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Hormone-Based Contraception:
An Update of Novel Delivery Systems

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LEARNING OBJECTIVES
1. Identify the 3 reproductive stages of the female lifespan and the corresponding contraceptive goals.
2. Describe the stepwise approach used to facilitate contraceptive choices at each of the reproductive stages.
3. List advantages and disadvantages of the intrauterine, intravaginal, transdermal, and injectable hormone-based contraceptives.
4. Identify monitoring parameters that correspond to hormone-based contraceptives and the novel delivery systems.

ABSTRACT: The contraceptive market in the United States has undergone expansion over the last decade, including 4 novel, hormone-based delivery systems. Although oral contraceptives are safe and effective options, the recently marketed intravaginal, transdermal, and injectable combinations and progestin-only intrauterine formulation provide important alternative methods for patients.

Determining the most appropriate contraceptive choice can be facilitated by a 3-step approach that matches the goals of 3 reproductive stages, including delaying first pregnancy, spacing births, and completed childbearing. The first step addresses patient safety by screening for a patient's eligibility for a hormone-based contraceptive. It also involves identification of a need for non-contraceptive benefits, such as cancer prevention or treatment of acne or perimenopausal symptoms. The second step considers factors that influence the efficacy of a method, including the frequency and route of administration and adverse effects. The newer formulations offer non-oral options that are dosed at extended intervals, including weekly, monthly, and every 5 years. The combination methods are associated with efficacy, adverse effect, and bleeding profiles that are similar to oral contraceptives. A patient's preference is an important determining factor when choosing among the newer delivery systems. The third step is to identify a patient's concerns regarding future fertility and lactation. All hormone-based methods are reversible, but progestin-only formulations are preferred during lactation.

The 3-step approach for initial contraceptive selection must be accompanied by continued monitoring of adverse effects, device placement, and adherence to the regimen. The novel delivery systems allow for further options when matching contraceptive choices with individual patient needs.

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INTRODUCTION

Access to effective and safe contraception remains a top priority in the United States, as recent data estimate 3 million unintended pregnancies occur annually, with half reported in current contraceptive users.[1] Female sterilization is the most commonly used form of contraception in the United States overall, but hormone-based contraceptives are the most popular reversible methods.[2] Although barriers such as male condoms are typically more accessible and avoid systemic adverse effects (excluding rare latex allergy), hormone-based options offer more effective long-term contraception. Oral contraceptives have historically dominated the hormone-based options, as evidenced by their use in approximately 27% of respondents of a 1995 survey, while implantable, injectable, and intrauterine methods were used by only 5%.[2] Since the publication of this survey, the hormone-based contraceptive market in the United States has undergone drastic changes, as the Progestasert® intrauterine device (IUD) and the Norplant® implants have become unavailable. The loss of 2 options has been balanced by the introduction of 4 novel, hormone-based delivery systems, which join combination oral contraceptives, progestin-only oral contraceptives and the depot medroxyprogesterone acetate injection. Although oral contraceptives are expected to remain an important and widely used method, it is imperative that the potential roles of these newly marketed agents be clearly defined as contraceptive decisions become more individualized to patients' needs. This review will compare the contraceptive profiles of the OrthoEvra® transdermal patch, Nuvaring® vaginal ring, Mirena® IUD, and Lunelle® monthly injection with other available hormone-based options in an effort to identify their place in therapy across the reproductive lifespan.

The variety of available contraceptives allows practitioners to match the needs and preferences of each patient with the most appropriate method. Distinct goals accompany each of 3 reproductive stages in the female lifespan, which cover an average of 36 years.[3] Patients may be in the stage of postponing first pregnancy, spacing births, or completed childbearing. While high-method effectiveness and reversibility are primary concerns in the first stage, the second stage focuses on the timing of the return of fertility and potential effects of contraception on lactation. Finally, women who have completed childbearing desire highly effective methods with little concern for reversibility.[3,4] If practitioners consider these goals, it is likely that contraceptive choices will be modified several times as a woman passes through each stage.

