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MODERN TRENDS

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Why consider vaginal drug administration?

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Objective: To review the anatomy and physiology of the vagina, the merits of vaginal drug administration, and the currently available vaginal drug-administration systems.

Design: Review of basic and clinical research.

Result(s): Although clinicians commonly use topically administered drugs in the vagina, this route for systemic drug administration is somewhat novel. Experience with a variety of products demonstrates that the vagina is a highly effective site for drug delivery, particularly in women's health. The vagina is often an ideal route for drug administration because it allows for the administration of lower doses, steady drug levels, and less frequent administration than the oral route. With vaginal drug administration, absorption is unaffected by gastrointestinal disturbances, there is no first-pass effect, and use is discreet. Knowledge of anatomy, physiology, histology, and immunology of the vagina should allow clinicians to reassure their patients concerning this mode of delivery. Greater understanding and experience by clinicians should lead to increased use and acceptance of the vagina as a route for drug administration.

Conclusion(s): The safety and efficacy of vaginal administration have been well established. The vaginal route of drug delivery is acceptable and may even be a preferable route of administration for many drugs, particularly hormones, whether for contraception or postmenopausal estrogen therapy. (Fertil Steril® 2004;82: 1–12. ©2004 by American Society for Reproductive Medicine.)

Key Words: Intravaginal administration, vaginal rings, contraceptives, hormone therapy

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Technologic advancement in drug delivery has led to a wider choice of sites for drug administration. Traditionally, the routes most commonly used were oral for systemic effects and topical for local effects. Medication could also be self-administered by inhalation, suppository, and, in some cases, injection. Other routes of delivery were available but limited, because healthcare providers were required to administer them. By the 1980s and 1990s, attention had shifted to subdermal and intrauterine routes, which allowed a single intervention by a healthcare provider to provide sustained therapy.

Patients were also offered intranasal and transdermal formulations that could be self-administered. In the case of transdermal patches, patients were given an opportunity to administer several days' worth of therapy with a single application. These approaches represented an improvement over oral delivery because the hepatic first-pass effect could be avoided. Today, there is growing interest in the vaginal route of administration, which also avoids the hepatic first-pass effect. The vagina allows women to self-administer medication continuously for weeks or months at a time with a single application.

Modern technology has yielded vaginal drug-delivery systems that provide optimized pharmacokinetic profiles. These characteristics make the vagina an excellent route for drug administration.

Before 1918, the vagina was considered to be an organ that was incapable of absorbing drugs systemically. In 1918, Macht reported the absorption of morphine, atropine, and potassium iodide following vaginal administration (1). Since then, numerous compounds have been administered vaginally, including sodium salicylate, quinine hydrochloride, and various hormones including insulin, estrogens, progestogens, androgens, and prostaglandins (2). Several drugs have been approved for vaginal administration; although most are indicated for the treatment of local conditions, a

number of them achieve serum levels sufficient to have systemic effects. Other compounds are being investigated for administration via the vagina (Table 1).

TABLE 1

Compounds being clinically investigated for administration via the vagina.

Drug	Use being investigated
Glyminox gel (3)	Contraception, prevention of sexually transmitted diseases
Terbutaline vaginal gel (4)	Dysmenorrhea, endometriosis
Demegen gel (5)	Prevention of sexually transmitted diseases
Lidocaine-releasing intravaginal ring (6)	Cervical anesthetic
Oxybutynin vaginal ring (7)	Overactive bladder
Tenofovir vaginal gel (8)	Prevention of vaginal HIV transmission
Antibody III-174 vaginal implant (9)	Prevention and treatment of herpes simplex virus 2 infection

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In addition, several drugs approved for oral administration are used vaginally to treat nonindicated conditions. These include misoprostol for induction of labor (10) and sildenafil to increase blood flow to the uterus for the treatment of infertility (11) (Table 2). Advantages of the vaginal route include avoiding the hepatic first-pass effect and thus enabling lower dosing (17) plus the potential to use controlled-release dosage forms. In addition, the convenience of longer-term dosing regimens with decreased reliance on the user may aid in improving patient compliance.

Although vaginal drug administration has many advantages, misperceptions and poor education about vaginal anatomy and physiology, particularly among patients, can lead to reluctance to use vaginal medications. By counseling and educating patients, clinicians can help to establish the vaginal route of drug administration as safe, effective, and convenient so that more women can experience the potential benefits.

TABLE 3

Characteristics of an ideal drug delivery system.

- Easy to use
- Painless for the patient
- Requires no intervention by medical personnel
- Discreet/private
- Reversible
- Minimal interference with body functioning and daily life
- High bioavailability with little variability
- Minimal interference with other medications

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To decide whether the vaginal route is indeed an ideal way to deliver drugs into the human body, one must first define the prerequisites of an ideal method of chronic drug administration. Characteristics of an ideal drug-delivery system are shown in Table 3. This article reviews the anatomy and physiology of the vagina before discussing the merits of vaginal drug administration and examines whether the characteristics of this route meet the defined prerequisites. Finally, we review the vaginal drug-delivery systems that are currently available.

