moved to the recommendation to begin screening at age 21 years regardless of a patient's past sexual or behavioral history. This recommendation was recently reaffirmed in guidelines published by United States Preventive Services Task Force (USPSTF), the ACS/ASCCP/American Society for Clinical Pathology (ASCP) and ACOG (3–5).

Rationale and Evidence

A very low incidence of cervical cancer and a lack of data showing the effectiveness of screening in young women support the most recent recommendations to initiate screening at age 21 years. In the developed world, cervical cancer is not very common, and it is even rarer in younger women. Based on combined data from the National Program of Cancer Registries and the Surveillance, Epidemiology and End Results Program, Benard documented an average of 3,063 cases of invasive cervical carcinomas annually from 1999 through 2008, with an average of 14 carcinomas per year among those aged 15–19 years and 125 cases among those aged 20–24 years (7). The rate of cervical cancer in 15–19 year olds, approximately 0.1 per 100,000, has remained unchanged from that reported nearly 40 years ago (1973–1977) (7, 27).

As with teens, screening in younger women has not been shown to reduce the rate of cervical cancer. For example, in a population based case-control study in the United Kingdom, investigators found that cervical screening in women aged 20–24 had no detectable impact on rates of cervical cancer at ages 25–29 (28). Reasons for why screening appears to be ineffective in young women include the presence of cancers in this age group that are less detectable by current screening methods or are more aggressive and therefore more likely to arise during screening intervals (29). In the analysis by Benard discussed

previously, a larger proportion of non-carcinomas were detected among the youngest age groups. These non-carcinomas were often childhood cancers (e.g., embryonal rhabdomyosarcoma) that would not have been detected through cervical cancer screening (7).

Recommendation

As some younger women will continue to be screened, it is reasonable to follow the 2006 Consensus Guidelines for the management of adolescents with abnormal cervical screening tests.

Rationale and Evidence

Although providers often continue to screen and treat younger women (30, 31), recent evidence from the Behavioral Risk Factor Surveillance System (BRFSS) does point to both less frequent screening initiation and screening frequency in women under the age of 21. In 2010, 52.5% of young women aged 18–21 years reported having been screened (compared to 73.7% in 2000) and 41.5% reported having had a Pap test in the past 12 months (compared to 65% in 2000). Early adoption of the 2009 cervical cancer screening guidelines or increased awareness of the potential harms of screening were likely associated with these observed changes in screening behaviors (32).

While this evidence is reassuring, over 25% of women under the age of 21 in the BRFSS were still screened in 2010. The consequences of both screening and treating adolescents include not only the emotional effect of telling a teen that she has both a sexually transmitted infection and a potential precancer and the anxiety associated with colposcopy, but also the potential risk of preterm delivery should she be over-treated (5). Evidence that excisional therapy poses long-term obstetrical risks is particularly salient in adolescents, many of whom have not yet begun or completed childbearing. Cervical conization, including loop electrosurgical excision procedures (LEEP), has been shown to increase the risk of pregnancy complications such as preterm premature rupture of the membranes (33) and preterm delivery (34). Treatment with LEEP has been estimated to result in an approximately 2- to 3-fold increased risk of preterm birth (34, 35). Increasing cone depth as well as multiple procedures have both been shown in a number of studies to be associated with a further increase in the risk of preterm delivery (8, 36).

On the other hand, in a recent population-based record linkage study of nearly 175,000 Welsh women, Reilly found that women referred for colposcopy had an increased and similar risk of preterm delivery whether or not they received excisional therapy compared to women with negative cytology (37). Lastly, ablative therapy, often suggested as an alternative to excisional procedures in young or nulliparous women, has also recently been found to be associated with an increase in preterm delivery rates, although the magnitude of this effect was less pronounced (9). While avoiding unnecessary excision or ablation is advisable in young women, the long-accepted association between LEEP and adverse pregnancy outcomes continues to be challenged.

In order to reduce the risk of such complications, several special populations were identified, including adolescent women (defined as those aged 20 and younger) in the 2006 Consensus Guidelines. Given the high rates of HPV infection and concomitant mild cytologic abnormalities in young women that are highly likely to regress, immediate colposcopy was discouraged. For young women with ASC-US or LSIL, repeat cytology in 12 months is recommended. If repeat cytology test at that time reveals HSIL or greater, colposcopy is indicated. If repeat cytology is ASC-US or LSIL, cytology should be repeated again in 12

months, and any cytologic abnormality at the second visit should prompt colposcopic evaluation (38).