A Stepwise Approach

Reproductive goals are not the only considerations when making contraceptive choices, but they provide a framework for further evaluation of needs. To facilitate contraceptive decisions at each stage in the reproductive lifespan, a 3-step approach can be employed. First, the patient is screened for medical eligibility and the need for non-

contraceptive benefits. Second, factors associated with maximizing efficacy are addressed, such as frequency and route of administration and adverse effects. Third, fertility and lactation concerns are considered. Although oral contraceptives have been the most popular methods in the past, this stepwise approach may help identify patients who are more appropriate candidates for the newly marketed, non-oral options.

Step One: Screen patient for medical eligibility and need for non-contraceptive benefits

Prior to the selection and initiation of any hormone-based contraceptive, each patient must be screened for the existence of potential precautions or contraindications through a comprehensive medical history. Barrier methods are typically preferred for women who are deemed ineligible for hormone use. Although the defined criteria are often age related and associated with women in the latter portion of the reproductive cycle, it is imperative to address them at every stage. The screening criteria for the newer routes of administration are based on the data derived from the worldwide use of combination oral contraceptives and progestin-only oral and injectable methods. In general, the safe use of these methods requires consideration of risk factors for cardiovascular and thrombotic disease, reproductive cancers, gastrointestinal disorders, osteoporosis, and sexually transmitted infections. This review is limited to a general summary of recommendations. A detailed classification system for determining medical eligibility for all contraceptive methods is available from the World Health Organization (WHO).[5]

Combination oral contraceptives have been historically associated with increased risk for myocardial infarction, venous thromboembolism, and stroke. The risk appears highest in patients with risk factors such as advanced age, cigarette smoking, hypertension, hyperlipidemia, and diabetes, and is minimized in healthy nonsmokers.[4,6-9] In the presence of multiple risk factors or a current or past history of thromboembolism, valvular heart disease, stroke, or migraine headaches, the risks of estrogen-based methods outweigh the benefits.[5] While progestin-only methods have been recommended in the past as alternatives for patients who have cardiovascular or thrombotic risk factors, recent updates recommend caution with all hormone-based formulations in these patients.[5] In patients who smoke but do not have other cardiovascular risk factors, progestin-only alternatives are still the preferred hormone-based method.[5]

The use of either combination oral contraceptives or depot medroxyprogesterone acetate (DMPA) has been associated with an increased risk for breast cancer.[4] Recent data conflict with past reports, indicating that past or current users do not have an increased risk for the development of breast cancer.[10,11] Family history appears to not increase risk, although data are conflicting and there is little data on risk in patients with the BRCA1 and BRCA2 genetic markers. For patients with a personal history of breast cancer, estrogen- or progestin-based contraceptives should be avoided.[5]

Cervical cancer is highly associated with infection with the human papillomavirus (HPV). Users of hormone-based contraceptives may not use barrier methods that reduce the risk of HPV transmission, and are, therefore, at a higher risk of cervical cancer. However, oral contraceptive use in the presence of HPV may further increase

risk if used for longer than 5 years.[12] The WHO criteria allow use of hormone-based contraceptives while patients await treatment for cervical cancer.[5]

Gallbladder disease, cholestasis, and liver disease should be considered as precautions for hormone contraceptive use. Both estrogen and progestin-containing methods have been associated with a small risk for gallbladder disease.[5] A history of cholestasis, especially related to past use of combined oral contraceptives, may increase the risk for future disease.[5] In severe liver disease, hormone-based methods should be avoided because of the effects on drug metabolism.[5]

Bone mineral density declines with use of DMPA because of a reduction in ovarian production of estradiol. This decline appears temporary, as a prospective study of women aged 18-39 showed reversal of bone density loss at the spine and hip after 30 months of discontinued use.[13] The use of DMPA in adolescent and perimenopausal women remains controversial owing to the potential effects on bone growth and maintenance of bone density. It is advisable to consider individual risk factors for osteoporosis such as race, age, smoking status, and family or personal history of fractures when evaluating patient eligibility.[5] Data specific to the combined injection containing estradiol cypionate and medroxyprogesterone are currently lacking. The estrogen component of the product may be an important difference, however, as evidenced by the beneficial effects of estrogen-based contraceptives reviewed later.

