

CONTROVERSIES IN WOMEN'S AND MEN'S HEALTH



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LEARNING OBJECTIVES

1. Apply recent data regarding emergency contraception (EC) to the care of women who have had unprotected intercourse.
2. Estimate the best times during the menstrual cycle to administer EC for maximal effectiveness.
3. Assess recent literature regarding the effects of EC accessibility on pregnancy prevention, safe sex practices, and timing of administration for maximal effectiveness.
4. Analyze differences between the human papillomavirus (HPV) vaccine products available.
5. Evaluate the proper use and available evidence regarding the HPV vaccine in diverse male and female patient groups.
6. Design individualized postmenopausal hormone regimens to maximize efficacy and minimize risks.
7. Evaluate cancer risks associated with postmenopausal hormone therapy.

INTRODUCTION

Many controversies exist in women's and men's health care. Chapters in this book will address different therapeutic topics that may involve clinical

controversies. This chapter discusses several reproductive and postmenopausal health issues that require specialized pharmacotherapeutic knowledge and that offer opportunities for pharmacist involvement.

Pharmacist provision of emergency contraception (EC) and vaccines that prevent sexually transmitted infections (STIs) continues to evolve as new data emerge. Likewise, the everchanging balance of risks and benefits of postmenopausal hormone therapy (HT) requires pharmacists to marry current data with clinical judgment. By being well-versed in all of the pharmacotherapeutic options in these areas, pharmacists can apply the appropriate insight into risk assessment to best individualize recommendations.

EMERGENCY CONTRACEPTION

Product Updates

In 2006, the U.S. Food and Drug Administration (FDA) approved EC with levonorgestrel 0.75 mg without prescription in women 18 years and older. Controversy surrounded the approval delay and age limitation, with some claiming that the FDA did not act on sound scientific evidence but rather considered political views in these decisions. In 2009, pursuant to a legal challenge, EC was made available to women 17 years and

BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Stewart FH, Trussell J, Van Look PF. Emergency contraception. In: Hatcher ER, Trussell J, Nelson AL, Cates W Jr, Stewart FH, Kowal D, eds. *Contraceptive Technology*, 19th ed. New York: Ardent Media Inc., 2007:87–116.
- Policar MS. Female genital cancer screening. In: Hatcher ER, Trussell J, Nelson AL, Cates W Jr, Stewart FH, Kowal D, eds. *Contraceptive Technology*, 19th ed. New York: Ardent Media Inc., 2007:559–81.
- Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2007;56(No. RR-2):1–23. Available at www.cdc.gov/mmwr/PDF/rr/rr5602.pdf. Accessed May 27, 2010.
- The North American Menopause Society. *Menopause Practice: A Clinician's Guide*, 3rd ed. Cleveland, OH: The North American Menopause Society, 2007.

ABBREVIATIONS IN THIS CHAPTER

CHD	Coronary heart disease
CIN	Cervical intraepithelial neoplasia
CVD	Cardiovascular disease
EC	Emergency contraception
EPT	Estrogen plus progestogen therapy
ET	Estrogen therapy
HERS	Heart and Estrogen/Progestin Replacement Study
HPV	Human papillomavirus
HT	Hormone therapy
QALY	Quality-adjusted life-year
STI	Sexually transmitted infection
VAERS	Vaccine Adverse Event Reporting System
VTE	Venous thromboembolism
WHI	Women's Health Initiative

older without prescription. State laws in nine states (i.e., Alaska, California, Hawaii, Massachusetts, Maine, New Hampshire, New Mexico, Vermont, and Washington) allow pharmacists to provide EC to women younger than 17 years through pharmacist-initiated prescriptions and collaborative agreements.

Other methods of hormonal EC include the Yuzpe method, which contains high-dose ethinyl estradiol in addition to high-dose levonorgestrel. The marketed formulation for the Yuzpe method was voluntarily removed in 2004. Despite removal of the product, special dosages of regular combined oral contraceptives may be used for EC.

A generic progestin-only formulation is now available, making EC more affordable. In July 2009, Teva Pharmaceuticals, Inc. announced FDA approval for marketing of its new product that contains levonorgestrel 1.5 mg in one tablet. The original product consisted of two tablets taken 12 hours apart; however, studies suggested improved effectiveness and adherence when both tablets were taken at the same time. The new product, a single tablet taken within 72 hours of unprotected intercourse, formulated to improve ease of administration and adherence. Emergency contraception is also more effective the sooner it is taken after unprotected intercourse. Although the package information recommends that EC be taken within 72 hours of unprotected intercourse, studies have shown it may be effective up to 120 hours after coitus.

Effectiveness

Midcycle Effectiveness

Controversy exists about whether EC is less effective if taken during or after ovulation than before ovulation, and data remain unclear on this question. One study assessing 99 women reported three pregnancies in 17 women who

had intercourse within 2 days of ovulation and who took levonorgestrel 1.5 mg 2 days after ovulation. The expected number of pregnancies in this subgroup of the study was four. In contrast, no pregnancies were reported among 34 women who had unprotected intercourse and took levonorgestrel 1.5 mg within 2–5 days before ovulation. The expected number of pregnancies in this group was also four. In comparison, no pregnancies were observed in the remaining 51 women who reported having intercourse 1 day or more after ovulation. The authors concluded that administering EC during or promptly after ovulation might not prevent pregnancy and that, once fertilization occurs, EC likely does not have a postfertilization effect. The study was criticized for its small sample size, inaccuracy of participant self-report, imprecise measurement of EC effectiveness, and inability to exclude the possibility of a postfertilization effect of EC.

Another study reached similar conclusions by evaluating the timing and effect of levonorgestrel on bleeding patterns and pituitary-ovarian function. However, this study failed to include the pregnancy rates in the assessment. The investigators reported a shorter menstrual cycle when levonorgestrel was administered before ovulation, and no change in menstrual cycle when it was administered during or after ovulation. Administering levonorgestrel before the luteinizing hormone surge resulted in ovulation inhibition and shortening of the menstrual cycle by $10.9 \text{ days} \pm 1 \text{ day}$. In contrast, administering levonorgestrel after ovulation did not have an effect on menstrual cycle length and did not interfere with the luteinizing hormone surge. Data from both studies suggest that EC, taken before ovulation, alters the cycle and is more effective in preventing pregnancy than when taken during or after ovulation. Because these data are preliminary, and because its overall effectiveness in preventing unintended pregnancy is reported to be 60% to 89% when administered within 120 hours of unprotected intercourse, EC should be offered to all women regardless of ovulation timing.

Pregnancy Prevention Data

A few studies have addressed the accessibility and availability of EC, in particular, advance provision of EC and the prevention of pregnancy. One study assessed self-reported pregnancy and substitution of other birth control methods with EC in 1490 girls and women aged 14–24 years. This study had two treatment arms: one group was provided increased access to EC with advance provision of two packs in case of a contraceptive mishap or event of unprotected intercourse and unlimited supplies; the other group had standard access. The results showed that the increased-access group used EC sooner after intercourse and more often than the standard-access group; however, the incidence of pregnancy was similar between groups.

A meta-analysis of advance provision of EC found that in 6389 patients, advance provision increased single use 2.5-fold and multiple use 4.5-fold; however, there was no difference in pregnancy rates. Another systematic review of 23 studies found that advance provision of EC was associated with greater use but no decrease in pregnancy rates. Researchers speculate that these results were caused by the patients' lack of understanding and inability to recognize the risk of pregnancy after unprotected intercourse. In addition, misunderstanding of perceived risks, the stigma associated with obtaining EC, and misperceptions about the method were cited. Uncertainty regarding precise EC efficacy was also cited as a reason for these conclusions, and it was postulated that the effectiveness of EC may have been overstated.

Behavior

With increased access to EC, concerns have emerged about its potential effect on safe sex practices. Most studies have shown no differences in contraceptive use or sexual behavior between groups with increased access to EC compared with standard access. The same study that investigated pregnancy rates in 1490 girls and women aged 14–24 years also found no difference in self-reported contraceptive use. In addition, the study found similar rates of STIs (e.g., gonorrhea, chlamydia, trichomonas) between the two groups. Other studies found similar results including the aforementioned meta-analysis, which included 6389 women from the United States, India and China.

An earlier study from California found similar results when evaluating EC accessibility through a clinic, a pharmacy, or advance provision in 2117 female patients aged 15–24 years. The primary outcomes of pregnancy and STIs were similar between the groups, as were secondary outcomes of condom use and unprotected intercourse. Although increased access to EC may be perceived to change sexual behavior, data have not substantiated this concern.

HUMAN PAPILLOMAVIRUS VACCINE

Background

Human papillomavirus (HPV), the most common viral STI, includes about 100 different types of virus, with around 40 of them known to affect the genital tract. Genital HPV is transmitted sexually and can infect the vaginal mucosa, cervix, penis, anus, and rectum, causing genital warts and malignancies. In particular, HPV types 6 and 11 are known to cause about 90% of genital warts in men and women. Although most HPV infections resolve, persistent infection by one or more oncogenic types can cause cervical neoplasia and other cancers.

Of the 40 genital HPVs, 12 or 13 are considered high risk and may lead to anogenital cancers. Men also are at risk of HPV infections that can lead to penile and anal cancers. Because HPV infects the epithelial lining of the

aerodigestive tract, it is implicated in head and neck cancers as well as anogenital cancers. With these potential health hazards facing both sexes, HPV prevention and treatment are important.

An estimated 6.2 million people are infected with HPV each year. By age 50, about 80% of women will have been infected with HPV. The highest rates of infection occur in women younger than 25, and the highest risk of infection is within the first 5–10 years after initiation of sexual activity. Some studies have shown an annual incidence of 10% in women older than 25 and a second peak of infection in women older than 45.

For most people, HPV infections are cleared naturally by their immune systems. In an individual with impaired immune function, the risk is more complex. Even in those with adequate immune function, genital warts may require surgery. About 40% of HPV infections are latent, with 5% to 10% progressing to dysplasia and 1% to cancer. However, the risk of cancer increases with persistent infections. According to the American Cancer Society, cervical cancer is the second most common cause of death from cancer in the world and the leading cancer in developing countries.

