Adolescent Sexually Transmitted Diseases: Recent Developments

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Adolescents and young adults continue to have the highest rates of sexually transmitted diseases. New chlamydia and gonorrhea diagnostic tests are being used in innovative ways to increase the number of infections that are detected. Nevertheless, challenges such as gonorrhea resistance and partner notification and treatment continue to hinder efforts to reduce the prevalence of these two bacterial infections. Although recent surveillance data suggest a decreasing trend of herpes simplex virus 2 (HSV-2) incidence among adolescents and young adults, the incidence of sexually transmitted human papillomavirus (HPV) in adolescent and young adult females remains high. Progress has been made toward the development of vaccines that may become available in the future to prevent infection with and sequelae from HSV-2 and HPV.

Introduction

Adolescents and young adults have the highest rates of sexually transmitted diseases (STDs) in the United States. Of the estimated 15 million cases of STDs diagnosed annually, more than 25% (4 million) occur among teenagers [1]. This review presents recently published literature describing adolescent STD epidemiology, diagnosis, management, and prevention for four of the most common STDs among US adolescents.

Epidemiology

Chlamydia trachomatis

Young people aged 15 to 24 years continue to have the highest rates of reported chlamydia infections in the United States (Fig. 1) [2]. Whereas male chlamydia rates are also highest among those aged 15 to 24 years, the reported rates are significantly lower than among their female counterparts (Fig. 1) [2]. Published clinical guidelines recommend annual screening of sexually active females aged younger than 25 years; yet, recent reviews have found insufficient evidence to recommend for or against routinely screening asymptomatic males for chlamydial infection [3••,4]. Consequently, *C. trachomatis* diagnostic tests are not commonly performed on men, and few infections are detected and reported [5].

Females aged 15 to 24 years also have the highest rates of chlamydia reinfection [6]. An epidemiologic longitudinal study among females residing in an urban setting found that during the 33-month study period, 87% of the 167 repeat *C. trachomatis* infections occurred in females aged younger than 25 years [6]. The median time to repeat infection was 7 months among females aged younger than 25 years, compared to 11 months for females aged 25 years or older.

Neisseria gonorrhoeae

Although the prevalence rates of reported gonorrhea infections do not approach those of chlamydia, gonorrhea rates remain highest among adolescents and young adults (aged 15 to 24 years) compared with older age groups (Fig. 2) [2].

Herpes simplex virus

Herpes simplex virus (HSV) type 2 is the most common cause of genital ulcerative disease in the United States. However, HSV-1 has been reported to cause an increasing proportion of genital infections, especially among adolescents [7,8]. The incidence of new HSV-2 infections in the seronegative population increased by 82% between 1970 and 1985 [9]. Yet, the most recent National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2000 suggest a significant decreasing trend of HSV-2 incidence among adolescents aged 14 to 19 years and young adults aged 20 to 29 years [10]. Prevalence estimates from the 1999 to 2000 NHANES data suggest that 1.5% of 14- to 19-year-olds and 8.9% of 20- to 29-year-olds are seropositive for HSV-2 [10]. Most persons who have serologic evidence of HSV infection are asymptomatic [11].

Genital human papillomavirus

Genital human papillomavirus (HPV) infection is the most common STD among young, sexually active people and is of increasing public health concern. Approximately 40 of the more than 80 identified HPV types infect the genital tract [12]. Genital HPV types have been subdivided into low-risk types, such as types 6 and 11, which are found mainly in genital warts, and high-risk types, such as