Assessment of risk for sexually transmitted infections (STIs) is vital at all reproductive stages as none of the available hormone-based options provide adequate protection. Although adolescents are commonly identified as a high-risk age group, the sexual history and behaviors of women of all ages must be evaluated. While not ineligible for hormone-based contraception, patients at risk must consider concomitant use of a barrier method, such as the male condom, which specifically reduces the risk of transmission of human immunodeficiency virus, gonorrhea, chlamydia, and trichomoniasis. Patients should be informed that no barrier method provides protection from all STIs, as infections such as herpes simplex virus, HPV, syphilis, and chancroid may be transmitted through skin contact despite correct condom use.[14] Counseling regarding contraceptive decisions is a prime opportunity to identify and address risk-taking behaviors.

Medical conditions and risk factors are not the only criteria by which patient eligibility for hormone-based contraceptives is determined. The potential for drug interactions is an important assessment, as patients requiring short-term or chronic use of interacting drugs may not achieve the serum hormone levels required for effective contraception. Because of the lack of available data regarding the newer formulations, the drug interactions common to combination oral contraceptives are currently applied to all non-oral, combination methods, such as the vaginal ring, transdermal patch, and monthly injection. Lower levels of estrogen and progestin components result from the effect of hepatic enzyme inducers, such as rifampin, protease inhibitors, St. John's Wort, phenylbutazone, and several anticonvulsants. In addition, reports of reduced contraceptive efficacy have been linked with concomitant use of antibiotics, such as ampicillin, tetracyclines, and griseofulvin.[15-17] General guidelines regarding the use of combination hormone

methods in women requiring therapy with these agents urge use of back-up, non-hormonal contraception for short-term situations, and either avoiding hormone-based contraceptives altogether or using high-dose estrogen products for long-term concerns.[4] Combination hormone methods may also affect levels of other drugs, as increased concentrations of cyclosporine, prednisone, and theophylline and reduced concentrations of acetaminophen, temazepam, salicylic acid, and morphine have been identified.[15-17]

In addition to drug interactions generalized from combination oral preparations, there are some data specific to the non-oral formulations. The vaginal ring has been evaluated in pharmacokinetic studies with vaginal miconazole and nonoxynol-9 preparations, which were shown to not reduce serum concentrations.[15] Tetracycline administration had no effect on the pharmacokinetic parameters of the hormone constituents of the transdermal patch, which bypasses gut absorption.[17] Because the combination injection also contains medroxyprogesterone, the manufacturer warns of a potential interaction with aminoglutethamide, which has been shown to decrease levels and contraceptive efficacy of DMPA.[16] The levonorgestrel IUD has not been specifically evaluated for drug interactions.[18] Cautious interpretation of the data and a conservative approach incorporating generalized precautions is important until widespread use of these formulations allows for further determination of drug interactions and identification of important differences with oral preparations.

As the comprehensive medical history is used to screen each patient for medical eligibility, the practitioner should also address the potential applicability of various non-contraceptive health benefits documented with the use of hormone-based methods. Combination oral contraceptives have been associated with improved menstrual cycle control; reduced risk of certain cancers; pelvic inflammatory disease; and ectopic pregnancy; and improvements in acne, hot flashes, and bone mineral density.[4] Effects of hormone-based methods on menstrual cycle control will be reviewed at length under step 2 of the stepwise approach. Increasing evidence from epidemiologic studies shows a reduction in ovarian cancer risk by 40%-80%, endometrial cancer risk by approximately 50%, and colorectal cancer risk by approximately 18% in users of oral contraceptives, with higher rates of risk reduction associated with increased length of use. The risk reduction appears to persist after oral contraceptives are discontinued.[19,20] Changes in cervical mucus and menstrual blood flow and prevention of ovulation are proposed reasons for the reduction in pelvic inflammatory disease and ectopic pregnancy.[4] Acne is reduced as a result of reduced sebum production from increased levels of sex-hormone binding globulin, reduced androgen production, and reduced free testosterone seen with the use of oral contraceptives with low androgenicity profiles.[19] Estrogen in combined oral contraceptives used during perimenopause, a period of fluctuating estrogen levels and declining ovarian function, has been associated with a reduction in signs and symptoms of estrogen withdrawal, such as vasomotor symptoms and loss of bone density.[21,22] Because long-term data regarding the new delivery systems are limited, evidence linking them to similar benefits seen with oral contraceptives or progestin-only contraceptives must be extrapolated. It is possible that the combination formulations