Cervical cancer can affect women as young as 20 years; however, the average age reported for women with cervical cancer is 48 years. For women who are mid-career or caring for a family, cervical cancer has additional implications of cost-effectiveness, quality of life, and total years of life lost that may be greater than with cancers having a later onset. Risk factors associated with cervical cancer include smoking, older age, STIs, and immune suppression (e.g., human immunodeficiency virus infection, long-term use of immunosuppressant drugs). Prevention, early screening, and detection can decrease cervical cancer incidence. However, not all women have access to early screening and detection, which is a worldwide public health challenge. It is HPV types 16 and 18 that cause most cervical cancer cases worldwide. When HPV infects the cervical epithelium, cytologic and low-grade intraepithelial changes result that may progress to cervical intraepithelial neoplasia (CIN).

Cervical intraepithelial neoplasia is graded from 1 to 3 on the basis of the histology of the lesion (Table 1-1). Grade 1 (CIN 1) is not considered cancer and is generally not treated. Although grade 2 (CIN 2) is generally treated, an estimated 40% of lesions resolve spontaneously. Grade 3 (CIN 3) has the lowest potential of resolving and is likely to be invasive. The FDA considers CIN 2 and CIN 3, together with adenocarcinoma in situ, adequate markers for cervical cancer outcomes. The general time frame for cervical cancer to develop is about 20 years. In industrialized countries, the widespread use of Papanicolaou (Pap) smears and regular cervical screening help detect abnormal cytology or dysplasia earlier before cancer develops, thereby reducing the mortality rate. For additional prevention, HPV vaccines are administered.

Table 1-1. Classification of Cervical Pathology^a

Histopathology Grading	Clinical Findings	HPV Strains 6 and 11 ^b	HPV Strains 16 and 18 ^c	HPV Strains 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 ^d
Cervical condyloma	Cervical condyloma	Yes	No	No
CIN 1	Mild dysplasia	Yes	Yes	Yes
CIN 2	Moderate dysplasia	No	Yes	Yes
CIN 3	Severe dysplasia or carcinoma in situ	No	Yes	Yes

^aChart is based on current data and does not include all possible outcomes.

^bResponsible for 75% to 90% of genital wart cases. No risk of progression to CIN 2 or cancer.

^cResponsible for about 70% of cervical cancer cases. High risk of progression to cancer.

^dResponsible for about 30% of cervical cancer cases. Intermediate risk of progression to cancer.

CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.

Products Available

Two vaccines are available for the prevention of HPV infection (Table 1-2). The first HPV vaccine was licensed in the United States in 2006; this quadrivalent vaccine provides coverage against HPV types 6, 11, 16, and 18. The first two types are known to cause genital warts, whereas the latter two are most commonly associated with cervical cancer. Because the yeast *Saccharomyces cerevisiae* is used in the production process, people who have an allergy to yeast should not receive the quadrivalent vaccine. A bivalent vaccine licensed in 2009 provides coverage against HPV types 16 and 18 and contains an immunostimulatory adjuvant intended to increase immunogenicity.

The quadrivalent vaccine has been approved for girls and women ages 9–26 years in the United States. The bivalent vaccine is approved for use in girls and women 10–45 years old in other countries and for girls and women 10–25 years old in the United States. Both vaccines require a series of three separate intramuscular injections, with the quadrivalent vaccine given at 0, 2, and 6 months and the bivalent product given at 0, 1, and 6 months. The duration of efficacy is believed to be 6.4 years for the bivalent vaccine and at least 5 years for the quadrivalent vaccine. Insufficient information exists to determine whether efficacy lasts longer than 6 years, and there is not enough experience to know whether a booster dose will be needed to prolong protection.

Although the vaccine is intended for use in younger people not yet been exposed to the virus, it may have value in older women who have not been exposed to the viral strains covered by the vaccine. The Advisory Committee on Immunization Practices recommends vaccinating girls ages 11–12 years with the quadrivalent or bivalent vaccine, with the vaccination series starting as early as 9 years old. A catch-up series of injections given to those who did not receive the vaccine at the recommended time is available for women up to age 26; women may

receive remaining vaccinations after age 26 if necessary. The Advisory Committee on Immunization Practices recommends the bivalent vaccine for the prevention of cervical cancers and precancers and recommends the quadrivalent vaccine for the prevention of cervical cancers, precancers, and genital warts.

The HPV bivalent or quadrivalent vaccine may be administered concurrently with the recombinant hepatitis B vaccine at separate injection sites; because no data are available, it should not be administered in combination with other vaccines. Neither the bivalent nor quadrivalent vaccine has been well studied in pregnant or breastfeeding women, so they cannot be recommended for these patients. If a woman is found to be pregnant after the series has been initiated, it is recommended that she wait until the pregnancy is completed before finishing the series. The manufacturer of the quadrivalent vaccine is providing a pregnancy registry to collect additional data.

Administration of the HPV vaccine is not a substitute for routine cervical screening. Current cost of the quadrivalent vaccine is about \$120 for one injection and \$360 for the series. The cost of vaccinating large populations versus the cost of treating a smaller number of people with genital warts, CIN, or adenocarcinoma in situ remains to be evaluated. Availability of care should also be considered, especially among medically underserved groups for whom treatment of precancers and cancer might not be readily available.

Benefits

Several studies of women younger than 26 years have shown vaccine effectiveness at or near 100% in preventing HPV infection in women who are HPV-naïve; this would subsequently prevent HPV progression to high-grade CIN. These prospective randomized, double-blind, placebo-controlled studies enrolled large numbers of girls and women 16–24 years old and used the quadrivalent

Table 1-2. HPV Vaccines

Vaccine (Date of U.S. Approval)	Administration/Contents	Indications	ACIP Recommendations
Quadrivalent HPV (types 6, 11, 16, and 18) recombinant vaccine (June 2006 for use in girls and women; October 2009 for use in boys and men)	0.5-mL intramuscular injection provided at 0, 2, 6 months (three injections) Formulations: single-dose vials and prefilled syringes Each 0.5-mL dose contains: 20 mcg of HPV 6 L1 protein 40 mcg of HPV 11 L1 protein 40 mcg of HPV 16 L1 protein 20 mcg of HPV 18 L1 protein Inactive ingredients: 225 mcg of aluminum (as amorphous aluminum hydroxy phosphate sulfate) 9.56 mg of sodium chloride 0.78 mg of l-histidine 50 mcg of polysorbate 80 35 mcg of sodium borate Less than 7 mcg of yeast protein/dose ^a Water for injection	<i>Girls and women:</i> For prevention of genital warts and vulvar, vaginal and cervical cancer caused by HPV 6, 11, 16, and 18 in girls and women ages 9–26 years For precancerous lesions and dysplasias that include CIN 1, adenocarcinoma in situ, vaginal intraepithelial neoplasia grades 2 and 3, and vulvar intraepithelial neoplasia grades 2 and 3 <i>Boys and men:</i> For prevention of genital warts caused by HPV 6 and 11 in boys and men ages 9–26 years	<i>Girls and women:</i> Provide vaccine to girls between 11 and 12 years old at 0, 2, and 6 months Catch-up series for girls and women 13–26 years old at 0, 2, and 6 months; remaining catch-up injections may be administered after age 26 is necessary <i>Boys and men:</i> Provide vaccine to boys and men 9–26 years old at 0, 2, and 6 months
Bivalent HPV (types 16 and 18) recombinant vaccine (September 2009 for use in girls and women)	0.5-mL intramuscular injection provided at 0-, 1-, and 6-month intervals (three injection series) Formulations: single-dose vials and prefilled syringes Each 0.5-mL dose contains: 20 mcg of HPV 16 L1 protein 20 mcg of HPV 18 L1 protein Inactive ingredients: 50 mcg of 3-O-desacyl-4'-monophosphoryl lipid A 0.5 mg of aluminum hydroxide 4.4 mg of sodium chloride 0.624 mg of sodium dihydrogen phosphate dihydrate Residual amounts of viral protein less than 40 ng and bacterial protein less than 150 ng	For prevention of cervical cancer caused by HPV types 16 and 18 in girls and women ages 10–25 years For precancerous lesions and dysplasias that include CIN 1 or worse and adenocarcinoma in situ	Provide vaccine to girls 11–12 years old at 0, 1, and 6 months Catch-up series for girls and women ages 13–26 years at 0, 1, and 6 months

^aPatients allergic to yeast should not receive vaccine.

ACIP = Advisory Committee on Immunization Practices; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.

vaccine to prevent genital warts, vulvar or vaginal epithelial neoplasia, CIN, adenocarcinoma in situ, or cancer associated with HPV 6, 11, 16, or 18.

The efficacy rate in all women enrolled, regardless of prior exposure to HPV, was 44% for high-grade cervical lesions related to type 16 or 18 and 17% against high-grade cervical lesions from any HPV type.

Similar results were observed with the bivalent vaccine, reporting 90% efficacy for the prevention of CIN 2 in girls and women 15–25 years old. The bivalent HPV vaccine was also noted to provide some benefit against type 31 (about 36%) and type 45 (about 60%). Both types 31 and 45 are oncogenic similar to HPV types 16 and 18 and are responsible for about 10% of cervical cancer cases. The authors stated that a longer follow-up for this particular finding was indicated.

A 3-year follow-up to this study also found an efficacy of 93% against CIN 2 in women who were HPV-naïve, and efficacy of 30% against CIN 2 in women with prior HPV infection. Efficacy against types 31, 33, and 45 was noted in addition to a 33% efficacy rate against CIN 3. However, these findings were not primary end points of the study. The authors concluded that, based on the findings, vaccination of all women would be beneficial regardless of their HPV history. This is an important finding because women already infected with HPV may benefit from vaccination and decrease their risk of infection, precancerous states, or early cancer progressing to CIN 2 or CIN 3.

Overall, the two vaccines are efficacious in preventing cervical cancer associated with HPV types 16 and 18. Although both decrease the risk of HPV-associated cancers, questions remain about the immunogenicity of both and whether they are similar. Studies have shown that the bivalent vaccine elicits a stronger immune response, and antibodies may last longer without requiring a booster vaccine. One study compared the immunogenicity and safety of the quadrivalent vaccine with the bivalent vaccine in women ages 18–45 years. Results showed a 2.3- to 4.8-fold increase in geometric mean titers of serum neutralizing antibodies for HPV type 16 and a 6.8- to 9.1-fold increase for HPV type 18 in women regardless of age compared with the quadrivalent vaccine. Both groups reported similar adverse events and had adherence rates of at least 84%. This increased immunogenicity has yet to be evaluated with outcomes, and long-term data are lacking.