Of note, in 2006, HPV DNA testing was found to be unacceptable for adolescents with ASC-US (again based on reports of a high prevalence of HPV among adolescents with this cytologic diagnosis (39)) and if inadvertently done was not to be used in management decisions. Immediate colposcopic examination continues to be advised for all women, including adolescents, with atypical squamous cells, cannot exclude HSIL (ASC-H), HSIL, and atypical glandular cells on cervical cytologic testing (38).

Screening of 21 to 29 Year Old Women

Recommendation

Screening with cytology (either conventional or liquid based) alone should be performed every three years. This recommendation does not apply to HIV-seropositive young women, immunocompromised women or women previously treated for CIN2, CIN3 or cancer (3–5).

In the past

Screening was previously recommended annually for women in this age group (1).

Rationale and Evidence—Few studies specifically address the optimal screening interval for women aged 21 to 29 years. Data from several modeling studies have assessed the impact of different screening regimens and intervals in this age group. Although the likelihood of high-grade cervical neoplasia increases with age, most women have neither CIN 2 nor CIN 3 at the time of screening. Indeed, more than 95% of referrals to colposcopy are either false positive (no lesion detected) or potentially excessive (CIN 1 only). For example, among a cohort of 1,000 20 year-old women screened for a 10-year period with cytology and triage HPV testing for ASC-US, screening every 5 years, compared to annually or every 3 years, would result in the fewest number of excessive colposcopies (defined as CIN 1 or less) but at the cost of missing 2 of 7 expected cases of high-grade neoplasia. Screening annually compared to every three years confers no additional benefit (both result in detection of 7 cases of CIN 2 or CIN 3), but results in 396 compared to 180 excessive referrals to colposcopy, respectively (40).

Kulasingam looked specifically at cervical cancer screening performed annually, every 2 years and every 3 years, and found little additional benefit between the 2-year and 3-year screening regimens. Here again, the trade-off between a negligibly increased risk of cancer (37 cases per 100,000 screened versus 39 cases per 100,000) and unnecessary colposcopies (176 versus 134 procedures per 100,000 women) favored the 3-year screening recommendation (41). Based on such results, screening women aged 21–29 with cervical cytology every three years provided the best balance between the benefits and harms of screening.

Recommendation

HPV testing, either in the setting of cotesting or as a stand-alone test, should not be performed in women under the age of 30 (3–5).

Rationale and Evidence

As with younger women, the high prevalence of HPV in women aged 21 to 29 years precludes the addition of HPV testing to primary screening with cervical cytology or the use of HPV testing as a primary screening test alone. For example, analysis of the 2003–2006 National Health and Nutrition Examination Surveys indicated that HPV infection, both

overall and with types 6, 11, 16 and 18, is highest among young women aged 20–24 (42, 43). Detecting largely transient HPV infection in this population would result in marked increases in referral to colposcopy with no benefit in the detection of high-grade cervical disease. Stout, for instance, assessed the impact of screening 20 year-old women over the course of 10 years. Comparing screening with cytology and HPV triage testing for ASC-US to cotesting with cytology and HPV testing would result in a 5-fold increase in the number of excessive referrals to colposcopy with no change in the detection of CIN 2 or CIN 3 (40).

Recommendation

For women with unsatisfactory Pap tests, early repeat cytology at 2–4 months is recommended. If repeat cytology is again unsatisfactory, colposcopy is indicated (6).

Rationale and Evidence

As most women are now screened with liquid-based cytology, unsatisfactory tests are largely a result of obscuring factors, scant cellularity and technical problems. In a recent study of 226 unsatisfactory tests, the presence of lubricant (96 cases) and blood (64 cases) were most commonly encountered. Cases affected by blood or technical problems showed significant improvement after reprocessing (56% and 91%, respectively), while only 17% of those impacted by lubricant improved following reprocessing (44).

Studies done in clinical practice, however, have not consistently confirmed an increased rate of unsatisfactory tests among conventional cytologic samples where water-soluble lubricants have been used (45). In a randomized trial of a small amount (3 mL) of lubricating gel compared to water used to cover both speculum blades, use of the gel resulted in significantly lower pain scores with speculum insertion and digital examination and did not impact the interpretability of liquid-based cytologic specimens (46).