of the patch, vaginal ring, and injection may mimic the benefits of oral contraceptives.
Progestin-only contraceptives have also been associated with amenorrhea, which can be an advantage in women who develop anemia related to heavy menstrual blood loss, and a decreased risk of endometrial cancer and pelvic inflammatory disease. DMPA may reduce the risk for ectopic pregnancy attributable to the prevention of ovulation.[4] The progestin-only oral contraceptives do not consistently suppress ovulation, and are, therefore, not associated with a reduced risk for ectopic pregnancy.[4] Unlike DMPA, the levonorgestrel IUD may increase the risk for ectopic pregnancy and pelvic inflammatory disease. These risks are related primarily to the insertion of the device into the uterus and limited suppression of ovulation, as evidenced by 45% of cycles remaining ovulatory after one year of use.[18]

Step Two: Address factors associated with efficacy

Hormone-based contraceptives prevent ovulation and/or implantation owing to suppression of luteinizing hormone and changes in cervical mucus and the endometrial lining.[23] Because of this mechanism of action, hormone-based contraceptives have inherently high, method-related efficacy rates. In measurements of perfect use, hormone-based methods are associated with one-year unintended pregnancy rates of less than 1%. This is contrasted with unintended pregnancies occurring in 3%-9% of perfect users of barrier methods such as condoms, diaphragms, and fertility awareness. Nevertheless, rates of correct and continued use that are influenced by route and frequency of administration and adverse effects greatly impact efficacy in typical use. While injectable and intrauterine methods continue to display unintended pregnancy rates of less than 1% even in typical use, the oral methods increase to 5%.[4,5] Initial data from clinical trials of the vaginal ring, transdermal patch, IUD, and combined injection indicate unintended pregnancy rates of less than 1%-2%.[15-18] Typical use rates outside clinical trials will be available as the methods become more widely used.

Physical characteristics of patients, such as age and weight, have little impact on the efficacy of most methods. Patient weight affects the efficacy of only one non-oral formulation, the transdermal patch. Because a greater number of pregnancies were reported in women over 90 kg during clinical trials, the manufacturer warns that contraceptive efficacy may not be retained in these women.[17] Method selection cannot be made on physical characteristics alone, as other factors must be considered.

Unintended pregnancy rates are directly associated with continued use of contraceptive methods. It has been estimated that 20% of the unintended pregnancies in the United States are a result of discontinuation of oral contraceptives.[24] The highest one-year continuation rates of hormone-based contraceptives have been documented with implantable and intrauterine products at over 80%, but oral contraceptives and injectable formulations approximate 70%.[4] Among adolescents, continuation rates are lower, with one study showing only 45% of DMPA and 12% of oral contraceptive users continuing after one year.[25] It is, therefore, reasonable to account for factors that may affect a patient's willingness to continue use of a method when making contraceptive choices.

Frequency and route of administration are factors that may influence the continuation of contraceptive methods. Past formulations of hormone-based contraceptives have

included oral, intrauterine, injectable, and implantable routes. Non-oral methods currently available in the United States are summarized in Table 1.

Table 1. Non-Oral, Hormone-Based Contraceptives[15-18,26]

Category	Product	Manufacturer	Dosage and Administration
Estrogen and Progestin Combinations	Lunelle® injection (medroxyprogesterone acetate 25 mg and estradiol cypionate 5 mg)	Pharmacia & Upjohn	Inject 0.5 mL intramuscularly every 28-30 days.
	NuvaRing® vaginal ring (etonogestrel 11.5 mg/ethinyl estradiol 2.7 mg)	Organon	Insert ring vaginally for 3 weeks, then remove for one week. Delivers 0.120 mg etonogestrel and 0.015 mg ethinyl estradiol daily.
	OrthoEvra® contraceptive patch (6.0 mg norelgestromin and 0.75 mg ethinyl estradiol)	Ortho-McNeil	Apply patch once weekly for 3 weeks (21 days), then allow for one week, patch free. Delivers 150 mcg norelgestromin and 20 mcg ethinyl estradiol daily.
Progestin Only	Mirena® intrauterine system (levonorgestrel 52 mg)	Berlex	Insert device into uterus every 5 years. Initially releases 20 mcg levonorgestrel daily.
	Depo-Provera® injection (150 mg medroxyprogesterone acetate)	Pharmacia & Upjohn	Inject 1 mL intramuscularly every 3 months.