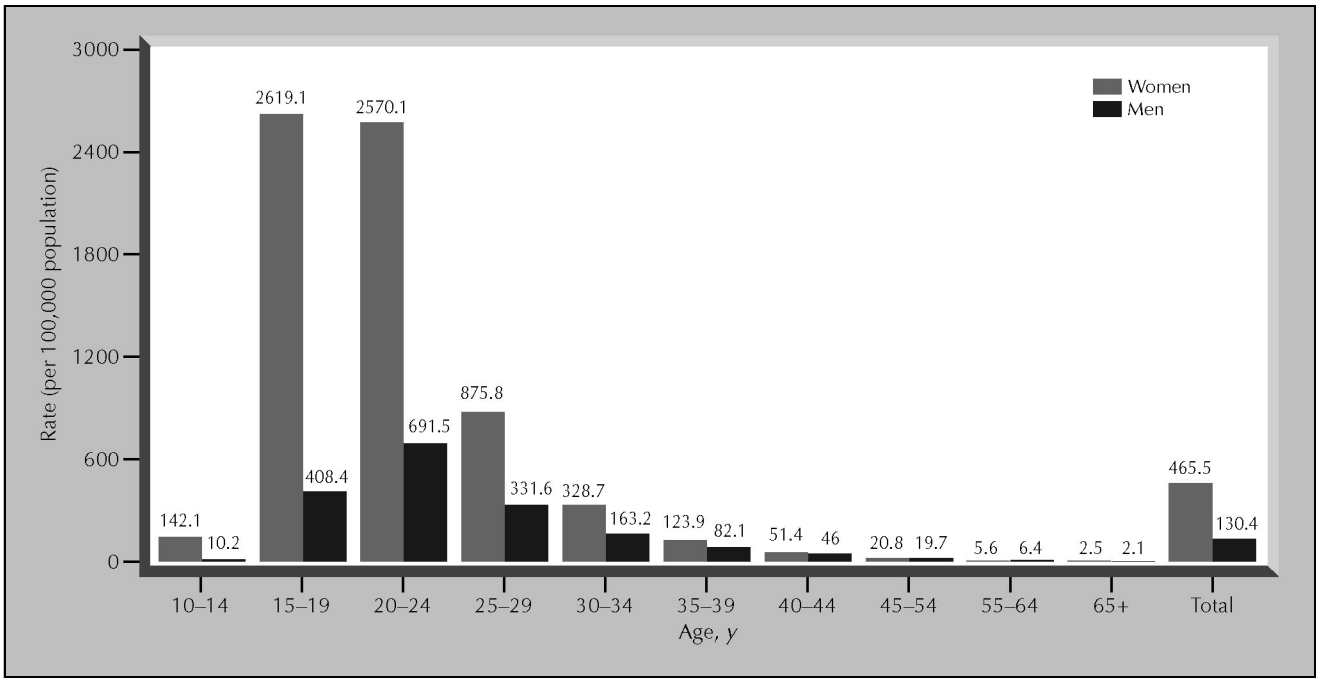

Figure 1. Chlamydia: age- and sex-specific rates, United States, 2002. (*Adapted from* Centers for Disease Control and Prevention [2].)

