Cervical Cancer and HPV: Screening and Prevention

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Screening for cervical cancer: should start at 21 yr of age, regardless of sexual history (<21 yr, risk so low that not worth screening); for women 21 to 29 yr of age, Papanicolaou (Pap) test alone every 3 yr recommended; testing for high-risk human papillomavirus (HPV) performed if Pap test shows atypical squamous cells of undetermined significance (ASCUS), followed by colposcopy if test HPV-positive or routine screening if HPV-negative; if any other abnormality found, proceed to colposcopy, except in women 21 to 24 yr of age with only low-grade changes (for them, 2 more chances to clear abnormality before colposcopy); high-risk HPV cotesting — speaker performs with Pap test, regardless of Pap test result, for women ≥30 yr of age; however, necessary per recommendations of American Congress of Obstetricians and Gynecologists (ACOG), American Academy of Family Physicians (AAFP), and United States Preventive Services Task Force (USPSTF); they consider it acceptable, but not necessarily preferred, alternative; on the other hand, American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) do recommend Pap test plus high-risk cotesting as preferred alternative for women >30 yr of age, because more sensitive than cytology alone; screening interval — for woman 32 yr of age with negative Pap test and negative HPV cotest, next screening should wait 5 yr; with Pap test alone, next screening in 3 yr

Discontinuation: discontinue screening at 65 yr of age for woman at average risk who has been adequately screened (ie, 2 negative cotests or 3 negative Pap tests in last 10 yr, with most recent in past 5 yr); if history of cervical intraepithelial neoplasia grade 2 (CIN2) or greater present, screening interval — for woman 32 yr of age with negative Pap test and negative HPV cotest, next screening should wait 5 yr; with Pap test alone, next screening in 3 yr after treatment for abnormality indicated

Testing for low-risk HPV: not indicated in clinical practice (does not change management decisions if positive)

Clinical practice: 2011 survey — 25% did not perform HPV testing; of 75% who used HPV testing, two-thirds performed cotesting if patient <30 yr of age; 28% used low-risk HPV testing, and 50% used reflex HPV testing if Pap test showed high-grade squamous intraepithelial lesion (requires colposcopy, regardless of HPV testing result)

Goals of screening: maximize detection of disease (CIN grade 2 or 3 or cervical cancer) while minimizing harm

Rationale for guidelines: initiation at 21 yr of age — risk for cervical cancer in adolescence 0.0014%; women 21 to 24 yr of age given chance to recover because of very low risk for cervical cancer and highly effective immune system to reverse abnormal Pap test (if high-grade change present, colposcopy indicated); cytology alone recommended only for 21- to 29-yr age group; 90% of individuals become HPV-positive in their lifetime, but most <30 yr of age when disease contracted; 90% of individuals clear HPV infection; because of high incidence of infection, positive predictive value for abnormal test very low and results in more testing and more colposcopies for minimal increase in disease detection; for women ≥30 yr of age — Pap test alone every 3 yr or Pap test with HPV testing every 5 yr (normal Pap test with positive HPV test identifies risk for future disease); sensitivity of Pap test 33% to 94% and increases to 92% to 100% with HPV cotesting; negative Pap test and HPV test has 99.9% to 100% certainty of absence of disease; lag time between when disease acquired and time signs of dysplasia seen on Pap test; study — tested women with cotesting for HPV, HPV testing, or both, and watched for 6 yr; looked at risk of developing CIN grade 3 in 6 yr; found that if Pap test normal, risk for CIN grade 3 0.97% within next 6 yr (0.25% if HPV testing normal); Italian study — looked at women tested with Pap alone vs Pap plus HPV cotesting and risk for cervical cancer up to 8 yr; rise in disease seen after ≥3 yr in women tested with Pap alone; in those who had Pap and HPV cotesting, several more years before any abnormality seen