The daily administration required for oral preparations can complicate continued use, as it is estimated that 30%-50% of women miss one or more pills per cycle.[27] Furthermore, use of progestin-only oral contraceptives requires little variation in timing of the daily dose, as fluctuations of as little as several hours may reduce efficacy.[4] Non-oral formulations allow for less frequent administration, such as weekly application of the contraceptive patch and monthly administration of the combined injection and the intravaginal ring. Non-oral, progestin-only formulations offer even longer intervals, with administration of depot medroxyprogesterone every 3 months and the IUD every 5 years.

Consideration of route of administration must accompany the frequency, as patient preference is an important determinant. The oral route of administration is familiar, and allows for self-administered dosing and infrequent provider visits for prescriptions, but vomiting; diarrhea; drug interactions; and hepatic, first-pass metabolism can negatively affect absorption from the oral route. Transdermal and intravaginal formulations are also self-administered and associated with limited provider visits, but

are not susceptible to gut absorption factors and avoid the fluctuations of hormone serum concentrations associated with daily oral dosing. There are several route-specific complications that must be addressed.

Transdermal formulations generally require consideration of adhesion, visibility, and site reactions. Clinical trials of the patch resulted in a low incidence of complete or partial detachment, requiring replacement in approximately 5% of participants. Although the patch can be applied to many discreet areas, including the buttocks, abdomen, upper arm, and upper torso (except breasts), patients may be concerned with the visibility of the method, especially during intimate contact.[17] In a comparative clinical trial with oral contraceptives, the patch resulted in mild-to-moderate site reactions in 20% of participants, which led to discontinuation of the method in only 2.6%.[28] To avoid site reactions and encourage adhesion, patients should be instructed to rotate application sites; to place the patch only on intact skin; and to avoid use of creams, lotions, or powders where the patch is placed.[17] In contrast to the transdermal system, the vaginal ring requires determination of the patient's comfort with vaginal device insertion and removal. Intravaginal administration is accompanied by local reactions, such as leukorrhea and vaginitis, which occurred in approximately 5% of users in 2 clinical trials. Device-related concerns, such as discomfort during intercourse, foreign body sensation, and expulsion also occurred in approximately 5% of patients. Overall, discontinuation of the vaginal ring based on adverse events occurred in 10%-15% of patients, with device-related events accounting for only 2.5%.[29,30] To reduce the likelihood of a device-related event, the manufacturer recommends avoiding use in patients with vaginal irritation, genitourinary abnormalities, and severe constipation.[15]
The combination injection and IUD also allow for less frequent dosing, but provider visits are required for administration or insertion, which may limit the acceptability for some patients. Although intramuscular injections every one to 3 months may not be desirable to all patients, pain at the injection site, rash, or allergic reactions are uncommon.[16] There are rare complications associated with the insertion of the levonorgestrel IUD, including device displacement, pelvic inflammatory disease, and uterine perforation. To maximize safe use of the device, the manufacturer recommends avoiding use in patients with a history of uterine fibroids, pelvic inflammatory disease, uterine or cervical cancer, genital infections, or ectopic pregnancy.[18]

Method continuation is affected by adverse effect profiles in addition to the route and frequency of administration. It is estimated that adverse effects are the most common reason for discontinuation of oral contraceptives.[27] Common adverse effects associated with estrogens are nausea, breast tenderness, and headache. Progestins are associated with weight gain, fatigue, and varying degrees of androgenic effects, such as acne or worsened lipid levels or glucose tolerance.[4] Clinical trials of the non-oral methods resulted in general adverse effect profiles similar to oral contraceptives. Nevertheless, specific adverse effects that did not occur at similar rates were identified. The transdermal patch was associated with significantly higher reports of breast tenderness and dysmenorrhea compared with the oral contraceptive groups, primarily during the early cycles.[28] Weight gain was cited as the most common reason for discontinuation of the combined injection during clinical trials, which occurred in 6%

of participants. The patients gained an average of 4 pounds during the first year, but 19% of women reporting a weight gain of 10-20 pounds.[16] This pattern mimics that associated with DMPA, as the average weight gain over one year is approximately 5 pounds, with sequential increases with length of therapy to an average of over 16 pounds after 6 years of therapy. Weight gain caused discontinuation in 2% of women enrolled in clinical trials of DMPA.[26] Although the patch, vaginal ring, and combination injection avoid oral administration, there were no reports of reduced nausea compared with the oral formulations.[16,28-30]