Adverse Effects

Concerns surround the safety of HPV vaccines in young women. Safety data are available from several trials, most enrolling girls and women ages 9–26 years who received the quadrivalent vaccine or placebo. Phase II and III studies showed overall patient safety and tolerability. Local adverse effects included pain, swelling, and erythema. Other adverse effects include headache,

nausea, and fever. The package labeling lists fever as the most common adverse effect at 13% versus 11.2% in the placebo group.

Postmarketing concerns have emerged with respect to serious adverse effects. A postmarketing study in Australia reported a higher than usual incidence of anaphylaxis among 114,000 girls and women 15–26 years old with 2.6 cases per 100,000 doses reported; this is higher than the average of less than 1 per 100,000 doses with other vaccines. However, the World Health Organization categorization of vaccine adverse events still considers the number of cases very rare (defined as less than 1 in 10,000).

The study comparing bivalent HPV vaccine and hepatitis A vaccine found no significant differences in adverse events. As of May 1, 2009, 13,758 adverse events attributed to the quadrivalent vaccine had been reported to the Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System (VAERS). About 7% of the adverse events were considered serious. The highest number of reports was in girls and women ages 11 to 18, the primary age group receiving the vaccine.

A postmarketing safety surveillance group for the quadrivalent vaccine reviewed 12,424 adverse reports received by VAERS between June 1, 2006, and December 31, 2008. This group reported a rate of 53.9 adverse events per 100,000 doses. The distribution rate of reports was 8.2 for syncope; 7.5 for local site reactions; 3.1 for hypersensitivity reactions; 0.2 for venous thromboembolism (VTE); 0.2 for autoimmune disorders and Guillain-Barre syndrome; and 0.1 for anaphylaxis and death. Reported serious adverse events were 6.2%, with 32 deaths identified.

Only 20 deaths had sufficient information for a thorough clinical review. Of those deaths, most were associated with other causes, and four cases were unexplained. The deaths were not associated with specific age groups, time of onset, or number of doses received. The authors note that 68% of the reports were from the manufacturer, and most cases lacked sufficient information for clinical follow-up. The authors state that the reporting rate for the HPV vaccine was higher than the manufacturer's reports for four other vaccines; these other vaccines, when combined, accounted for the other 32% of reports.

Syncope and VTE are among the adverse events that have generated the most controversy. A subset of VAERS data (from June 1, 2006, to August 31, 2008) report that about 50% of the syncopal episodes occurred the same day as the vaccination, and about 50% required hospitalization. Syncopal episodes in girls and women 11–18 years old have been more commonly reported with the addition of adolescent vaccinations such as tetanus toxoid, acellular pertussis, reduced diphtheria toxoid, and quadrivalent meningococcal conjugated vaccines. The authors stated that this female age group also had a higher background rate of syncope. With the HPV vaccine given

only to girls during the time of the study, notable reports of syncope in this age group may reflect reporting bias. Current Advisory Committee on Immunization Practices guidelines recommend waiting 15 minutes after vaccination, especially in this age group, to observe for potential syncopal events. The data for VTE should be interpreted with caution because about 90% of the 41 cases had a known risk factor for VTE. Overall, the surveillance report concluded the vaccine is safe despite disproportionate reports of syncope and VTE. Safety monitoring of the vaccine will continue because of the difficulty in inferring causality from VAERS data.

Use in Women Older than 26 Years

The value of HPV vaccination in older women remains controversial. It was first postulated that HPV vaccines would only be worthwhile in women who were HPV-naïve and had not yet become sexually active. In the United States, about 50% of women are sexually active by age 18, with 20% of those women having four or more sexual partners. About 98% of all women are reported to be sexually active by age 25. Therefore, the HPV vaccine seemed to have the most benefit in younger women.

A few studies have indicated value in vaccinating older women based on the premise that those with new sexual partners after age 26 may also be vulnerable to infection with new or higher-risk strains of HPV. A study in the United Kingdom reported that 11% of women and 17% of men had a new partner within the prior year. Data from Australia and the United States show similar findings. Studies have shown that the HPV infection rate decreases throughout the life span, but continued acquisition occurs as well.

The annual incidence of HPV infection is reported to be 5% to 10% in women ages 25–80 years. Women may be exposed to the more oncogenic types later in life. In some phase II studies that included women previously exposed to HPV, only 0.15% had evidence of infection with all four HPV strains covered by the vaccine. Another study of 40,000 women ages 16–26 years found only 7% had evidence of exposure to both HPV types 16 and 18. This study suggests there are various strains of HPV, and it is unknown in what sexual encounter a woman will be exposed. With sexual partners potentially changing throughout life, the vaccine may indeed benefit women older than 26 years.

One European open-label, nonrandomized, phase III study evaluated the bivalent vaccine in women ages 26–55, providing three phases of follow-up for up to 48 months. During the first year of follow-up, the primary and secondary outcomes included evaluating vaccine-induced immune response to HPV types 16 and 18 on the basis of seroconversion rates. Subsequent phases evaluated seropositivity rates and serum antibody concentrations at all time points. The antibody concentrations were compared with those of girls and women

15–26 years old from a previous study. Cervicovaginal secretions were also collected in a subset of women to evaluate antibody values. The study enrolled 667 women, with 531 completing all phases of the study. Findings from the study revealed 100% seroconversion for all age groups (i.e., 15–25, 26–45, and 46–55 years). Immunogenicity remained through month 24 regardless of age. The study also showed that most women were seronegative for HPV type 16 or 18, indicating that not all sexually active women are infected with HPV and seropositive. For women 46–55 years old who were seropositive on entry in the study, geometric mean antibody titers were 57- to 84-fold higher at month 7. Titers were 8- to 16-fold higher in month 24, indicating a possible boost in immunity for women already infected, which may help them fight off the infection. Antibodies were also detected in cervical secretions. All age groups tolerated the vaccine with similar rates of adverse events. The study suggests that the vaccine is beneficial in older women, even in those already infected with HPV. This may be particularly important because as women age, immunity may decline, placing women at increased risk of persistent HPV infections.

Another randomized, parallel, placebo-controlled, double-blind study with a follow-up of 2 years showed a per-protocol efficacy of 91% in preventing infection from HPV types 6, 11, 16, and 18 and 83% for HPV types 16 and 18 in women ages 24–45 years. Intention-to-treat analysis showed a lower efficacy of about 31% for type 16 and 23% for type 18. The authors concluded that the quadrivalent vaccine was safe and effective for women 24–45 years old who were not infected with the relevant HPV types at the time of vaccination. The 4-year study is ongoing.

A 7-year population-based, cohort study examining more than 9000 women ages 18–42 and older in Costa Rica suggested that as women age, the potential benefit of HPV vaccination decreases. Investigators concluded that the rate of new HPV infections decreases as women age, and that new infections do not progress to CIN 2 or worse in older women. Though the study had a large sample size, the short duration of 7 years does not adequately address the risk of developing cervical cancer, which may take 20–25 years to appear after the initial HPV infection. Consequently, benefits of the HPV vaccine in this age group are still being studied and recommendations are not yet established.

With conflicting studies and questions about cost-effectiveness, the HPV vaccine has not been approved for use in women older than 26. The FDA recently denied label approval of quadrivalent vaccine for use in women older than 26 because of a lack of data supporting its cost-effectiveness in this age group. The evaluation included weighing the vaccine cost against the cost of cervical cancer screening and treatment of high-grade CIN and other conditions that are vaccine preventable.

One study evaluated the cost-effectiveness of administering HPV vaccine to girls up to age 12 (assuming lifelong immunity). Using quality-adjusted life-years (QALYs), the cost was found to be \$43,600 per QALY gained compared with current screening practices. Reported cost was about \$97,000 per QALY for vaccinating women 18–26 years and \$150,000 per QALY for women older than 26 years. The costs increased if a booster immunization was needed after 10 years. Internationally, a pharmacoeconomic threshold of \$50,000 or less per life-year saved is considered cost-effective. The manufacturers of both the bivalent and quadrivalent vaccine continue to provide information and seek an FDA-approved indication for women older than 26.

Use in Boys and Men

Men as well as women are affected by HPV, although anal and penile cancers from HPV occur at rates much lower than cervical cancer in women. Penile cancer is rare, accounting for about 0.5% of cancers worldwide; however, HPV is responsible for about 50% to 75% of these cases. Furthermore, some oropharyngeal cancers may be attributable to HPV. Bladder and prostate cancer have also been linked to HPV. Because HPV is often asymptomatic in men, transmission between men and women or men and men may occur unknowingly. Transmission is not necessarily prevented by condom use.

There are fewer data on HPV testing available for men than for women. Authors of a retrospective review identified 40 publications on HPV DNA detection and risk factors for HPV in men. The studies varied in sites and methods of collection, as well as in DNA analysis method, test sensitivity, and populations. Standardization of testing in men is an important issue. The authors also stated that few studies have evaluated the natural history of HPV in men. Data about the incidence of acquisition and duration of HPV infection in men are lacking, making it difficult to assess the efficacy of vaccines.

A recent study presented at the International Papilloma Congress discussed the use of the quadrivalent vaccine in men ages 16–26 years. The study evaluated the vaccine use in 3463 heterosexual and 602 homosexual men in 18 countries. Participants were randomized to receive either the vaccine or placebo at 0, 2, and 6 months. Primary end points included the efficacy of the vaccine against HPV types 6, 11, 16, and 18 and the development of external genital lesions, warts, and penile, perineal, and perianal intraepithelial neoplasia. At baseline, about 16% of men had at least one HPV type targeted by the vaccine, but less than 1% had all four types. None of the participants had evidence of genital warts or lesions.

Samples from the penis, scrotum, and perineal/perianal area were taken during genital examinations at 7 months. The results revealed a per-protocol analysis efficacy of 90% against external lesions (79% in men having sex with men), 89% against anogenital warts, and 100%

against intraepithelial neoplasia. Adverse effects were similar in each group. The investigators concluded that the vaccine was safe and efficacious in men and may be beneficial, but these findings have not been published.