Adenocarcinomas: make up 15% of all cervical cancers (remainder squamous cell carcinomas); Pap test not effective for detection; HPV testing beneficial (HPV type 18 closely linked to adenocarcinoma)

Discontinuation of screening at 65 yr of age: with menopause, transformation zone shrinks and pulls up into cervical canal (less accessible; also, may make woman less susceptible to dysplastic changes from HPV); 90% of infections cleared; median time 20 to 25 yr from initial infection to cancer

Resources for interpretation of tests: ASCCP website and app; Pap Reader app

Primary screening for HPV: cobas system (Roche Pharmaceuticals) approved by Food and Drug Administration (FDA) for detection of HPV; this approach starts with HPV test and, if necessary, obtains Pap test before deciding on action; if HPV test negative, repeat in 3 yr; if HPV test positive for type 16 or 18, proceed directly to colposcopy; if HPV high-risk type positive (but not 16 or 18), perform Pap test (or reflex Pap test); if Pap test negative, repeat in 1 yr; if Pap test shows ASCUS or greater, proceed to colposcopy; approach goes from most sensitive (HPV test) to less sensitive but more specific (Pap test); offers simpler “decision tree” for providers (only 3 possibilities [HPV-negative, HPV-positive for type 16 or 18, or HPV-positive for other type])
Addressing the Need for Advanced HPV Diagnostics (ATHENA) study: looked at 3 screening strategies (cytology alone, cytology with HPV testing [traditional], or HPV plus cytology [ie, primary HPV screening]); primary HPV screening superior to cytology alone in detecting CIN3 and equivalent to cytology plus HPV test; also showed benefit of HPV testing for women 25 to 29 yr of age; Society of Gynecologic Oncology, ASCCP, ACOG, ACS, and ASCP — stated that HPV primary screening acceptable alternative to routine Pap test with HPV cotesting, but must use HPV detection system approved by FDA; HPV testing more sensitive than Pap test but not more specific, so HPV testing alone results in more colposcopies

Bimanual pelvic examination: no data to support as effective screening tool for cancer screening but screening tool that remains important for increasing compliance and for ovarian cancer based more on symptoms (speaker believes pelvic examination should be performed only if symptoms present)

Vaccination against HPV: persistent infection with high-risk HPV type necessary precursor for cervical cancer; types 16 and 18 account for 66% of all cervical cancers worldwide (other 12 high-risk types account for remaining 34%); types 6 and 11 account for 90% of genital warts (low-risk types); recommendations until April 2015 — bivalent or quadrivalent vaccine for boys and girls during health maintenance visit at 11 to 12 yr of age, but can use as early as 9 yr of age, with catch-up to ≤26 yr of age; change after April 2015 — after types 16 and 18, next-highest-risk types account for 24% of cervical cancers and 10% of HPV-related diseases; 9-valent HPV vaccine approved by FDA, protects against HPV associated with 90% of cervical cancers, 80% of high-grade cervical dysplasias, 85% to 95% of vulvar cancers, 80% to 85% of vaginal cancers, and 90% to 95% of anal cancers; 9-valent vaccine considered noninferior to bivalent and quadrivalent vaccines for protection against types 16 and 18; ≥96% protective against next 5 HPV types; based on Advisory Committee on Immunization Practices recommendations, may use 9-valent or 4-valent vaccine for males and females, and bivalent vaccine for females; dosing schedule same; may continue schedule with 9-valent vaccine if 4-valent vaccine not available; primary care physicians and counseling on vaccination — in survey, >50% of parents reported that vaccine never recommended by physician

Suggested Reading


Contraception

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Menstrual cycle: first day of menstrual cycle (day 1) — low level of progesterone and gradually increasing estradiol; midcycle — increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), followed by surge in progesterone and relative drop in estrogen, leading to shedding of endometrial lining