Adverse effects related to altered bleeding patterns, such as breakthrough bleeding and spotting, are commonly cited as reasons for discontinuation of both oral contraceptives and progestin-only injectable and implantable formulations.[4] Definitions of bleeding irregularities differ among sources, making comparisons of data from various studies difficult. Bleeding irregularities may include frequent bleeding, prolonged bleeding, infrequent bleeding, intermenstrual bleeding, spotting, and amenorrhea. The newer non-oral formulations provide varying degrees of cycle control, which may be a basis for choosing one method over another.

With long-term use, combination oral contraceptives provide regular withdrawal bleeding and a very low incidence of amenorrhea, often seen as an advantage by patients who desire regular reassurance that pregnancy has not occurred. Approximately 10%-30% of patients, however, experience irregular bleeding patterns with oral contraceptives during the first few cycles of use, which diminishes over time.[31] Patients who miss doses are more likely to experience irregular bleeding, which further increases the likelihood of discontinuation and method failure. Data regarding the effects of the newer, non-oral combination methods on bleeding patterns are conflicting. Studies of the vaginal ring have resulted in regular withdrawal bleeding in approximately 98%-99% of cycles.[29,30] In a 6-cycle comparative trial of the vaginal ring and an oral contraceptive containing ethinyl estradiol and levonorgestrel, the intended bleeding pattern occurred in 65%-68% of cycles in the ring group and only 28%-47% of the cycles in the oral contraceptive group.[29] In a comparative trial of the transdermal patch and an oral contraceptive containing ethinyl estradiol and levonorgestrel, a statistically significant higher rate of breakthrough bleeding or spotting was reported during the first 2 months with the patch (18.3%) versus the oral contraceptive (11.4%), but similar rates were reported for the remaining 11 cycles. When breakthrough bleeding was evaluated alone, less than 5% of subjects reported it during the 13 cycles in either group.[28] Of the newer combined hormone methods, the monthly injection is associated with the highest rates of irregular bleeding. Approximately 30% of users report irregular bleeding patterns throughout the first year.[16] In comparative trials with oral contraceptives, evidence of bleeding irregularities was conflicting, with both higher and lower rates reported in comparison with the oral contraceptive groups.[32,33]

Progestin-only contraceptives are typically associated with irregular bleeding patterns leading to amenorrhea.[4] Lack of regular bleeding may be desirable to some women or preferred in those with a history of anemia attributable to blood loss. DMPA is associated with amenorrhea in 55% of patients after one year of use.[26] This pattern is similar in patients who use the

levonorgestrel IUD, which is associated with frequent irregular bleeding over the first 6 months and amenorrhea in 20% of patients after one year.[18] In a study designed to evaluate the use of the IUD in women aged 35 to 45, the primary reason for discontinuation of the method was bleeding irregularities.[34]

There are few long-term studies that translate the effects of route and frequency of administration and adverse effect profiles of the newer delivery systems into method continuation and efficacy data. In a study that pooled data from 3 short-term trials of the transdermal patch, self-reported compliance was significantly higher in patch users than that reported with oral contraceptives and was consistent across all age groups.[35] High satisfaction rates are associated with the vaginal ring, as 85% of users reported that they were "satisfied" or "very satisfied" and 90% reported that they would recommend the device to others. In addition, more than 80% of the partners found the use of the vaginal ring acceptable during sexual intercourse.[30] More patients reported discomfort with the use of the monthly injection in a study comparing it with a triphasic oral contraceptive containing norethindrone, but over 90% of patients would still recommend the method.[36]

A factor influencing method continuation that is independent of formulation is the benefits derived from effective patient counseling. In studies of oral contraceptives and DMPA, efficacy and continuation rates are increased in patients who receive information regarding the correct use and potential adverse effects of the method, establish personal reminder systems for dosing, and are satisfied with their patient-provider relationship.[37,38] Although not confirmed in clinical trials, it is likely these concepts can be applied to the newer, non-oral methods as well. Educating the patient throughout the decision-making process may further improve the probability of efficacy.