Among adolescents and young women, barriers to cervical screening include most commonly pain or discomfort with speculum insertion, along with embarrassment, fear, poor rapport with the provider, and the advice of their peers (47). For those adolescents inadvertently screened and who now require a speculum examination, application of a small amount of water-soluble lubricating gel to the exterior bills of the speculum should have little to no impact on the interpretability of cervical cytology. While water is often used to make speculum insertion more comfortable, evidence demonstrates that gel is superior in this regard.

To ensure adequate collection of cells, all women should be cautioned to avoid intercourse, tampons, intravaginal medication and douching for at minimum 48 hours prior to screening. If using the combination of spatula and brush, use of the spatula first minimizes bleeding. In general, avoidance of specimen collection during menses is advised, although women with irregular bleeding should be sampled as these symptoms could indicate a more concerning lesion (6).

Recommendation

For women aged 21 to 29 years with cytology reported as negative for intraepithelial lesion or malignancy (NILM) but with absent or insufficient endocervical cells or transformation zone (EC/TZ) component, routine screening with repeat cytology in 3 years is indicated. HPV testing in this age group is unacceptable (6).

Rationale and Evidence

Although interpretable, these cytologic samples lacking in metaplastic cells indicate inadequate sampling of the squamocolumnar junction. This in turn increases concern for

missed cancers that often arise at or above the SCJ and led to prior recommendations for early repeat cytology (48). More recent data, however, demonstrates that women missing these components are not at higher risk for CIN 3+ (49).

HPV Vaccination

Recommendation

Recommended screening practices should not change based on HPV vaccination status (3–5).

Rationale and Evidence

Despite recommendations in 2006 to vaccinate girls aged 11–12 years (as young as 9, with catch-up vaccination of those 13 to 26), and in 2011 to vaccinate young boys and men aged 11–12 years (with catch-up for those 13 to 21), vaccination rates remain low in U.S. compared to other developed nations (50). Many factors play a role in ensuring high participation in vaccination, cost and acceptability being primary. In the U.S., the Vaccines for Children Program supplies private and public health care providers with federally purchased vaccines for use among children 18 and younger. Despite availability, coverage with at least one dose of HPV vaccine among 13–17 year-old girls has increased slowly, from 25% in 2007 to only 53% in 2011. Vaccination with all three doses rose to 35% from 32% in 2010. Geographic disparities in HPV vaccine rates, with the lowest rates seen in the southeastern U.S. where cancer rates are higher, continue to exist, as does even lower vaccination rates among the target population of 11–12 year-olds. Vaccination with all three doses of vaccine occurred in 16% of eligible adolescents in Arkansas and was highest in Rhode Island, where 57% of eligible girls were fully vaccinated (50). Acceptability of the vaccines remains problematic as well. Data from the 2008 and 2009 National Immunization Survey-Teen, for example, revealed that the third of parents of unvaccinated girls did not intend to have their daughters vaccinated, a decision driven by lack of knowledge about the disease risks and benefits of the HPV vaccine as well as failure of providers to recommend vaccination (51).

HPV vaccine trial data (both with the quadrivalent vaccine FDA-approved in 2006 and the bivalent vaccine approved in 2009) has consistently shown that rates of subsequent vaccine-type HPV infection, as well as related CIN2+, are markedly reduced in per-protocol populations as well as intention-to-treat populations (52, 53). Both vaccines target oncogenic HPV 16 and 18, while the quadrivalent is also directed against two non-oncogenic types, HPV 6 and 11. Data continues to emerge demonstrating the long-term impact of vaccination on CIN 3, cervical cancer as well as genital warts (quadrivalent vaccine only). In a linkage study of 18–19 year old Finns vaccinated in a multinational Phase III HPV 6/11/16/18 vaccine (FUTURE II) trial and the Finnish Cancer Registry, Rana reported a CIN 3 incidence rate of 0/100,000 among vaccinated women after 4 years of passive follow-up. In both the placebo and unvaccinated groups, the corresponding rates were 87.1/100,000 and 93.8/100,000, respectively (54). In Australia, where vaccination rates exceed 80%, dramatic declines in the number of young women and men presenting with genital warts occurred within 4 years of beginning a program of free quadrivalent vaccines to adolescent girls (55).