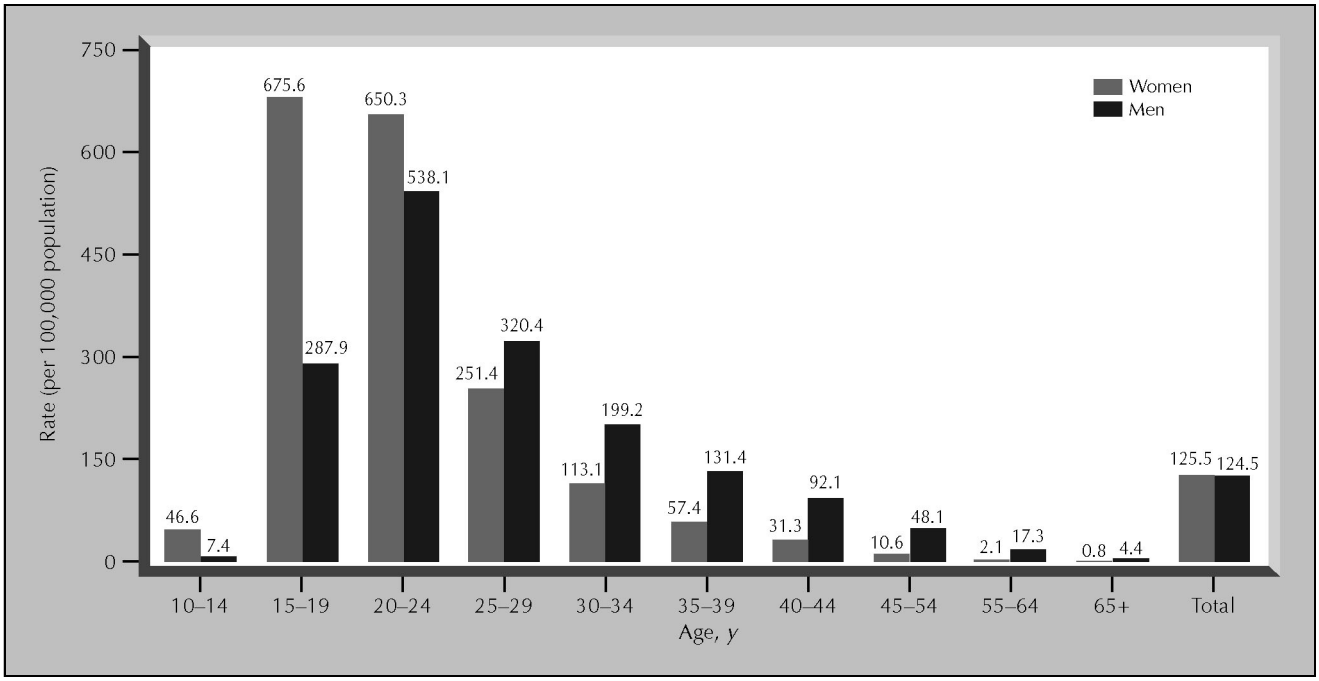

Figure 2. Gonorrhea: age- and sex-specific rates, United States, 2002. (*Adapted from* Centers for Disease Control and Prevention [2].)

16, 18, 31, 35, and 45, which are associated with invasive cervical cancer [13].

The incidence of sexually transmitted HPV in adolescent and young adult females is high. In one study following 105 HPV-negative 13- to 21-year-old females for a median of 50 months, 54 incident cases were detected by DNA amplification tests [14]. The risk for HPV infection increased nearly 10-fold for each new partner per month reported. However, most females with detected HPV DNA revert to an HPV-negative status within a 24-month period [15]. Among a cohort of 618 HPV DNA–positive 13- to 21-year-old females followed with HPV DNA testing at 4-month intervals, most were determined to have HPV regression by 24 months [15].

Diagnostic Tests

Chlamydia and gonorrhea

Over the past several years, a new generation of chlamydia and gonorrhea tests, nucleic acid amplification tests (NAATs), have been developed. Because NAATs amplify specific nucleic acid sequences from the organism, they can theoretically detect as little as one copy of the target DNA or RNA [3••].

The sensitivities of these amplification tests are superior to previous generations of chlamydia tests, including culture and nonamplified nucleic acid hybridization tests. Studies have demonstrated that chlamydia NAAT sensitivities exceed hybridization tests by up to 20% and culture by up to 11% [3••]. Gonorrhea NAAT sensitivities are comparable to culture and nonamplified nucleic acid hybridization tests. Specificity of NAATs for chlamydia and gonorrhea has been reported in the 99% range and higher, which is comparable to other nonculture chlamydia and gonorrhea tests [3••]. Because most commercial NAATs can be performed on endocervical and urethral swabs, and on urine from men and women, noninvasive screening can be offered in traditional and nontraditional venues [3••]. Additionally, Gen-Probe (San Diego, CA) received US Food and Drug Administration (FDA) clearance on January 6, 2004 to test vaginal swabs for chlamydia and gonorrhea using its APTIMA Combo 2 nucleic acid amplification test, further extending the possibilities for noninvasive screening.

Currently FDA-licensed amplified chlamydia and gonorrhea tests include the Roche Amplicor (Roche Diagnostics Corporation, Basel, Switzerland) test that uses polymerase chain reaction (PCR), the Abbott LCx (Abbott Laboratories, Abbott Park, IL) test that uses ligase chain reaction, the Becton Dickinson BDProbeTec ET (Becton, Dickinson and Company, Franklin Lakes, NJ) test that uses strand displacement amplification, and the Gen-Probe APTIMA and APTIMA Combo 2 tests that use transcription-mediated amplification [3••]. However, on July 18, 2002, Abbott Laboratories issued a recall of the gonorrhea LCx test because of problems with false-negative results, and production of all Abbott LCx products was discontinued on June 30, 2003.

Innovative chlamydia and gonorrhea screening venues

Several creative approaches for offering chlamydia and gonorrhea urine-based NAAT screening to adolescents and young adults have demonstrated success in detection of asymptomatic infections [16–20].