In summary, efficacy of a contraceptive method under "typical" conditions is a factor of continued use, which appears to be influenced by factors such as the route and frequency of administration and adverse effects. When making contraceptive choices, practitioners should become aware of a patient's comfort level with oral, vaginal, intramuscular, and intrauterine routes of administration. The patient's preference for daily or non-daily dosing and self-administered or provider-administered dosage forms should be considered. Finally, determination of the desired bleeding pattern, along with individual concerns for specific adverse effects, such as weight gain or breast tenderness, must be made. The availability of the newer, hormone-based formulations has greatly increased the complexity of the decision-making process, but improves the probability of truly individualizing therapy. Future data from widespread use and long-term trials will further clarify this process.

Step Three: Consider fertility and lactation concerns

The return of fertility and effects on lactation are important variables to consider depending on the reproductive stage of the patient. It is likely to be most applicable in the first 2 stages of either delaying the first pregnancy or spacing births. Women who have completed childbearing are likely to be unconcerned about these issues.

All hormone-based contraceptive methods are reversible, however; DMPA is associated with the longest time period required for the return of fertility and is not generally recommended in women planning

pregnancy within one to 2 years. The median time to conception is 10 months after the last injection, and the one-year fertility rate is 68%. Thinner women experience return of ovulation sooner than overweight women with the depot formulation.[26] One-year fertility rates reported for the IUD and the combined injection are 80% and 83%, respectively.[16,18] Interestingly, return of ovulation may be delayed in users of the combined injection who have a body mass index of 29 kg/m^2 or less and receive the injection in the arm because of higher levels of medroxyprogesterone.[16] For patients spacing pregnancies, the combined injection and patch offer non-oral methods that have a short duration of effect. In contrast, women who have completed childbearing may find the 5-year IUD and 3-month DMPA injection more desirable owing to longer duration of effect and a lack of concern regarding the time to regain fertility.

A popular non-hormonal method of contraception, the lactational amenorrhea method, can be effective in women who are fully breastfeeding and amenorrheic, and is based on the observed decline in fertility during lactation.[4] Hormone-based methods recommended during lactation are typically progestin-only, which is attributable to the negative effects of estrogen on the quality and quantity of breast milk, especially prior to establishing lactation.[4] The progestin-only oral contraceptives and DMPA are commonly prescribed for this purpose, depending on the desire for a quick return of fertility or a preference for a daily oral or non-daily injectable formulation. Although controversial, it is recommended that use of combined hormone contraceptives, such as the vaginal ring and the transdermal patch, be avoided until weaning has occurred.[15,17] If used prior to weaning, it is generally desirable to establish lactation prior to initiation of the method.[4] According to the manufacturer, the levonorgestrel IUD or combined injection should not be used 6 weeks postpartum.[16,18]

Monitoring and Follow-Up

The stepwise approach previously described accounts for most considerations for initial selection of a non-oral, hormone-based contraceptive. Routine monitoring by both patients and practitioners is required to maximize the safety and efficacy of these methods. In addition to monitoring for common adverse effects such as breast tenderness, bleeding abnormalities, and nausea, patients should be made aware of the signs and symptoms of the more rare but serious adverse effects of myocardial infarction, stroke, venous thrombosis, and gallbladder disease. The "ACHES" mnemonic is an important tool to teach patients to detect and immediately report signs of abdominal pain (A); chest pain, cough, or shortness of breath (C); headache, weakness, or numbness (H); eye or speech problems (E); and severe leg pain (S).[4] Early risk factors for medical conditions that may change the eligibility status of the patient can be detected through recommended age-related screening of blood pressure, blood glucose, and lipids.