Recent modeling data has shown that vaccinating 12-year-old girls with the bivalent or quadrivalent vaccine is predicted to reduce the cumulative incidence of CIN2 and CIN3 by 51% for the bivalent vaccine and 46% for the quadrivalent (56). In order to see significant reductions, however, at least 80% of sexually naive females need to be vaccinated (57), and it will likely take decades to recognize the effect of vaccination (58). At this time, then, continuation of cervical cancer screening remains critical. Understanding the impact of

vaccination on cervical cytology, however, is equally important in determining future guidelines for screening (59).

Current recommendations for screening young women include almost exclusively cervical cytology, with little role played by HPV testing except in the triage of ASC-US. Cytology has a number of limitations, however, including a low sensitivity (51% in a systematic review by Nanda (60)) as well as a lower specificity for high-grade disease than low-grade, leading potentially to overtreatment (60, 61). Such limitations are predicted to increase with the implementation of HPV vaccination. As vaccination rates increase, the prevalence of cytologic abnormalities will decrease, thus limiting the effectiveness of cytology as a screening tool. For example, estimates indicate widespread vaccination would result in a reduction from the current 50% to 70% positive predictive value to approximately 10–20%. Interobserver variability in cytologic interpretation will also increase, leading to more false-negative diagnoses and further reductions in the sensitivity of cytology (62).

As regards the impact of HPV vaccination on screening algorithms in younger women (including potentially increasing the age at which to initiate screening), considerable uncertainty remains as to changing current recommendations. More data is needed regarding the effect of vaccination on the development of non HPV 16/18 lesions (i.e., type replacement), the timing and impact of vaccination relative to sexual initiation, adherence to screening guidelines following vaccination as well as duration of immunity. It has been difficult in the U.S. to evaluate the impact of vaccination due to the lack of a national HPV vaccine registry. Linkage of a vaccination registry with screening and HPV testing databases would allow for comparison of HPV types, screening behaviors and histologic outcomes between vaccinated and unvaccinated populations (63). Surveillance mechanisms have been established by both CDC in sentinel sites (HPV-IMPACT including sites in California, Connecticut, New York, Oregon and Tennessee) (64) and in New Mexico (65) and will allow for linkage of vaccination histories to screening practices and clinical outcomes. Finally, clinical trials of a nonavalent vaccine (addition of HPV 31/33/45/52/58) as well as immunogenic studies of L2-based vaccines (would confer broader protection) are currently underway, and if successful, would further decrease the risk for CIN 2/3 lesions and impact screening decisions (66, 67).

Conclusions

Recent guidelines from multiple organizations, including the USPSTF, ACS/ASCCP/ASCP, ACOG and most recently the 2013 Update to the 2006 ASCCP Consensus Guidelines, all stress screening initiation no sooner than the age of 21 years and conservative management of both cytological and histological abnormalities in young women. Adherence to these guidelines should help to not only decrease the number of unnecessary diagnostic procedures in this specific population of women, but also to reduce the anxiety associated with repeat screening and colposcopy and the long-term obstetrical risks of excisional or ablative therapy and help prevent the potential negative impact on future screening behaviors.

Primary prevention with HPV vaccination has the potential to significantly impact the development of high-grade cervical lesions, including cancer. In the U.S., linkage studies are underway to assess the impact and timing of vaccination with clinical outcomes in young women, findings which will help tailor future changes to current guidelines for screening and management of abnormal cervical testing in women. Expanded coverage with a nonavalent vaccine is likely, and will result in the need for continued evaluation before consideration of its impact on screening strategies. The use of cervical cytology as a primary screening tool in younger women remains unchanged at present, and adherence to this

recommendation is important for providers to convey to their patients. With screening starting at the age of 21, it remains equally important that adolescents continue to have access to family planning services as well as prevention and treatment services for sexually transmitted infections, including HPV vaccination. Maximizing vaccination uptake and assessing clinical outcomes among vaccinated and unvaccinated women will allow for development of screening strategies that lead to significant reductions in cancer risk, health care savings, and patient harm.

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Key Points

- Cervical cancer screening should begin at age 21 years regardless of a young woman's risk factors for HPV acquisition.
- For young women between the ages of 21 and 29 years with normal cytology, screening should be repeated no sooner than 3 years. Cervical cytology alone should be used for screening in this population.
- The addition of HPV testing to routine cervical cancer screening is not indicated in women aged 21 to 29 years due to the high prevalence of high-risk HPV infection in this population.
- The impact of HPV vaccination in real world settings is underway in the US, but at the present, vaccination status does not change screening guidelines.