Effectiveness and efficacy: effectiveness represents how well treatment works in clinical practice (ie, typical or patient-driven use); efficacy how well treatment performs in clinical trials (perfect use); comparative effectiveness — withdrawal and spermicide or chemical contraception least effective, followed by barrier methods, then injectables, pills, patch, ring, combined contraception, and breastfeeding; implants, IUD, sterilization, and vasectomy most effective; unintended pregnancies — small percentage of women not using contraception accounts for ≥50% of all unintended pregnancies; among women who begin contraceptive therapy, 28% discontinue by 6 mo (by 1 yr, 33% to 50%); typical vs perfect use — in control group using no contraception, ≥85% became pregnant within first year; transdermal patches, rings, and IUDs showed increasing rates of efficacy (showed minimal differences between typical use and perfect use)

Individualizing therapy: important for increasing compliance and helping patient choose best method for particular needs

Risk for VTE: pregnancy increases risk; absolute risk — 10 to 15 VTEs/100,000 woman-yr with low-dose oral contraception; 20 to 30 events with pills containing desogestrel; >100 events during pregnancy; 551 events during postpartum period

Assess medical eligibility: smoking (consider age and number of cigarettes smoked per day); headaches (consider type); liver disease; inherited coagulopathy (no evidence supports screening of women without symptoms of coagulopathy before starting birth control, even with positive family history); systemic lupus erythematosus and rheumatoid arthritis; hypertension; anticonvulsant therapy (side effects and interactions); ischemic heart disease; criteria — Centers for Disease Control and Prevention released eligibility criteria based on common medical conditions in United States in 2011 with updated HIV guidance; offers rating scale for determining safest contraceptive method based on patient’s contraindications; from category 1 (use) to category 4 (not recommended)

Optimizing therapy: coexisting conditions may influence choice of contraceptive; may include acne, dysmenorrhea, polycystic ovarian syndrome, irregular menstrual control or unpredictable pattern, premenstrual syndrome (PMS), and migraine without aura; noncontraceptive benefits — decreased ovarian and endometrial cancers ≤20 yr after discontinuation of hormonal contraception; decreased incidence of pelvic inflammatory disease (PID); decrease in tubal pregnancies and total bleeding days; protection of fertility; control of hirsutism; acne management; treatment of PMS and premenstrual dysphoric disorder

Managing side effects and cost: side effects — ask what patient considers tolerable; give anticipatory guidance; cost — use of formularies; ability or requirement to return for follow-up; Affordable Care Act mandates no copay or coinsurance for contraceptive counseling; covers barrier, hormonal, implanted devices, emergency contraception, sterilization, patient education, and counseling

Assessment of breakthrough bleeding (BTB): potential causes — pregnancy; infection; gastrointestinal disturbances or disease causing chronic diarrhea; missed pills; bicycling or tricycling regimens; estrogen and progestin activity; formulation or delivery route; evaluate timing of BTB

Bleeding patterns by contraceptive choice: combined oral contraceptives (COCs), ring, or patch — spotting or BTB initially, followed by regular menses in longer term, except with continuous use of COCs; progestin-only pills — higher
risk for spotting or BTB; typically used in breastfeeding women or those with contraindications to estrogen use; *depot medroxyprogesterone acetate* — spotting or BTB initially, with ≈50% experiencing amenorrhea at ≈12 mo of use; *implant method* — ≈20% experience amenorrhea at 24 mo; important to determine when bleeding occurs in menstrual cycle; if bleeding in first half of OC pack, usually related to estrogen, so increase estrogen activity of OC; if bleeding in second half, usually progesterone deficiency, so increase dose of progesterone

**Symptoms of varying estrogen and progesterin states:** *estrogen excess* — cystic changes in breasts; *estrogen deficiency* — bleeding or spotting; absence of withdrawal bleeding; vasomotor symptoms in perimenopausal women; nervousness; *vasovagal atrophy*; *progesterin excess* — increase in blood pressure; increased appetite; depression; fatigue; decreased libido; *progesterin deficiency* — BTB in second half of cycle; heavy flow or clotting; dysmenorrhea; PMS symptoms (similar to those of estrogen excess)