The transdermal patch, vaginal ring, and IUD require further monitoring of device placement by the patient and practitioner. The patient must monitor the transdermal patch for signs of partial or complete detachment. If the patch is detached for up to 24 hours it can be reapplied or a new patch applied without back-up contraception.[17] The vaginal ring requires the patient to monitor for device expulsion. If the device is removed for less than 3 hours, it can be replaced without loss of contraceptive efficacy.[15] The IUD, while effective for 5 years, requires clinical

reexamination within 3 months of insertion to validate correct placement. Patients monitor placement by detecting the thread near the cervix after menstrual periods and also monitor for signs of vaginal infection. If displacement occurs, contraceptive efficacy is lost immediately.[18]

Monitoring of method continuation is vital to maintain efficacy. It is important that non-daily methods are accompanied by personal reminder systems. All of the non-oral methods are dosed based on time intervals, not bleeding patterns. The dosage interval for the combined injection allows for some variation, as it should be dosed every 28-30 days, but not to exceed 33 days.[16] This flexibility is important, as a provider visit is required for each injection, and accessibility may be limited on certain days of the week. Although differing in the recommended frequency of administration, the transdermal patch and vaginal ring both require monthly, one-week, medication-free intervals to allow for withdrawal bleeding. It is preferred that the initiation of the first dose after this interval is performed at approximately the same time of day.[15,17] In addition, unintended, prolonged use of the ring or patch results in a need to follow manufacturer-specific instructions for use of alternative contraception and re-administration of the device.[15,17] These are dosing complexities that require follow-up to ensure that the patient is not having difficulties that could potentially reduce the efficacy of the method.

Summary of Novel Delivery Systems

The stepwise approach provides a framework for determining whether non-oral, hormone-based contraceptive methods may be appropriate alternatives to oral contraceptives for patients at particular reproductive stages. Oral contraceptives are backed by years of data regarding safety, efficacy, and non-contraceptive benefits, and will continue to be prescribed widely. The availability of many oral contraceptive formulations allows for modifications of doses and types of progestins in order to achieve high levels of tolerability. Nevertheless, non-oral formulations that demonstrate equal efficacy are highly desirable, as switching between various oral contraceptive formulations may not be beneficial in all patients. Although all non-oral methods have non-daily dosage intervals and are reversible, many of the distinguishing characteristics previously reviewed can be summarized as advantages and disadvantages associated with each method.

The combination transdermal patch may be desirable for a patient under 90 kg who prefers self-administration, but wants to avoid vaginal dosing. Irregular bleeding may be associated with early cycles, but should gain regularity over time. The patient must be willing to monitor for patch adhesion and understand the instructions for patch application and replacement.

The combination vaginal ring may offer an alternative to oral dosing for patients who are comfortable with vaginal insertion and removal of the device and who are willing to monitor for device displacement. The once-monthly dosing may be preferred over the weekly dosing of the transdermal patch. The bleeding profile appears to achieve greater regularity than that of oral contraceptives.

The combination injection is best fit for patients whose schedule, geographic location, and medical coverage allow for monthly provider visits and who are not concerned with receiving routine intramuscular injections or the possibility of weight gain. Unlike the patch, ring, and

IUD, there is no need for monitoring the device between dosage intervals. Bleeding patterns may or may not be more regular than with oral contraceptives. Careful consideration should be given to patients who have not tolerated medroxyprogesterone in the depot formulation, as this product may cause some of the similar progestin-related adverse effects.

The best candidates for the levonorgestrel IUD are those who desire long-term contraception and the potential for amenorrhea and are willing to perform routine vaginal monitoring of device placement. As a progestin-only alternative, it may be an option for patients unable to tolerate some of the estrogen-related adverse effects.

Conclusion

The recent expansion of hormone-based contraceptive options provides important alternatives to oral contraceptives. In general, the non-oral, combined formulations offer highly effective contraceptive options. Important differences include device-related adverse effects, dosage intervals, and effects on fertility and lactation. With careful consideration of the reproductive stage and a stepwise approach addressing health risks and benefits, efficacy, and fertility, patients who would benefit from these alternatives can be identified. Although the stepwise approach addresses many of the important considerations for selection of non-oral, hormone-based formulations, it does not address all factors in contraceptive decision making. The cost of methods and a patient's access to medical and prescription coverage often dictate choice and must be incorporated into the equation. Improving access to the most appropriate method for a patient at each stage of her reproductive lifespan will continue to have an impact on the rates of unintended pregnancy in the United States.

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