WHY IS THE VAGINA AN IDEAL SITE FOR DRUG DELIVERY?

Anatomy

A common misperception is that the vagina is a straight tube pointing upward to the sacral promontory. Most illus-

TABLE 2

Oral medications that are commonly administered vaginally.

Drug	Indicated use (oral route)	Nonindicated use (vaginal route)
Misoprostol	Prevention of nonsteroidal anti-inflammatory drug (NSAID)–induced gastric ulcers in patients at high risk of complications from gastric ulcer	Induction of labor, cervical ripening (10), pregnancy termination (12)
Sildenafil	Treatment of erectile dysfunction	Increased bloodflow to the uterus in preparation for embryo implantation (11)
Bromocriptine	Treatment of hyperprolactinemia	Treatment of prolactinoma in those intolerant of nausea/vomiting side effects (13)
Indomethacin	Treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder, and acute gouty arthritis	Treatment of preterm labor (14)
Oral contraceptive pills	Contraception	Avoidance of decreased absorption with vomiting (15)
Oral hormone therapy preparations	Vasomotor symptoms, vulvar and vaginal atrophy, prevention of osteoporosis	Intolerance of oral delivery (16)

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trations (in both patient and clinician educational materials) are inaccurate and perpetuate this image. They give the impression that items placed in the vagina could easily fall out. Historically, knowledge of the human anatomy has come from the dissection of cadavers. Tissue death and embalming processes distort the normal anatomic position, mainly by the loss of support from the endopelvic fascia and the levator ani complex. Radiographic colpography (18, 19) has shown that the vagina is normally a curved organ with two distinct portions: a lower convex portion and a wider upper portion that lies in an almost horizontal plane when the woman is standing. The angle between the upper and lower axes is 130 degrees.

The average posterior length of the vagina is 8 to 12 cm. A transverse cross-sectional view shows that the vagina is a collapsed organ with the anterior and posterior walls in contact with each other. As the vagina enters the pelvis, it passes through two diaphragms: the urogenital and the pelvic diaphragms. The bulbocavernosus muscle from the urogenital diaphragm and the pubococcygeus from the pelvic diaphragm act as sphincters to the vaginal introitus. The vagina of a reproductive-age woman contains numerous folds called rugae. These provide distensibility and support as well as an increased surface area of the vaginal wall (20).

The vagina's nerve supply comes from two sources. The peripheral, which primarily supplies the lower quarter of the vagina, makes it a highly sensitive area; the autonomic primarily supplies the upper three quarters. Autonomic fibers respond to stretch and are not very sensitive to pain or temperature. In addition, there are few sensory fibers in the upper vagina, making it a relatively insensitive area. This is why women rarely feel localized sensations or any discomfort when using vaginal products such as tampons, suppositories, or vaginal rings, and are often unaware of the presence of such items in the vagina.

The vascular supply consists of an extensive network of arteries that encompass the vagina from multiple sources, including the uterine artery, the pudendal artery, and the middle and inferior hemorrhoidal arteries. The venous system is just as complex. The primary venous drainage occurs via the pudendal veins. The vaginal, uterine, vesical, and rectosigmoid veins from the middle and upper vagina provide drainage to the inferior vena cava, which bypasses the hepatic portal system (20). Because of the extensive vascular connections between the vagina and uterus, a "first uterine pass effect" has been hypothesized when hormones are administered vaginally (21).

For example, vaginally administered P induces a normal secretory transformation of the endometrium even though low serum P levels are measured (22–24). It is theorized that a direct transit of P into the uterus is primarily responsible for the endometrial changes. A significant amount of literature addresses the pharmacokinetics and effects of P administered vaginally (22, 25). The consensus is that a preferential distribution of P to the uterus occurs when it is administered through the vagina. In fact, several groups have demonstrated that endometrial concentrations of P were higher with vaginal administration as compared with IM administration (25, 26).

The same has been noted with E_2. Endometrial E_2 levels were significantly higher with vaginal administration as compared with the same dose administered orally (27). At present, there are no data available on the endometrial concentrations of synthetic progestogens or ethinyl E_2 after vaginal administration.

Histology

The vaginal histology is composed of four distinct layers. Nonsecretory stratified squamous epithelium forms the most superficial layer. The next is the lamina propria, or tunica, made of collagen and elastin, which contains a rich supply of vascular and lymphatic channels. The muscle layer is third, with smooth muscle fibers running in both circular and longitudinal directions. The final layer consists of areolar connective tissue and a large plexus of blood vessels. Vaginal tissue does not contain fat cells, glands, or hair follicles. Secretions from the vaginal wall are transudate in nature and are produced by the engorgement of the vascular plexus that encompasses the vagina (28).