Health care visits of any type provide an opportunity for offering adolescents gonorrhea and chlamydia screening [16,17]. Six hundred eighty-one student athletes in an urban Louisiana school district were offered urine-based chlamydia and gonorrhea testing during their preparticipation sports examination [16]. The proportion of positive chlamydia and gonorrhea tests among the 200 screened females was 6.5% and 2.0%, respectively, and among the 436 screened males was 2.8% and 0.7%, respectively. In another study, females presenting for emergency contraception at a family planning clinic in Scotland were offered urine-based chlamydia screening [17]. Almost 75% of the females aged younger than 20 years agreed to be tested, and 7.6% had positive chlamydia test results.

The US Centers for Disease Control and Prevention (CDC) Jail STD Prevalence Monitoring Project demonstrated a high prevalence of chlamydia and gonorrhea infection among more than 40,000 male and female adolescents aged younger than 20 years detained in juvenile detention facilities in five jurisdictions in California, Maryland, and Texas [18]. Among adolescent female detainees, positivity by site ranged from 8% to 19.5% for chlamydia and 3% to 10% for gonorrhea. Among adolescent male detainees, positivity by site ranged from 3% to 9% for chlamydia and 1% to 3% for gonorrhea.

Taking STD testing services into settings where adolescents congregate has proven to be an effective approach to identifying infection in at-risk teens who otherwise might not receive testing [19,20]. A collaboration between the Denver Department of Public Health and an outreach team from a community-based organization serving homeless youth found that 12.4% (23/186) of young men and 14% (18/129) of young women were infected with chlamydia, and 3% (4/135) of the young men and 4.9% (4/82) of the young women were infected with gonorrhea [19]. Unfortunately, treatment was only documented for 61% of the total infections. In Louisiana, a mobile van-based STD screening program detected 10 (5.4%) gonorrhea and 14 (7.5%) chlamydia infections among 185 males aged 12 to 19 years and 33 gonorrhea (10.9%) and 61 (20%) chlamydia infections among 305 females aged 12 to 19 years [20]. More than 90% of the infected participants in this study received documented antibiotic treatment.

The proportion of asymptomatic chlamydia and gonorrhea infections demonstrated among males in two of these studies is of note. Between 67% and 93% of the gonorrhea infections were asymptomatic, and between 91% and 97% of the chlamydia infections were asymptomatic [18,20]. This degree of asymptomatic urethral infection is higher than previously reported, particularly for gonorrhea [5,21,22].

Chlamydia screening economic analyses

Although the benefits of NAATs include noninvasive sampling with superior sensitivity and specificity, their high cost has been a major barrier to the widespread adoption of these tests [3••]. Because males suffer few if any of the adverse sequelae associated with untreated infection, this is even more pertinent to male screening. Four recently published economic cost-effectiveness analyses, conducted in different populations and settings, provide conflicting conclusions regarding the cost effectiveness of screening adolescent males for chlamydia

[23–26]. In all four studies, cost effectiveness of the favored screening strategy was primarily attributed to the outcome of preventing pelvic inflammatory disease and its sequelae in female partners of infected index males. Two of the analyses were conducted for populations of detained adolescent males [25,26], another for a population of male high school students [23], and the fourth for populations of males aged younger than 25 years from several settings [24]. Chlamydia prevalences in the four analyses ranged from 3.1% to 9.1%.

The findings of any economic analysis are highly sensitive to the estimates used for key costs and event probabilities. The two studies in which universal NAAT screening was favored [23,26] used higher estimates for risk for PID and for treatment costs for PID and its sequelae, compared to the two studies that favored leukocyte esterase screening over universal NAAT screening [24,25]. Wang *et al*. [23] and Blake *et al*. [26] also used a lower estimate for NAAT cost than one of the studies that favored leukocyte esterase screening [24]. Because the estimates of these three key parameters vary, the inconsistency in the study conclusions is not unexpected. Given the conflicting conclusions of these cost analyses, developing recommendations for cost-effective chlamydia screening of adolescent males may not be possible. Nevertheless, it appears that in some settings universal NAAT screening for chlamydia among males may prove cost effective in terms of preventing PID and its sequelae in female partners.