The FDA recently approved a label indication for use of the quadrivalent vaccine in boys and men. The approval was based on data showing the vaccine to be 89% effective in preventing genital warts associated with HPV types 6 and 11 in men; 79% effective in preventing persistent infections from HPV type 16; and 96% from HPV type 18. Adverse effects reported included headache, fever and pain, erythema, itching, swelling, and bruising at the injection site.

The Advisory Committee on Immunization Practices guidelines provisionally recommend the use of the quadrivalent vaccine in boys and men ages 9–26 years to prevent genital warts. As with girls, cost-effectiveness has also been considered in vaccinating boys. Using QALYs, a study in the United States assessed the use of the HPV vaccine in 12-year-old girls and found a cost-effectiveness of about \$15,000 per QALY, with a 62% reduction in cervical cancer from all HPV types and a 95% reduction associated with types 16 and 18. When boys were included for vaccination, the decline in cervical cancer cases declined by another 5%, but the costs increased to more than \$440,000 per QALY.

Another study assessing the use of the HPV vaccine in 12-year-old girls found an incremental cost-effectiveness of \$40,310 per QALY gained when assuming 75% vaccination coverage and lifelong immunity compared with cervical cancer screening alone. When boys were added to the model, the cost-effectiveness ratio was \$290,290 per QALY. The investigators did not consider men having sex with men or cost-effectiveness on anal cancer in men in the analysis. This information conflicts with a study by the manufacturer of the quadrivalent vaccine that calculated about \$20,000 per QALY if both girls and boys were vaccinated at age 12 or had a catch-up series before age 24 in the United States.

Routine vaccination of boys may decrease the spread of anogenital warts and infections that cause cancer. The theory is that by vaccinating all, the risk of transmission from men to women is reduced.

POSTMENOPAUSAL HT

The use of postmenopausal HT has a long, controversial history. When results from the Women's Health Initiative (WHI) were published in 2002, the long-term benefits and risks associated with HT sparked further debate. Although the use of HT has declined, interest in HT products and regimens with improved tolerability has increased. This is likely because symptoms of menopause adversely affect the quality of life of many women, potentially for a prolonged period, and HT remains the most effective therapy for providing relief. It is a

well-publicized recommendation that HT be used at the lowest effective dosage for the shortest possible time. However, women who are younger or who experience premature menopause because of hysterectomy or chemotherapy usually need higher HT dosages to relieve symptoms.

Trends in Product Development

In the search for alternative HTs, three trends have emerged: (1) additional estrogens and progestogens, (2) exposure to lower hormone dosages, and (3) non-oral routes of administration. Historically, most HT regimens in the United States contained orally administered conjugated estrogens and medroxyprogesterone acetate. The use of 17 β -estradiol alone, rather than as a component of conjugated estrogen formulations, is now widespread. There is interest in the use of estriol and estrone in compounded HT formulations, but safety and efficacy data are lacking. Additional progestogens available for HT include micronized progesterone; and, as in combined oral contraceptives, levonorgestrel, norethindrone, and drospirenone. Micronized progesterone and drospirenone offer the advantage of having no mineralocorticoid effects.

A greater variety of doses are now available for oral and non-oral HT. This enables individualized treatment regimens and incremental dose titration, starting with lower doses when appropriate. Examples include conjugated estrogens in 0.3-mg and 0.45-mg doses; 14-mcg/day and 25-mcg/day transdermal estradiol patches; very low-dose vaginal estrogen tablets; and estrogen-eluting vaginal rings, including a very low-dose ring to provide only local estrogen. Administering oral progestogens in HT at 3-month intervals has been tried, with the goal of limiting progestogen exposure, but safety data from large trials are lacking.

A 2009 systematic review of studies of endometrial safety with HT provides limited information on endometrial protection with intermittent use of progestogens. Three small studies incorporating a total of 325 women compared intermittent progestogen regimens with monthly progestogen use for up to 3 years and found a similar risk of endometrial hyperplasia among the groups. A fourth trial of 240 women receiving higher daily dosages of estrogen commonly used in Europe (2 mg of 17 β -estradiol) plus norethisterone for 10 days every 3 months found higher rates of endometrial hyperplasia at 3 years in the intermittent progestogen versus monthly use group (15% vs. 2%). This led to study termination at an average of 2.8 years rather than the planned 5-year duration. Additional studies are needed to clarify whether there is a maximal safe estrogen dosage or progestogen interval. The disadvantage to cycling progestogens, whether at 1-month or 3-month intervals, is that this can produce withdrawal bleeding, a highly undesirable effect in postmenopausal women.

Clinical studies are under way to evaluate the advantages of non-orally administered estrogens and progestogens. In addition to transdermal estrogen patches, a transdermal spray, topical emulsion, and several 17 β -estradiol transdermal gels are available. Options for vaginal estrogen administration include 17 β -estradiol and conjugated estrogen creams, a 17 β -estradiol ring and estradiol acetate ring, and an estradiol hemihydrate tablet. With non-oral administration, first-pass metabolism is avoided, so smaller estrogen dosages are required to achieve physiologic concentrations. In addition, there are reduced effects on coagulation and fibrinolytic factors, sex hormone-binding globulin, C-reactive protein, and lipid particles.

Progestogens given non-orally, bypassing first-pass metabolism, may prevent mood changes or sedation in women sensitive to these effects from oral products. Non-oral progestogen options include the levonorgestrel-containing intrauterine device, progesterone vaginal gel, and transdermal patches containing norethindrone acetate or levonorgestrel in combination with 17 β -estradiol. The levonorgestrel intrauterine device and the progesterone vaginal gel do not have an FDA-approved labeled indication for use as endometrial protection in postmenopausal women. Progesterone administered as a topical skin cream or gel does not provide systemic concentrations sufficient for endometrial protection.

Clinical Uses of Newer Products

Revised FDA labeling includes three possible indications for HT: (1) moderate to severe vasomotor symptoms, (2) moderate to severe vulvovaginal symptoms, and (3) osteoporosis prevention. The lower estrogen dosing regimens and non-oral routes of administration have a more limited scope. The topical and transdermal estrogen gels, emulsion, and spray are labeled for treatment of vasomotor symptoms but not prevention of osteoporosis. One topical gel formulation is approved for both vasomotor and vulvovaginal symptoms. The ultra low-dose 14-mcg/day estrogen patch improves bone density and is labeled for osteoporosis prevention. However, there are no data to support fracture risk reduction like that demonstrated in earlier trials with oral conjugated estrogens.

Vaginally administered estrogens can produce systemic blood concentrations, especially on initial use in women with atrophic vaginal tissue, but this is not sufficient or consistent enough for treating vasomotor symptoms or preventing bone loss. The estradiol acetate ring is designed to provide systemic concentrations sufficient to treat both vulvovaginal and vasomotor symptoms; in contrast, the lower-dose 17 β -estradiol ring is designed to treat local symptoms only. Proposed indications for compounded estrogen formulations are not FDA-approved at this time.

Safety Controversies

Postmenopausal HT was originally used to treat menopausal symptoms but since the 1970s has been promoted to prevent diseases associated with aging in women. In the 1990s, several prospective studies, including the WHI and the Heart and Estrogen/Progestin Replacement Study (HERS), were undertaken to provide evidence of the positive effects of HT on heart disease and other conditions such as osteoporosis and dementia. These studies incorporated the most commonly prescribed oral HT regimens at the time and were not designed to evaluate HT for symptomatic women at menopause because most subjects were age 60 and older. Unfortunately, HT did not reduce cardiovascular disease (CVD) events as anticipated. Breast cancer risk was not a new concern, but a possible relationship with medroxyprogesterone acetate was identified. Although the HT arms of the WHI were halted in 2002 and 2004, publication of post hoc analyses of the data continues. This, together with emerging data from more recent clinical trials, provides for frequent and often contradictory conclusions about the safety of postmenopausal HT.

Cardiovascular Disease

The unexpected lack of cardioprotection shown in HT users in the WHI and HERS prompted investigation into the effect of patient age and timing of HT initiation on cardiovascular risk. Most subjects in the WHI were 10 or more years beyond menopause when HT was initiated and were not stratified by age of onset. However, a post hoc evaluation showed a trend toward fewer coronary heart disease (CHD) events in women beginning HT within 10 years of menopause. This gave rise to the theory that initiating HT more than 10 years after menopause may have a destabilizing effect on already established atherosclerotic plaques, whereas early estrogen exposure may decrease plaque development.

A post hoc subgroup analysis of 1064 women ages 50–59 years in the WHI-Coronary Artery Calcium Study showed a lower coronary artery calcium score in women treated with estrogen therapy (ET) versus placebo (83.1 vs. 123.1). A recent post hoc analysis of the estrogen plus progestogen arm of the WHI, designed to further evaluate the time trend, documented an early increase in CHD risk within the first 2 years of HT use versus placebo. Women who initiated treatment within 10 years of menopause had a 29% higher CHD risk at 2 years and a 36% lower risk at 8 years, neither of which was statistically significant. Women who were more than 10 years past menopause had a more than 2-fold higher risk at both 2 years and 8 years, which was statistically significant. It appears that time past menopause and patient age will affect CHD risk, which will be important when interpreting the outcomes of future clinical trials.

Timing is also important in the development of other negative cardiovascular outcomes such as VTE

and stroke. Risk of VTE events in the WHI trials was increased in the first 1–2 years of therapy, but the absolute risk was greater in the cohort of women who initiated HT after age 60. In addition, ischemic stroke events in the WHI occurred primarily in the cohort of older study participants, particularly in those older than 70. Evaluation of this relationship was complicated by the low event rate in the trial.

Because the WHI was not intended to evaluate HT use in symptomatic women in the early postmenopausal period (only 33% of women in the estrogen plus progestogen arm were 50–59 years old), these data cannot be generalized to this population. To further complicate clinical decision making, it appears that the presence of vasomotor symptoms may impact the cardiovascular risk associated with HT. For example, combined analysis of the two arms of the WHI showed a trend towards higher CHD events in the older participants who displayed persistent vasomotor symptoms compared with recently menopausal women with symptoms. Subanalysis of participants in the HERS trial (average age about 67 years) showed a trend toward greater risk of CHD events within the first year of hormone therapy in women reporting menopausal flashes at study entry compared with those who were asymptomatic. Data beyond the post hoc subanalyses of WHI or HERS will be required to fully explore the CVD risk associated with the currently accepted use of HT, which is management of symptoms in early menopause.