Physiology

The vagina acts as a receptacle during coitus, an outlet for menstrual blood, and a birth canal. The physiology of the vagina is influenced by age, hormone status, pregnancy, and pH changes induced by several factors including semen, menstruation, estrogen status, and bacterial colonization. Reproductive hormones control the thickness of the vaginal epithelium, with E_2 thickening the epithelium and hypoestrogenism resulting in atrophy.

Vaginal fluids originate from a number of different sources. The fluid is mostly transudate from vaginal and cervical cells (29) but also contains vulvar secretions from sebaceous, sweat, Bartholin, and Skene glands; cervical mucus; endometrial and oviductal fluids; and microorganisms and their metabolic products. The composition of fluids is affected by cyclical changes caused by hormonal influences (30) and the state of arousal. When the vagina is in its sexually unstimulated state, vaginal fluid is primarily composed of plasma transudate from the vaginal wall together with secretions from the cervical and vestibular glands (31). On sexual arousal, when the vagina becomes engorged, vasoactive peptides are released locally, which increase arteriolar dilatation and suppress venous return (32). This has the effect of increasing vaginal lubrication, the extent of which will vary from individual to individual, depending on the hormonal milieu and situational factors.

VAGINAL DEFENSES

Epithelium

While the vaginal epithelium acts as a physical barrier (25 layers thick with estrogen present) (33), cervical mucus, vaginal secretions, and local bacterial flora also help to protect the vagina against infection. The stratified squamous epithelium sheds constantly, making it difficult for organisms to invade or access the basement membrane/capillary bed.

Flora

Desquamated cells have a secondary use: to provide a source of intracellular glycogen that can be converted to lactic acid by the lactobacilli that proliferate near the epithelium. Lactobacilli are beneficial for vaginal health because they compete with exogenous microbes for nutrients. The protective role is facilitated by the production of lactic acid and hydrogen peroxide (although not all strains produce hydrogen peroxide). Hydrogen peroxide is toxic to other microorganisms that produce little or no hydrogen peroxide–scavenging enzymes (e.g., catalase), thus enhancing the vaginal colonization by *Lactobacillus*. Thus, hydrogen peroxide–producing lactobacilli regulate the growth of other vaginal flora, making the environment less hospitable to other microbes such as *Escherichia coli* (*E. coli*), Group B *Streptococcus* (31), and even human immunodeficiency virus (HIV) (34).

An absence of hydrogen peroxide–producing lactobacilli in the normal vaginal flora may result in bacterial vaginosis, as overgrowth of catalase-negative organisms occurs (35). Estradiol is known to stimulate glycogen production in the epithelial cells, thus promoting the presence of *Lactobacillus*. High levels of estrogen during pregnancy result in a thick epithelium, high levels of lactobacilli, and a low pH. Low E_2 levels in users of depot-medroxyprogesterone acetate have been linked with a decrease in colonization of vaginal *Lactobacillus* (33). Antibiotics and some diseases (e.g., diabetes) can also disrupt the vaginal milieu, resulting in symptomatic vaginal candidiasis (36). Vaginal secretions contain a mixture of aerobic and anaerobic bacterial flora, at an average concentration of 10 billion/mL in healthy women of reproductive age (37). The numbers and prevalence of different bacteria vary according to the menstrual cycle (38, 39). Numbers decrease 10-fold to 100-fold in the week before menstruation, followed by a dramatic increase in the number of bacteria as menstruation commences (40).

Immune Cells

The lymphatic drainage of the vagina is distributed between the left and right sides of the pelvis. Generally, the upper third of the vagina drains into the external iliac nodes, the middle third drains into the common and internal iliac nodes, and the lower third drains into the common iliac, superficial vaginal, and perirectal nodes (28).

Protective immunity is provided by both the cellular and humoral systems. Langerhans' cells can be found with dendritic extensions exposed to the lumen of the vaginal epithelium, thus possibly serving as guardians of the local immune system. These cells can pass antigens to dendritic cells that migrate to the lymph nodes, where they activate B and $CD4^+$ T cells. Activated B lymphocytes return to the subepithelium, where they become IgA-secreting cells. The IgA is taken up by the epithelial cells and made into a dimer prior to release into the lumen. Priming may require sequential interactions with dendritic cells (41). Cervical mucus contains both IgG and IgM as well as IgA antibodies (42). Antigenic challenge at the epithelial surface is afforded by intraepithelial T lymphocytes, dendritic cells, and a subepithelial population of B lymphocytes that synthesize IgA locally.