Herpes simplex virus

The CDC recommends isolation of HSV by viral culture as the preferred method for diagnosis from mucosal lesions. PCR tests for detection of HSV-1 and HSV-2 are available and particularly useful for detection of HSV in spinal fluid [27••].

Commercially available type-specific PCR tests also are available to detect serologic evidence of infection with HSV-1 and/or HSV-2. Although several serologic tests claim to distinguish between HSV-1 and HSV-2, the CDC cautions that many older tests are incapable of doing so. The CDC recommends that only tests based on glycoprotein G (gG) assays be used for this purpose [27••,28]. Western blot tests are considered the gold standard. However, enzyme-linked immunosorbent assays (ELISAs) are faster and less expensive [28]. ELISAs using gG-based assays have compared well against Western blot, with sensitivity ranges of 93% to 100% [29–32]. These tests also have specificities that are comparable to Western blot [28]. Caution must be used in the interpretation of these test results because both HSV-1 and HSV-2 infect the genitalia as well as the oropharynx, and the serologic test can only determine the type of HSV and not the site of the infection [28].

Human papillomavirus

All HPV tests use some method of HPV DNA sequence detection because it has not been possible to culture HPV in vitro [33]. Most HPV DNA detection tests have only been available for research use because many of the high-risk HPV-type DNA sequences have been patented. Currently, the hybrid capture 2 (HC2) kit (Digene, Gaithersburg, MD) is the only commercially available test that detects most, if not all, of the high-risk oncogenic HPV types. HC2 also detects most of the low-risk HPV types [33]. HC2 is a signal amplification test that uses direct probe technology with enhanced sensitivity owing to improved detection methods. Although the system cannot identify individual HPV types, it can discriminate between oncogenic high-risk types and nononcogenic low-risk types [33]. In the future, HPV DNA target amplification using PCR technology may become commercially available to provide HPV type-specific detection [33].

The introduction of liquid-based cytology (Thin Prep; Cytyc Corporation, Boxborough, MA) coupled with HC2 HPV detection has made it possible to use presence or absence of a high-risk HPV type to base decisions about management of abnormal Pap smears. The ASCUS-LSIL Triage Study, a multicenter, randomized clinical study, was designed to evaluate the effectiveness of triaging colposcopy referral based on high-risk oncogenic HPV-type detection [34]. In this study, the prevalence of high-risk HPV types was too high among low-grade squamous intraepithelial lesion (LSIL) cytologic specimens to recommend use of HC2 for LSIL triage. Of the 3488 women with atypical squamous cells of undetermined significance (ASCUS) cytology results, 5% had cervical intraepithelial neoplasia, grade 3 (CIN3+) or cancer on colpobiopsy histologic examination. Ninety-six percent of these women with CIN3+ had a high-risk HPV type detected by HC2. Conversely, 44% of the 3488 women with ASCUS had low-risk HPV or no HPV detected. The authors concluded that colposcopy referral was not justified for almost 50% of the women with ASCUS Pap smears because neither CIN3 nor high-risk HPV types were detected. Based on these results, recommendations have been made to defer referral of women with ASCUS who do not have high-risk HPV and to continue with yearly Pap smear cytology. Women with ASCUS in which high-risk HPV types are detected and those with LSIL should be referred for colposcopy [34].

Treatment and Treatment Challenges

As outlined in the 2002 CDC STD Treatment Guidelines [27••], uncomplicated genital chlamydia and gonorrhea infections should be treated with single-dose therapy. Especially when directly observed, single-dose therapy has the potential to greatly increase compliance over multidose therapy. Azithromycin 1 g orally is the recommended single-dose therapy for chlamydia, and multidose doxycycline is an acceptable alternate regimen [27••]. Because many longitudinal studies of females diagnosed with chlamydia infection have found high rates of reinfection within a few months after treatment, the 2002 STD Treatment Guidelines recommend rescreening chlamydia-infected females 3 to 4 months after treatment.