Investigation of the cardiovascular safety of HT regimens beyond the traditional oral conjugated estrogens plus medroxyprogesterone acetate continues to be an area of focused research. When orally administered estrogens undergo first-pass metabolism, they increase activated protein C resistance, factor VII, and C-reactive protein and decrease concentrations of anti-thrombin III and protein S. In contrast, transdermal estrogens appear to have a neutral effect on coagulation factors and C-reactive protein. A 2008 pooled analysis of 17 randomized controlled and observational trials included four trials of transdermal estrogen use. The analysis found a 2.5-fold higher risk of VTE in users of oral estrogen versus placebo but no increased risk with transdermal estrogen versus placebo.

A French case-control study of 80,000 postmenopausal women ages 60–85 documented a 70% increased risk of VTE in users of oral estrogens and no increased risk with transdermal estrogens. This study also compared VTE risk among progestogens and showed no significant increase in the risk of VTE with micronized progesterone, medroxyprogesterone acetate, or other pregnane or nortestosterone derivatives. Norpregnane derivatives such as nomegestrol acetate and promegestone were associated with a 4-fold higher risk. Ongoing trials of non-oral estrogens and alternative progestogens

will further clarify any effect on VTE risk reduction with HT.

Breast Cancer

The association between breast cancer and the use of HT remains controversial, with implications for hormone dosing, types, and duration of use. It is accepted that estrogen promotes breast cell proliferation. The small increase in breast cancer observed in WHI data may be more consistent with stimulation of existing subclinical cancer rather than with development of new tumors. However, this theory does not address increases in both estrogen receptor–positive and –negative tumors.

The progestogen component of the regimen is a possible contributor. Data from randomized controlled and observational trials show an increased incidence of breast cancer with the use of estrogen plus progestogen therapy (EPT) versus ET. A 2005 review of postmenopausal HT evaluated the incidence of breast cancer with ET or EPT. The combined analysis of four randomized controlled trials involving about 20,000 women yielded a 20% risk reduction in ET users and a 24% higher risk in EPT users.

Estrogen receptor–positive breast cancer rates in the United States declined after the results of the WHI trial were published in 2002, and this has been attributed to the estimated 38% reduction in HT use occurring that year. An annual age-adjusted reduction of 8.6% occurred when the 2004 rates were compared with data from 2001 in the National Cancer Institute's Surveillance, Epidemiology, and End Results registries. This finding is distinct from a downward trend in breast cancer rates in women 45 years and older that began in 1998 and was attributed to increased rates of screening mammography.

A subgroup analysis of the WHI randomized controlled and observational trials compared the year after study discontinuation with the last year of the trial and found 28% and 43% reductions, respectively, in breast cancer. This finding was not accompanied by a change in the mammography rate. Of note, this effect was evident in a much shorter time than the several years it normally takes for a breast tumor to become evident. One theory is that the discontinuation of HT stopped stimulating the growth of existing estrogen receptor–positive tumors and allowed them to regress. It is not clear whether these tumors will become evident later. Many factors contribute to breast cancer (e.g., genetics, reproductive history, environmental exposures), and the causal effect of any of these, as well as of HT, is difficult to establish. Additional research may clarify the contribution of HT and help determine risk reduction strategies.

Mammographic density is also associated with breast cancer risk. When an increase in mammographic density was noted in a subanalysis of WHI data in association with breast cancer risk, the assumption of cause and effect was made. However, the type of mammographic

density associated with HT use has not been proved to increase breast cancer risk. Small sample sizes and short study durations limit the ability to confirm a direct association. Lowering dosages and discontinuing HT before mammography can result in inadequate control of menopausal symptoms and reduced quality of life; thus, these changes are not recommended.

The use of estriol-based regimens as a safer HT alternative is a poorly studied trend. In contrast with estradiol and estrone, estriol preferentially binds to estrogen receptor β , resulting in an antiproliferative effect on breast cancer cells. Animal and in vitro studies have shown promise, but it is too early to determine a clear safety advantage because randomized controlled data in humans are lacking.

There is continued focus on whether the type of progestogen influences the risk of breast cancer, given that most clinical trials in the United States used medroxyprogesterone acetate–based regimens. One proposed mechanism for this difference is a relative inhibitory effect of progesterone on estrogen-stimulated breast epithelial cells in vivo compared with synthetic progestogens. Analysis of a large French cohort study of cancer risk in about 100,000 women ages 40–65 years at entry showed that breast cancer rates were higher for the EPT regimens using progestogens other than progesterone. Specifically, medroxyprogesterone acetate was associated with a 48% higher risk than no EPT use. In this study, oral versus transdermal routes of progestogen administration did not affect risk.

A different risk pattern with synthetic progestogens was identified in a recent German case-control study of postmenopausal women ages 50–74 years at diagnosis. A 2.3-fold higher risk of breast cancer was documented with norethisterone or levonorgestrel-based regimens versus placebo compared with a 1.5-fold higher risk with progesterone-based regimens versus placebo. In the observational Million Women Study of women ages 50–64 in the United Kingdom, all analyzed progestogens were synthetic (medroxyprogesterone acetate, norethisterone, norgestrel, and levonorgestrel), and the risk of breast cancer was similar between the drugs.

Several analyses from the Finnish Cancer Registry have further evaluated the impact of synthetic progestogens on breast cancer risk. Although an earlier analysis of more than 17,000 Finnish women ages 30–54 years using the levonorgestrel intrauterine system showed no association with increased breast cancer rates, a recent analysis of about 9000 breast cancer cases diagnosed in postmenopausal women in the Finnish Cancer Registry showed a 2-fold higher risk. Another analysis of more than 200,000 postmenopausal women using HT in the registry found a 2-fold higher risk with norethisterone versus a 64% increase with medroxyprogesterone acetate. At present, the data are insufficient to recommend progesterone to

lessen the risk of breast cancer, but investigators continue to describe potential differences between progestogens.

The duration of HT use has been linked to breast cancer risk. This association is complicated by the delay between the time a tumor develops and when it becomes clinically detectable and is diagnosed. A 1997 analysis of 51 epidemiologic studies showed increased risk after 5 years of use, and latency time findings have varied in both clinical and observational trials. Participants in the WHI study receiving ET showed no increased risk of breast cancer in the mean 7.1 years of follow-up. An annualized analysis of risk in more than 16,000 EPT users of the WHI trial showed a 2-fold higher risk appearing 5 years after study entry, but the trend toward increased risk became apparent during year 4, and even earlier at year 3 in women with prior hormone use.

A 2005 review of epidemiologic studies published since the 1997 report found no increased risk associated with less than 5 years of ET; however, a 24% increased risk was found with 5 or more years of use. In contrast, a significantly increased risk was documented for EPT of less than 5 years (34%) and 5 years or more (89%). A 2009 analysis of more than 67,000 postmenopausal women in the Cancer Prevention Study II Nutrition Cohort suggested an increased risk of both lobular and ductal cancer after 2 years of EPT.

An additional influence appears to be the *gap time* (i.e., the time between menopause and initiation of HT). A combined analysis of the WHI randomized controlled and observational trials revealed that women exposed to hormones at the onset of menopause had a higher risk of breast cancer than those with a gap time greater than 5 years. A large French cohort study documented a similar finding.

As with CVD, results from ongoing trials will be necessary to define breast cancer risk associated with length of hormone exposure and timing of initiation.

Ovarian Cancer

Lack of data and conflicting findings from randomized controlled trials make the association between HT and ovarian cancer difficult to determine. Early observational trials documented increased risk of ovarian cancer associated with ET but not EPT, in contrast to studies associating EPT with breast cancer. However, a 2007 systematic review including data from observational and randomized controlled trials showed increased risk of ovarian cancer in users of both ET (28%) and EPT (11%).

Several observational trials have investigated duration of use and associated risk. Earlier trials showed risk with use greater than 10 years. However, an increased risk appearing after 5 years of EPT was evident in the more recent Million Women Study and the National Institutes of Health-American Association of Retired Persons Diet and Health Study. A 2009 prospective cohort study of

more than 900,000 Danish women ages 50 and older confirmed a higher incidence of ovarian cancer in current users of HT than in never users (0.52 cases per 1000 years vs. 0.40 per 1000 years). Risk was increased regardless of route of administration, type of progestogen, or length of therapy, and was evident even with the shortest duration of use up to 4 years. By 2–4 years after discontinuation, the risk was attenuated, and further reductions were evident beyond 6 years. The authors of this study did not adjust for prior use of combined oral contraceptives, which is associated with a reduced risk of ovarian cancer.

CONCLUSION

The controversial issues regarding EC, the HPV vaccine, and HT involve adolescent to geriatric patient populations. Pharmacists can make important contributions by clarifying therapeutic options in these controversial areas. By being informed about these complex topics and ongoing research, pharmacists can help other health care providers evaluate study data and guidelines, apply information to appropriate therapy, increase awareness of available dosage forms and routes of administration, and help develop treatment strategies and individualize patient care.

Pharmacists are well placed for direct interventions with patients. The nonprescription availability of EC provides pharmacist opportunities to counsel patients on optimal outcomes. In addition, many states allow pharmacists to provide immunizations. Pharmacists can educate and encourage appropriate HPV immunization. Pharmacists can use their knowledge of the different dosage forms and routes of administration to tailor HT to individual patient needs and provide ways to maximize convenience and adherence and minimize negative effects.

ANNOTATED BIBLIOGRAPHY

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This chapter is a standard tertiary reference for contraceptive options and reproductive health. In particular, this chapter highlights EC and provides useful background information including the history of EC. Dosage forms and formulations are discussed that may be used for EC such as the copper intrauterine device, RU-486, Yuzpe, and progestin-only methods. Clear charts indicate the product name and dosage for the Yuzpe method. The chapter also provides information on the effectiveness of EC, particularly in relation to the timing of ovulation. Adverse effects and ways to prevent them, in addition to standard counseling tips, are included. The chapter also

discusses EC initiation based on previous contraceptive methods used.