**Perimenopausal concerns:** needs for contraception continue until 12 mo of amenorrhea (menopause) or age 55 yr (95% in menopause); FSH level not helpful as indicator; benefits of COCs include regulating patterns and stabilizing mood or vasomotor symptoms; *when to stop COCs* — no clear age limit; ACOG and North American Menopause Society recommend stopping between age 50 and 55 yr; if hot flashes occur during placebo period, consider 3-mo trial off (with backup method); counsel patients on risks of hormonal contraception vs risks of hormone replacement therapy

**Use of IUDs**

Menorrhagia and IUDs: *Monteiro study (2002)* — small study looked at women awaiting hysterectomy or endometrial ablation; all had failed previous regimens; received levonorgestrel-containing IUD (Mirena); at 3 mo, only 2 menorrhagic; by 9 to 12 mo, 21 of 44 amenorrheic; 75% decided not to have surgical procedure

Misconceptions about IUDs: contraindicated by PID; increase risks for infertility and ectopic pregnancy; monogamy required; not for use in teenagers; parity required; contraindicated by history of sexually transmitted infection

Ideal candidates: postpartum; not candidate for estrogen therapy; seeking bridge to menopause; having heavy painful menses; noncandidate or high-risk candidate for surgery; woman unsure of future family planning needs; smoker (particularly older or heavy smokers); woman who does not wish to use hormones at all (indication for copper IUD)

Common side effects: increased vaginal discharge (likely due to levonorgestrel); pain with intercourse (cut strings shorter); BTB or spotting (can use COCs in first few months); acne (use COCs)

**Suggested Reading**

1. At what age should screening for cervical cancer be started regardless of a patient’s sexual history?
   (A) 16 yr  (B) 18 yr  (C) 21 yr  (D) 24 yr

2. The American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology recommend the Papanicolaou (Pap) test plus cotesting for high-risk human papillomavirus (HPV) as the preferred method for screening women:
   (A) >18 yr of age  (C) >24 yr of age
   (B) >21 yr of age  (D) >30 yr of age

3. When should the next screening test be performed in a woman 35 yr of age who has just had a negative Pap test and negative HPV cotest?
   (A) 2 yr  (B) 3 yr  (C) 5 yr  (D) 7 yr

4. The Pap test is effective for the detection of _______ but not for detecting _______.
   (A) Squamous cell carcinoma; adenocarcinoma  (B) Adenocarcinoma; squamous cell carcinoma

5. Which of the following 2 types of HPV account for 66% of all cervical cancers worldwide?
   1. Type 6  2. Type 11  3. Type 16  4. Type 18
   (A) 1,3  (B) 2,4  (C) 1,2  (D) 3,4

6. _______ is defined as how well a particular treatment works in clinical practice, while _______ is defined as how well a treatment performs in clinical trials.
   (A) Efficacy; effectiveness  (B) Effectiveness; efficacy

7. At which of the following times is a woman at the highest risk for venous thromboembolism?
   (A) While taking low-dose oral contraceptives  (C) While pregnant
   (B) While taking pills containing desogestrel  (D) During the postpartum period

8. An increase in blood pressure and decrease in libido are characteristic symptoms of:
   (A) Estrogen excess  (B) Estrogen deficiency  (C) Progestin excess  (D) Progestin deficiency

9. The American Congress of Obstetricians and Gynecologists and the North American Menopause Society recommend stopping oral contraceptives between ages:
   (A) 40 and 45 yr  (C) 50 and 55 yr
   (B) 45 and 50 yr  (D) 55 and 60 yr

10. A woman with heavy painful menses who is a heavy smoker and is seeking a contraceptive bridge to menopause is a strong candidate for the use of:
    (A) An intrauterine device  (C) An diaphragm
    (B) A combined oral contraceptive  (D) A contraceptive patch

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Attention, CME/CE Participants
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