Antimicrobial resistance to *N. gonorrhoeae* is a growing problem in the United States and globally. Overall, 21% of isolates collected in 2001 by the Gonococcal Isolate Surveillance Project were resistant to penicillin, tetracycline, or both [35]. Fluoroquinolones have been commonly used to treat uncomplicated gonorrhea infections because of the single-dose convenience and low cost [27••,36]. The increasing proportion of ciprofloxacin-resistant *N. gonorrhoeae* strains detected in Hawaii and California has resulted in discontinuation of fluoroquinolones to treat gonorrhea acquired in these areas [37]. Therefore, health care providers in Hawaii and California need to consider fluoroquinolone-resistance when managing adolescent and young adult STD syndromes that could be caused by *N. gonorrhoeae*. Health care providers in other regions of the United States should stay current with local fluoroquinolone resistance patterns as well.

In areas of the United States where fluoroquinolone-resistant *N. gonorrhoeae* has not emerged, ciprofloxacin remains an inexpensive single-dose treatment option for gonorrhea. However, ciprofloxacin has not been recommended for persons aged younger than 18 years (except for use in inhalation anthrax) because of irreversible articular cartilage damage demonstrated in large, weight-bearing joints of juvenile animals treated with very high doses of fluoroquinolones [38]. Nonetheless, a recent literature review found no reports of permanent joint damage attributable to therapy among fluoroquinolone-treated children [36]. Therefore, children who weigh 45 kg or more can be treated with any fluoroquinolone regimen recommended for adults [27••].

Cefixime is the only CDC-recommended oral antimicrobial agent without associated age-specific precautions to which *N. gonorrhoeae* has not developed significant resistance [39]. However, in July 2002, Wyeth Pharmaceuticals (Collegeville, Pennsylvania) discontinued manufacturing cefixime (Suprax) in the United States [39]. No other pharmaceutical company manufactures or sells cefixime tablets in the United States. The CDC has posted recommendations for alternative antibiotic regimens to cefixime for the treatment of uncomplicated *N. gonorrhoeae* urogenital infections on their web site at http://www.cdc.gov/STD/treatment/cefixime.htm [40•].

Treatment regimens for genital HSV infection and genital warts caused by HPV also can be found in the 2002 CDC STD Treatment Guidelines [27••]. Treatment recommendations for these two viral infections are similar to those published in the 1998 Guidelines.

Partner treatment for chlamydia and gonorrhea

The success of STD screening programs is often diminished by the substantial proportions of patients who do not return for treatment and by reinfection from the large proportion of partners who never receive therapy. One successful approach to increasing the rate of STD treatment is to bring treatment to the infected patients and their partners rather than requiring patients to return for treatment. A program that delivered single-dose medications (cefixime and azithromycin) for gonorrhea and chlamydia treatment to patients who were unable or unwilling to return for treatment of chlamydia and/or gonorrhea infections was able to increase the percent of infected adolescents (aged 12 to 19 years) who were treated from 54% to 81% [41].

Patient-delivered therapy also has been considered as a potential approach to increase the rate of partner treatment. A randomized controlled trial comparing the effect of patient-delivered azithromycin partner therapy to patient-referral of partners on repeat chlamydia infection rates found that young women who delivered the therapy to their partners reported that the method was acceptable and feasible [42]. However, there was only a small decrease in the rate of reinfection between the 14- to 19-year-old adolescent females randomized to patient-delivered partner therapy and the adolescent females randomized to patient-referral of partners (13% vs 17% reinfected) [42]. Given that patient-delivered partner treatment is dependent on the behaviors of the index patient and his or her partners, the limited success of this intervention is unsurprising. The authors suggest that patient-delivered treatment could be one of a menu of options for partner treatment but cannot stand alone.

Approach to abnormal cervical cytology (human papillomavirus sequelae)

Although persistent HPV infection is strongly associated with abnormal cervical cytology results, development of HPV-associated cervical cancer is extremely rare in adolescents [43]. Among 601 13- to 21-year-old females followed with HPV DNA testing, cytology, and colposcopic evaluation, those tested HPV DNA–positive were approximately seven times more likely to develop cervical LSIL, compared with those who were negative, and 109 of 496 HPV-infected females (0.21; 95% confidence interval = 0.17–0.25) developed LSIL over a 60-month period [14]. Nevertheless, the National Cancer Institute's Surveillance, Epidemiology, and End Results reported that from 1995 to 1999, no adolescents aged 19 years or younger developed invasive cervical cancer and only 1.7 per 100,000 of those aged 20 to 24 years developed invasive cervical cancer [43].