2. Pharmacy Access Partnership [homepage on the Internet]. A center of the Pacific Institute for Women's Health; c1999–2009. Available at www.pharmacyaccess.org. Accessed May 28, 2010.

This is the Web site of a nonprofit organization, Pharmacy Access Partnership, a subdivision of the Pacific Institute for Women's Health. The site provides information related to emergency and hormonal contraception. Links to other reputable resources are available, including locations for EC provision; references to key articles with information on EC use, effectiveness, and pharmacist provision; multilingual patient pamphlets; state legislation updates; and ways to become an EC provider.

3. Polis CB, Schaffer K, Blanchard K, Glasier A, Harper CC, Grimes DA. Advance provision of emergency contraception for pregnancy prevention: a meta-analysis. *Obstet Gynecol* 2007;110:1379–88.

This meta-analysis of advance provision of EC reviews eight studies involving 6389 participants from the United States, China, and India. Studies analyzed include the Yuzpe method, the levonorgestrel-only method, and the mifepristone regimens. Results from the analysis show that advance provision does not decrease pregnancy rates even though increased use was observed (single use, odds ratio [OR] = 2.52; 95% confidence interval [CI], 1.72–3.70; multiple use, OR = 4.13; 95% CI, 1.77–9.63). Results also did not show differences in STIs between the two groups (OR = 0.99; 95% CI, 0.73–1.34). Unprotected intercourse and changes in contraceptive methods also did not differ. This study supports previous research indicating that increased access to EC does not decrease pregnancy rates and does not alter safe sex behaviors and contraceptive use. This article is helpful for providers or those in an environment requiring education related to sexual behaviors and EC. The study includes diverse samples of women in different countries, indicating similar responses. Because it is a meta-analysis, it also provides a review of other studies and their references, a good resource for articles specific to this topic.

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This randomized controlled trial assessed the effect of maximal access to EC on pregnancy and rates of STIs. The study included 1490 sexually active girls and women ages 14–24 who were randomly assigned to receive either increased access at no cost (i.e., two EC packages in advance with unlimited resupply) or standard access with usual cost. Women were monitored for 1 year. Results showed that the increased-access group used EC sooner after intercourse and more often than the standard-access group. No differences between groups in the incidence of pregnancy were found (increased-access group 9.9/100 woman-years [95% CI, 7.7–12.6]; standard-access group

10.5/100 woman-years [95% CI, 8.2–13.2]). This study was one of the first to identify that increased use of EC does not necessarily result in decreased pregnancy rates compared with standard access. Studies continue to research this issue.

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This randomized, double-blind, placebo-controlled trial involved 5455 girls and women ages 16–24 years. About half were randomized to receive placebo, and the other half received quadrivalent vaccines at 0, 2, and 6 months. Coprimary end points were the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia, adenocarcinoma in situ, or cancer associated with HPV types 6, 11, 16, or 18. The analysis for the study was per protocol, defined as the women having no prior exposure to HPV before receiving the vaccine. Women were monitored for 3 years after the first injection. Results revealed that efficacy for the per-protocol group was 100% for all coprimary end points in the vaccine group; 34% (95% CI, 15–49) in the intention-to-treat analysis for vaginal, vulvar, or perianal lesions; and 20% (95% CI, 8–31) for cervical lesions. The data indicate that the vaccine is most effective for those who are HPV naïve. This article is one of the hallmark studies concluding that the quadrivalent vaccine is highly effective in preventing vaginal, vulvar, perianal, or cervical lesions related to HPV types 16 and 18 in women who are HPV naïve. The study included a large sample and a moderate follow-up period (other studies have had follow-up of 4–5 years). This study is useful for its discussion of HPV efficacy and associated adverse effects.

6. The Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions (FUTURE II trial). *N Engl J Med* 2007;356:1915–27.

This trial was one of the landmark studies showing the effectiveness of the quadrivalent HPV vaccine in decreasing the risk of HPV-related cervical cancers in young women who were HPV naïve. This randomized, double-blind, placebo-controlled trial involved 12,167 girls and women ages 15–26 (average age, 20) who received three doses of the quadrivalent HPV vaccine or placebo administered at day 1, month 2, and month 6. The primary composite end point was CIN grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV type 16 or 18. Participants were monitored for 3 years. Women received gynecologic examinations, Pap smears, and HPV DNA testing from genital swabs on the first day of randomization and on follow-up visits at 1, 6, 24, 36, and 48 months. The results showed 98% vaccine efficacy (95% CI, 86–100) for the prevention of the primary composite end point in per-protocol patients who were HPV negative, and 44% efficacy (95% CI, 26–58) in the intention-to-treat analysis. The estimated efficacy for the prevention of high-grade cervical lesions caused by any HPV type was 17% (95% CI, 1–31) in the

intention-to-treat analysis. Study authors concluded that the vaccine was highly effective in preventing high-grade cervical neoplasia in young women who had not been previously exposed to HPV-16 or 18. The data show good efficacy in the per-protocol analysis but not as much in the intention-to-treat arm. The study was well designed with a large sample size and was powered to detect differences specifically for high-grade neoplasia as requested by the FDA.

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This well-organized article provides a good background on the use of the HPV vaccine in older women. In particular, it discusses the mandate for using the vaccine in 12- and 13-year-old Australian girls and the vaccine availability to older women. It provides information on HPV epidemiology, burden of disease caused by infection, and patterns of HPV acquisition in older women. The article discusses the efficacy and safety of HPV vaccines in older women and provides estimates of past HPV exposures in women. It also discusses general recommendations and briefly reviews some of the important papers on this topic.

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This detailed report provides information about HPV vaccination with the quadrivalent vaccine. It reviews the epidemiologic information, background, and biology of HPV; describes clinical sequelae related to HPV infection; and lists incidence rates of the cancers associated with HPV. It also provides information about the quadrivalent vaccine such as antibody development and the associated local and systemic adverse effects. The report also provides information for vaccination in special populations that include pregnant and lactating women. Some cost-effectiveness data are available, but this is not the main focus. Recommendations for routine use and catch-up years are also available. Overall, the report provides detailed information on the quadrivalent vaccine and information about ongoing studies and ways to report adverse events. The main limitation of the report is that it does not discuss the bivalent vaccine or provide data on the use of the vaccine in women older than 26 or in men. It is good resource to review HPV, as well as to understand the vaccine and its associated risks and benefits.

9. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmeron J, Wheeler CM, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* 2007;369:2161–70.

The aim of this phase III, randomized, double-blind, controlled trial was to assess the efficacy of a prophylactic bivalent vaccine against HPV in 18,644 girls and women ages 15–25. Participants were randomized to receive either the bivalent vaccine or hepatitis A vaccine at 0, 1, and 6 months and were monitored for 12 months. The primary end point included vaccine efficacy against CIN 2 associated with HPV types 16 and 18 in women who were seronegative and DNA negative (81% for HPV type 16 and 87% for HPV type 18). The cohort included women with previous HPV infections and low-grade cytologic abnormalities. In women with positive cytology before receiving the vaccine, tests revealed oncogenic strains other than HPV types 16 and 18 in about 60%. Twenty-three cases of CIN 2 with HPV type 16 or 18 were reported, 2 in the bivalent vaccine group and 21 in the hepatitis A vaccine group. Of those, 14 cases (2 in the bivalent vaccine group) had acquired other oncogenic HPV types in addition to HPV type 16 or 18. The study concluded that the bivalent vaccine was efficacious for the prevention of CIN 2 and well tolerated. The estimated vaccine efficacy was 90.4% (97.9% CI, 53.4–99.3; $p < 0.0001$). The vaccine also provided some protection against HPV type 31 (36.1%; 97.9% CI, 0.5–59.5) and type 45 (59.9%; 97.9% CI, 2.6–85.2). A longer follow-up of this finding is indicated. Adverse events were similar in both groups, with pain, redness, myalgia, and swelling reported more often in the bivalent HPV vaccine group. This study provides efficacy data for the bivalent vaccine, cross-coverage of other HPV types, and safety data for the bivalent HPV vaccine in comparison with another vaccine.

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This 3-year follow-up to the PATRICIA trial evaluated the bivalent HPV vaccine against CIN 2. The primary end point was to assess vaccine efficacy against CIN 2 associated with HPV type 16 or 18 in women who were HPV seronegative and DNA negative at the start of the study and at 6 months. Mean (\pm SD) follow-up time was 34.9 (\pm 6.4) months. The study found a 92.9% (96.1%; CI, 79.9–98.3) vaccine efficacy in the primary analysis and a 98.1% (96.1%; CI, 88.4–100; $p < 0.0001$) efficacy against HPV types 16 and 18. An efficacy of 30.4% (96.1%; CI, 16.4–42.1) was found against CIN 2 in women with prior HPV infection, and an efficacy of 70.2% (96.1%; CI, 54.7–80.9; $p < 0.0001$) was found without prior infection regardless of HPV DNA type in the lesion. Efficacy against HPV types 31, 33, and 45 was also noted, in addition to a 33.4% efficacy rate (96.1%; CI, 9.1–51.5; $p = 0.0058$) against CIN 3 in women with prior HPV infection and an 87.0% efficacy rate (96.1%; CI, 54.9–97.7; $p < 0.0001$) in those without prior infection. These findings were not primary end points of the study. The adverse events were similar between groups. The study concluded that the bivalent vaccine was safe and efficacious against CIN 2 associated

with HPV types 16 and 18 and other nonvaccine oncogenic HPV types for 3 years after vaccination. The study is a good follow-up to the original trial assessing long-term efficacy and outcomes. The study was funded by the manufacturer of the bivalent HPV vaccine.

11. Munoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. (FUTURE III). *Lancet* 2009;373:1949-57

This randomized, parallel, placebo-controlled, double-blind study in several countries assessed the use of the quadrivalent vaccine in women ages 24-45 years. It is one of very few studies regarding HPV vaccine use in older women. This study provided participants with either the quadrivalent vaccine or placebo at 0, 2, and 6 months. Follow-up at the time of this assessment was 2.2 years; however, the study will continue for a total duration of 4 years. Coprimary end points include disease or infection with HPV types 6, 8, 16, or 18 and disease or infection related to HPV types 16 or 18 only. Per-protocol efficacy was 90.5% (95% CI, 73.7-97.5) for infections related to HPV types 6, 8, 16, and 18 and 83.1% (95% CI, 50.6-95.8) for HPV types 16 and 18. Intention-to-treat analysis showed lower efficacy of about 30.9% (95% CI, 11.1-46.5) and 22.6% (95% CI, -2.9 to 41.9), respectively. Adverse events were not significant in either group. The authors conclude that the quadrivalent vaccine is safe and effective for women ages 24-45 years not infected with the relevant HPV types at the time of vaccination. This study provides information related to the use of HPV vaccines in older women. The manufacturer of the quadrivalent vaccine funded the entire study.

12. Lalonde A. Chapter 7: cost-benefit analysis of HPV vaccination. *J Obstet Gynaecol Can* 2007;29(suppl 3):S43-S49. Available at www.sogc.org/guidelines/documents/gui196CPG0708revised_000.pdf. Accessed May 28, 2010.

This journal supplement provides helpful information regarding HPV vaccine use in Canada, the United States, and other countries. In particular, chapter 7 provides a good review of several HPV vaccine cost-benefit and cost-effective analyses in different countries by various investigators. This supplement compares data from manufacturers and includes variables such as vaccinations in men, vaccinations in older women, and length of immunity in the analyses. The information provided is clear and easy to follow, and tables are provided for comparisons. Other chapters in the supplement offer information on related topics such as HPV testing, prevention, and treatment and cervical cancer screening.

13. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. *Lancet Infect Dis* 2006;6:21-31.

This review article discusses the background of genital HPV in men. Data on HPV in men is limited, and this article provides a good overview of the available studies

and issues. This article provides a more in-depth review of the HPV types that cause cancer than other review articles. The article reviews the pathophysiology of HPV infection in men, risk factors, prevention, incidence of anal cancer, HPV vaccine data from phase I and II studies, and methods used to assess HPV in men. The article references 151 sources, which may be a starting point to obtain more information and resources associated with HPV in men.

14. Farquhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2009;2:CD004143.

This is an update of a 2005 review on the topic of long-term HT. The review incorporated 19 randomized controlled trials that addressed the use of ET and EPT in peri- and postmenopausal women. Because the focus was on the long-term use of hormones, the primary outcomes included VTE, CVD, breast cancer, gallbladder disease, fracture risk, colon cancer, and dementia. Issues of efficacy in the short-term treatment of menopausal symptoms are not addressed. The full review represents study data in detailed tables for comparison. General findings of EPT included an increased risk of VTE, CHD, stroke, breast cancer, and gallbladder disease. In women older than 65, there was an increased risk of dementia. No increased risk of breast cancer was associated with ET, but there was an increased risk of VTE, stroke, and gallbladder disease. Because observational trials are not included in this analysis, more recent findings that form the basis of HT controversies are not thoroughly discussed. The potential influence of various hormone types and routes of administration is not presented in discussions of CVD and breast cancer.

15. Birkhauser MH, Panay N, Archer DF, Barlow D, Burger H, Gambacciani M, et al. Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. *Climacteric* 2008;11:108-23.

This document reflects updates from a 2007 International Menopause Society workshop and updates the first such position paper from 2004. It provides a broad summary of benefits and risks of HT related to menopausal symptoms, osteoporosis, CVD, and cancers. Recommendations for dosing, routes of administration, and length of treatment are summarized for symptoms in the perimenopausal period as well as during postmenopause, for women up to 60 years of age. Updated data from recent analyses of CVD and breast cancer risks in the WHI and other studies are presented graphically. Other hormonal treatments of menopausal conditions are reviewed, including tibolone, selective estrogen receptor modulators, and androgens. In addition, nonhormonal management of menopausal symptoms is briefly addressed. Throughout the document, the authors highlight key practice points to facilitate clinical application of the information. A comprehensive list of recommended readings is divided by clinical topic and is a useful bibliography for key studies in menopausal health. As an international document, it is intended to provide general

principles for postmenopausal HT that can be adapted to specific regional needs and concerns.

16. Practice Committee of the American Society for Reproductive Medicine. Estrogen and progestogen therapy in postmenopausal women. *Fertil Steril* 2008;90:S88–S102.

This update from the American Society for Reproductive Medicine presents current data on the efficacy and safety of postmenopausal HT. Specifically, data on efficacy related to vasomotor and urogenital symptoms, fracture risk, cognitive effects, and colon cancer are summarized. Several useful figures and tables are provided, including definitions of common statistical terms used in the representation of clinical trial data. A table outlines the risks and benefits of EPT and ET in the WHI and HERS trials with hazard ratios and CIs for CHD, stroke, VTE, breast cancer, colon cancer, and hip fracture. An in-depth discussion of the current understanding of risks of stroke, VTE, and endometrial, breast, and ovarian cancers is provided. Data summaries are divided into evidence from epidemiologic studies versus randomized clinical trials when available, and expert commentary on the strengths and limitations of the studies is provided. Summary statements clarify the known risks and areas of future research that are needed.

17. The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:242–55.

This position statement updates a 2008 publication and summarizes current recommendations relevant to the benefits and risks of postmenopausal hormone use. Topics include vasomotor symptoms, vaginal symptoms, sexual function, urinary health, body weight, quality of life, osteoporosis, CVD, diabetes, endometrial cancer, breast cancer, mood and depression, cognitive function, and total mortality. Ovarian and lung cancer risks are new additions to the position statement. Although detailed data summaries are not the focus of the document, there is a summary of hazard ratios from the major randomized controlled trials in the areas of CVD, diabetes, and breast, ovarian, and lung cancers. There is additional information on dosage and regimen design, timing and duration of use, and use of bioidentical hormones, as well as issues with therapy discontinuation. The statement identifies areas requiring future research and provides an extensive list of recommended readings.

18. Canonico M, Plu-Bureau G, Lowe G, Scarabin P. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;336:1227–31.

The authors performed a systematic review and meta-analysis of eight observational trials and nine randomized controlled trials that evaluated the risk of VTE and postmenopausal HT. The pooled analysis of oral estrogen resulted in an OR of 2.1 (95% CI, 1.4–3.1). There was no difference in risk between users of ET (OR = 2.2; 95% CI,

1.6–3.0) and EPT (OR = 2.6; 95% CI, 2.0–3.2). The highest risk was observed in the first year of use (OR = 4.0; 95% CI, 2.9–5.7). In addition to the higher risk identified with oral (OR = 2.5; 95% CI, 1.9–3.4) versus transdermal (OR = 1.2; 95% CI, 0.9–1.7) route of administration, the analysis found that women with factor V Leiden mutation or prothrombin G20210A mutation were at highest risk (OR = 3.3; 95% CI, 2.6–4.1). Overweight or obesity was also associated with increased risk (OR = 2.6; 95% CI, 2.1–3.3). This study provides focus on a route of administration that is not discussed in previous meta-analyses. However, the pooled data are still from relatively small sample sizes. In addition, any potential impact on the risk of VTE by the type of progestogen cannot be determined.

19. Women's Health Initiative [homepage on the Internet]. Bethesda, MD: National Heart, Lung, and Blood Institute. Available at www.nhlbi.nih.gov/whi/index.html. Accessed May 27, 2010.

This dedicated Web site for the WHI trial includes a list of publications by topic areas (i.e., quality of life, calcium and vitamin D, cancer, CVD, cognition and dementia, diet, and HT). In addition, there is a summary of the design of the observational, HT, calcium and vitamin D, and dietary modification trials of the WHI, and updates intended for participants in the trials. Another useful link has information for investigators wishing to submit proposals for additional studies using WHI data. Overall, the Web site provides a comprehensive source for data linked with the WHI that extend beyond the better-publicized portions of the ET and EPT randomized controlled trials first released in 2002 and 2003. Because this document is organized by topic area, it is an easily accessible resource for those who wish to review an updated listing of related data for research, education, or clinical practice.

SELF-ASSESSMENT QUESTIONS

1. A 27-year-old woman comes to a community pharmacy to ask about emergency contraception (EC). She states that she had unprotected intercourse 2 nights before and is worried about becoming pregnant. After talking with her, you determine that she is around day 16 of her menstrual cycle. She states that her menstrual cycle is regular and that it occurs every 25 or 26 days. She is not consistently using one form of contraception. **Which one of the following is the best action to take for this patient?**

 - A. Inform her that EC is not appropriate.
 - B. Recommend a pregnancy test at her physician's office.
 - C. Provide EC and counsel her on how to use it.
 - D. Tell her to see a physician for an EC prescription.
2. A 34-year-old woman comes into a community pharmacy requesting EC. She states that she and her husband were out of town for the weekend and her husband's condom broke during intercourse 4 nights ago. She is worried about becoming pregnant. After talking with the patient, you determine that she is around day 8 of her menstrual cycle, which is regular, occurring every 27 or 28 days. The couple uses condoms as their method of contraception. **Which one of the following is the best assessment of EC effectiveness in this woman?**

 - A. It will likely be ineffective because she has already ovulated.
 - B. It will likely be ineffective because she is beyond the 72-hour time window.
 - C. It will likely be less effective because it will be taken during ovulation.
 - D. It will likely be effective because she is within the 120-hour time window.
3. A 17-year-old woman says she lost her oral contraceptive pack containing levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg over the weekend and has missed three pills. She had unprotected intercourse 3 nights ago and would like to buy the one-dose formulation of levonorgestrel 1.5 mg for EC. **Which one of the following is the best response to this patient's request?**

 - A. Deny provision of this EC formulation and instead refill her oral contraceptives.
 - B. Deny provision of EC because she is beyond the 24-hour time window for effectiveness.
 - C. Insist that she have a prescription to obtain this EC formulation.
 - D. Provide this EC formulation without a prescription to the patient.
4. A 16-year-old girl requests EC from the pharmacist without a prescription, stating she had unprotected intercourse 4 days earlier and is worried about becoming pregnant. **Which one of the following is the best response to her request?**

 - A. Provide EC now and give her an extra supply in case she has another emergency.
 - B. Recommend against the use of EC now and tell her to obtain an EC prescription for future use.
 - C. Provide EC now, as well as a supply of condoms for future use.
 - D. Provide EC with a prescription and instructions to take it as soon as possible.
5. You are approached by a clinic nurse who has concerns about a 21-year-old female patient. The patient has multiple sex partners and is requesting advance provision of EC. The patient uses condoms regularly, but the nurse is afraid to provide EC for fear the patient will stop using condoms. **Which one of the following is the best response to this concern?**

 - A. Recommend advance provision of EC for use after unprotected intercourse.
 - B. Recommend against EC advance provision and instead reinforce the use of condoms.
 - C. Recommend against EC advance provision and instead suggest spermicide.
 - D. Recommend advance provision for use as a regular contraceptive method.
6. A 29-year-old woman presents to her primary care physician for a routine physical examination. She has heard about the human papillomavirus (HPV) vaccine but is uncertain of its value. She is in a monogamous relationship and is sexually active. The cost of the vaccine is not an issue for her. **Which one of the following is the best recommendation regarding the HPV vaccine for this patient?**

 - A. Advise against the vaccine and monitor annually using Papanicolaou (Pap) smears.
 - B. Recommend the vaccine to reduce HPV transmission to future partners.
 - C. Advise against the vaccine because she is in a monogamous relationship.
 - D. Recommend the vaccine because her exposure status is unknown.