Given that the occurrence of cervical cancer and precancerous lesions in adolescents is rare and the occurrence of transient HPV infections and associated abnormal cervical cytology is common, the revised American Cancer Society Guidelines for the Early Detection of Cervical Neoplasia and Cancer [43] recommend beginning cervical cancer screening among adolescents approximately 3 years after the onset of vaginal intercourse but by no later than age 21 years. The American College of Obstetricians and Gynecologists released a practice bulletin with similar recommendations in July 2003.

Prevention

Herpes simplex virus

Vaccination before risk-exposure (*ie*, before coitarche) has the potential to protect adolescents from subsequent infection with STDs. Results from two recent large, multisite, randomized trials of HSV-2 glycoprotein-D–adjuvant vaccine suggest that the vaccine may provide some protection against genital herpes disease in females who are seronegative for HSV-1 and HSV-2 [44]. Vaccine-efficacy in study one was 73% (95% confidence interval = 19% to 91%) and in study two was 74% (95% confidence interval = 9% to 93%). However, the vaccine was not efficacious in females who were seropositive for HSV-1 and seronegative for HSV-2 at enrollment or in males regardless of HSV serostatus. The authors proposed that the vaccine was unable to confer additional protection against HSV-2 disease among females with HSV-1 antibodies beyond that already conferred by a previous HSV-1 infection. The authors proposed several hypotheses to explain the observed differences in gender vaccine response but acknowledged that the biologic explanation for this finding is unclear. Further study is needed before an effective HSV vaccine becomes available.

Daily suppressive antiviral therapy is another approach to reducing the rate of HSV transmission between discordant couples. The observation that use of suppressive antiviral therapy is associated with decreased mucosal shedding of HSV-2 in immunocompetent women prompted a randomized controlled study to determine whether suppressive antiviral therapy can prevent transmission of HSV between serodiscordant couples [45,46]. Infected partners from 1484 monogamous HSV-discordant couples were randomized to receive a 500-mg daily valacyclovir dose or placebo. Over the 8-month study period, nearly half as many susceptible partners of treated patients (14 of 743; 1.9%) acquired HSV, compared with partners of patients receiving placebo (27 of 741; 3.6%) [46].

Human papillomavirus

Human papillomavirus vaccination has the potential to prevent HPV infection and HPV-associated cervical cancer. A recent study demonstrated that an HPV-16 virus-like particle vaccine prevented persistent HPV-16 infection and reduced the risk for lesions that could lead to cervical cancer [47]. This randomized double-blinded study assigned 2392 16- to 23-year-old HPV-seronegative females to receive three doses of placebo or HPV-16 virus-like particle vaccine. Participants were followed with HPV-16 DNA and antibody tests and Papanicolaou tests 1 month after the third vaccination and every 6 months thereafter. Patients were referred to colposcopy according to protocol. Whereas the incidence of persistent HPV-16 infections was 3.8 per 100 woman-years in the placebo group, no cases occurred among the vaccine group (100% efficacy, $P < 0.001$). All nine cases of HPV-16–related cervical intraepithelial neoplasia occurred among the placebo recipients. Almost all (99.7%) of the females who received the HPV-16 vaccine seroconverted. The incidence of adverse events was similar in the placebo and vaccine groups. The most frequent adverse event experienced was pain at injection site. This promising vaccine is not commercially available but may be in the near future.

Conclusions

Utilization of new diagnostic tests for chlamydia and gonorrhea and vaccine development for HSV-2 and HPV have the potential to change the landscape of adolescent STD epidemiology. In order to fully capitalize on these advances and stem the tide of STD transmission, it will be necessary to broaden our reach so that more adolescents have the opportunity and are motivated to receive STD testing and vaccinations. Research suggests that some high-risk youth would be more motivated to undergo testing if they felt a greater sense of privacy, if they were to receive more information about STD sequelae, treatment, and testing options, and if they could be tested when they visited a health care professional for non-STD reasons [48]. An important step toward achieving these goals will be to provide better access to primary care services that also will improve our chances of immunizing young people against viral STDs as new vaccinations become available.

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- •• Of major importance

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