7. An 18-year-old woman presents to the clinic for an annual examination. When asked about her vaccine history, she states she has not received the HPV or hepatitis B vaccine and is interested in receiving them. Her medical history reveals that she has not had genital warts. **Which one of the following is the best treatment approach for this patient?**
- Catch-up series of the quadrivalent vaccine at 0, 2, and 6 months concurrently with the hepatitis B vaccine.
 - Catch-up series of the bivalent vaccine at 0, 2, and 6 months concurrently with the hepatitis B vaccine.
 - The bivalent vaccine at 0, 1, and 6 months.
 - The quadrivalent or bivalent vaccine at 0, 1, and 6 months.
8. A 47-year-old woman with a diagnosis of cervical intraepithelial neoplasia grade 1 (CIN 1) visits her physician to ask about receiving the HPV vaccine. She has been infected with oncogenic HPV types 16, 31, and 56. **Which one of the following is the best rationale for administering an HPV vaccine to this patient?**
- The bivalent HPV vaccine may stop the progression of CIN 1 to CIN 2 for her infected HPV types.
 - The quadrivalent HPV vaccine may stop the progression of CIN 1 to CIN 2 for her infected HPV types.
 - Either bivalent or quadrivalent HPV vaccine will result in the CIN 1 resolving without further treatment.
 - The quadrivalent vaccine is the most cost-effective in CIN 1 because of these HPV types.
9. A 21-year-old man who is receiving a catch-up series for hepatitis B asks if he can receive the HPV vaccine. Cost is not an issue for him. His social history reveals that he is sexually active with both men and women. **Which one of the following is the best approach to take for this patient?**
- Provide quadrivalent vaccine to decrease HPV transmission to his female partners.
 - Recommend against quadrivalent vaccine to decrease HPV transmission to men.
 - Recommend against quadrivalent vaccine and instead use the bivalent vaccine.
 - Provide quadrivalent vaccine to decrease his risk of genital warts and anogenital cancer.
10. A 9-year-old girl presents to her pediatrician for immunizations. Her parents would like her to receive the quadrivalent HPV vaccine. On review of her medical history, it is found that the child fainted once after receiving a different vaccine. **Which one of the following is the best recommendation to give her pediatrician and parents?**
- Recommend against the vaccine because she is at increased risk of syncope and venous thromboembolism (VTE).
 - Recommend the HPV vaccine with careful monitoring for at least 15 minutes afterward.
 - Delay the administration of the HPV vaccine until she is older and sexually active.
 - Delay administration until she is older and provide bivalent vaccine instead.
11. A 39-year-old woman asks her primary care physician about the quadrivalent HPV vaccine. She has heard about it and would like to know whether she would benefit from receiving it. She has no history of genital warts. She has been sexually active, but currently is single and not sexually active. She is working part-time but has no health insurance. **Which one of the following is the best justification for recommending against the HPV vaccine for this patient?**
- Given her medical history, she is unlikely to receive any health benefits.
 - Given her prior sexual activity, she is unlikely to benefit from a reduced risk of genital warts.
 - Given her age, her prior sexual activity, and the expense of the vaccine, it is unlikely to be cost-effective for her compared with having regular Pap smears.
 - Given her age, prior sexual activity, the expense of the vaccine, and the likelihood that she has CIN 2, she would receive no benefits from the vaccine.
12. A 32-year-old woman asks her primary care physician for the HPV vaccine. She is getting married in 4 months and has not engaged in sexual intercourse because she believes in waiting until marriage to become sexually active. **Which one of the following is the best counseling to provide this patient?**
- Given her age, she is unlikely to benefit by vaccine-associated reduction in genital warts.
 - Given her prior lack of sexual activity, she is likely to benefit from the vaccine.
 - Given her age and lack of sexual activity, the HPV vaccine will not be cost-effective.
 - Given her age, she is at high risk of HPV-associated cervical cancer and will benefit.
13. A 53-year-old postmenopausal woman requests hormone therapy (HT) for the uncomfortable hot flashes she experiences 10 times/day as well as

dyspareunia associated with vaginal dryness. Her medical history is significant for hypertension and hypothyroidism. Her uterus is intact, and her last menstrual period was at age 51. Her social history is significant for tobacco use (one pack/day for 32 years). Her current drugs include lisinopril, levothyroxine, and a nonprescription vaginal moisturizer.

Which one of the following hormone regimens is best for this patient?

- A. 17 β -estradiol topical emulsion (0.25%) applied once daily.
 - B. 17 β -estradiol vaginal ring (0.0075 mg/24 hours) inserted once every 3 months plus 200-mg micronized progesterone oral capsule once daily for 12 days/month.
 - C. 17 β -estradiol/levonorgestrel (0.045 mg/0.015 mg/24 hours) transdermal patch applied once weekly.
 - D. 0.625-mg conjugated estrogen/2.5-mg medroxyprogesterone acetate oral tablet once daily.
14. A 51-year-old woman seeks postmenopausal HT for severe vasomotor symptoms that have not responded to venlafaxine. She is otherwise healthy and has an intact uterus. Her last menstrual period was at age 50. Her physician wants to avoid oral estrogen administration. **Which one of the following regimens will best target this patient's symptoms?**
- A. Estradiol hemihydrate vaginal tablet (25 mcg) inserted two times/week plus levonorgestrel intrauterine system.
 - B. 17 β -estradiol/levonorgestrel (0.045 mg/0.015 mg/24 hours) transdermal patch applied once weekly.
 - C. Estradiol acetate (0.05 mg/24 hours) vaginal ring inserted once every 3 months.
 - D. Conjugated estrogen vaginal cream 1 g three times/week plus progesterone vaginal gel (4%) once daily for 10 days each month.
15. A 52-year-old woman with a family history of breast cancer is concerned about taking HT for severe menopausal symptoms. She has not had a hysterectomy, and her last menstrual period was at age 50. **Which one of the following approaches has the best evidence to minimize her risk of breast cancer?**
- A. Use a custom-compounded regimen containing estriol.
 - B. Administer micronized progesterone instead of medroxyprogesterone acetate.
 - C. Limit the dose of estrogen to the equivalent of 0.3 mg of conjugated estrogens.
 - D. Use an intermittently dosed medroxyprogesterone acetate regimen.
16. A 53-year-old woman seeks advice about postmenopausal HT for osteoporosis prevention. She had a hysterectomy 1 year ago because of fibroids. She has a family history of osteoporosis and a personal history of using oral corticosteroids for severe asthma when she was younger, and she is concerned about minimizing her risk. She does not smoke, she exercises daily, and she takes supplemental calcium and vitamin D. **Which one of the following regimens has the best evidence for reducing the risk of osteoporotic fracture in this patient?**
- A. 17 β -estradiol patch (14 mcg/24 hours) applied once weekly.
 - B. 17 β -estradiol vaginal ring (0.0075 mg/24 hours) inserted once every 3 months.
 - C. Conjugated estrogens 0.625 mg orally once daily.
 - D. Estriol 2 mg/estradiol 0.5 mg orally once daily.
17. A 56-year-old woman whose last menstrual period was at age 49 has used the 0.05-mg/day 17 β -estradiol patch two times/week plus 2.5 mg of medroxyprogesterone acetate orally daily for the past year for hot flashes. She is now choosing to discontinue HT because of concern about her risk of breast cancer. **Which one of the following attributes of this patient's HT regimen is most associated with increased risk of breast cancer?**
- A. Use of HT for 1 year.
 - B. Use of transdermal estrogen.
 - C. Use of oral medroxyprogesterone acetate.
 - D. Initiation of HT 6 years after menopause.
18. A 52-year-old woman whose uterus was removed 6 months ago because of fibroids is considering HT for treatment of severe hot flashes. She read in a magazine that HT could increase her risk of a blood clot. There is nothing in her or her family's history to suggest risk, but she is still worried. **Which one of the following would be most likely to minimize this patient's VTE risk?**
- A. Delay treatment for 2 years.
 - B. Limit use to not more than 5 years.
 - C. Use of transdermal estradiol.
 - D. Use of oral estriol.
19. The following healthy postmenopausal women are considering using HT for the first time. Each experienced menopause at age 51. **Which one has the greatest likelihood of increasing her coronary heart disease risk?**

- A. A 62-year-old with persistent vasomotor symptoms.
 - B. A 51-year-old with severe vasomotor symptoms.
 - C. A 64-year-old with evidence of osteopenia.
 - D. A 58-year-old with atrophic vaginitis.
20. **Which one of the following women has the lowest risk of ovarian cancer related to her postmenopausal hormone use?**
- A. A 60-year-old who initiated oral conjugated estrogens and oral medroxyprogesterone acetate at age 52 and discontinued 4 years ago.
 - B. A 54-year-old who has taken oral conjugated estrogens for 4 years.
 - C. A 63-year-old who has taken oral 17β -estradiol plus oral micronized progesterone for 6 years.
 - D. A 58-year-old who has used conjugated estrogens vaginal cream and oral medroxyprogesterone acetate for 10 years.