Some studies have shown that long-term use of depot-medroxyprogesterone acetate results in thinning of the vaginal epithelium and increased susceptibility to HIV infection (43). Animal studies indicate that other infections including *Chlamydia trachomatis* (44) and herpes simplex (45, 46) may also be worsened in progestogen-dominant environments. A recent human study demonstrated that changes in leukocyte subtype concentrations varied depending on whether depot-medroxyprogesterone acetate or levonorgestrel was administered (47). Studies have shown that estrogen treatment makes monkeys completely resistant to simian immunodeficiency virus (SIV), whereas progestogen treatment makes them susceptible (48). It is unclear whether the beneficial effects of estrogen are due to its effect on the integrity and thickness of the cervicovaginal epithelium, or whether they are due to the inaccessibility of certain immune cells. It is clear that an acidic vagina, whether as a result of the presence of estrogen or exogenous products, does enable the vagina to resist infection.

pH

For healthy women of reproductive age, normal vaginal pH is 3.8 to 4.2 (28); this naturally acidic environment is maintained by the production of lactic acid by the vaginal microflora. Vaginal pH is altered by the presence of semen, which is slightly alkaline (pH 7.0 to 8.0) (49). The effect is rapid (pH is altered within seconds after ejaculation) and lasts for several hours (50). Female hygiene products and douches wash away a variety of the vaginal defenses and can promote colonization of bacteria or alter vaginal pH, allowing pathogenic bacteria and yeast to proliferate (51). Tampons or any absorbent material become media for bacterial colonization and growth.

Menstrual blood absorbed by the tampon alkalinizes vaginal pH to levels where protective lactobacilli cannot survive. For a product to be used in the vagina for days, weeks, or months, at a minimum it must be made of a material that does not damage the surrounding tissue, must not interfere

with the normal immune functions, and must be nonabsorbent.

ADVANTAGES OF VAGINAL DRUG ADMINISTRATION

Like some other non-oral drug-delivery methods, vaginal systems (e.g., suppositories, gels, vaginal rings) aim to provide not only a localized effect, but through drug absorption, sustained therapeutic levels compared with the traditional oral route (52). Vaginal administration enables the use of prolonged dosing regimens, lower daily doses, and continuous release of medication.

Longer intervals between doses are generally welcomed by patients as a more convenient alternative to daily intake, and this can enhance regimen compliance (52). There is evidence that a substantial proportion of oral contraceptive users become tired of taking pills on a daily basis, particularly over a number of years. It has also been shown that the number of missed pills increases over time as women "learn" that they can miss pills and then do (53). Efforts to develop alternative hormonal delivery systems are ongoing and include injectables, implants, and intrauterine devices (IUDs), with the recent introduction of the weekly transdermal patch and the monthly vaginal ring for contraception. The advantage of the transdermal patch and the vaginal ring over implants, IUDs, and injectables is that women are in control of their method, making use of the products more easily reversible. Although the pill is also user controlled and can be used in the vagina, the vaginal ring has the advantages of being nondaily, with constant serum levels.

One of the major advantages of vaginal administration over oral administration is that drugs avoid gastrointestinal (GI) absorption and the hepatic first-pass effect. Absorption from the GI tract can be unpredictable and may be compromised by vomiting, drug–drug interference, or decreased intestinal absorption capacity. Moreover, the GI lumen and the liver are sites of elimination for many compounds (54). Avoidance of the hepatic first-pass effect is particularly advantageous for compounds that undergo a high degree of hepatic metabolism. For example, natural estrogens are 95% metabolized by the liver when administered orally. The potential benefits of vaginal drug delivery over oral, therefore, include lower dosing and lower systemic exposure plus lower incidences of side effects while achieving the same pharmacodynamic effect.

Avoiding the fluctuations resulting from daily intake may also lower the incidence of side effects. Side effects are identified as the most important factor associated with discontinuation of oral contraception (55). Lowering the incidence of side effects will increase the acceptability of a product and thus enhance patient compliance.

The transdermal patch also avoids the daily peaks and troughs of serum hormone levels that are seen with oral contraceptives; however, the required weekly patch change makes the pharmacokinetic profile less stable than with continuous dosing via the vagina (Fig. 1). Unlike vaginal rings, transdermal patches administer drugs through a keratinized surface, which presents an obstacle that must be overcome by permeation enhancers, usually alcohol (59). Furthermore, hormone delivery via a transdermal patch may be affected by the adiposity of the skin. In clinical trials, the contraceptive patch was found to be less effective in heavier women, with weight variability accounting for up to 20% decrease in serum hormone levels (60). It is not known whether this effect was related to the transdermal delivery system or to a general effect seen in a higher-weight population using hormonal contraception.

Vaginal drug delivery can also allow for selective regional therapeutic administration, that is, local drug exposure where needed, producing little or no change in exposure throughout the rest of the body (54). This effect is critical for steroids administered vaginally for the treatment of urogenital atrophic complaints.

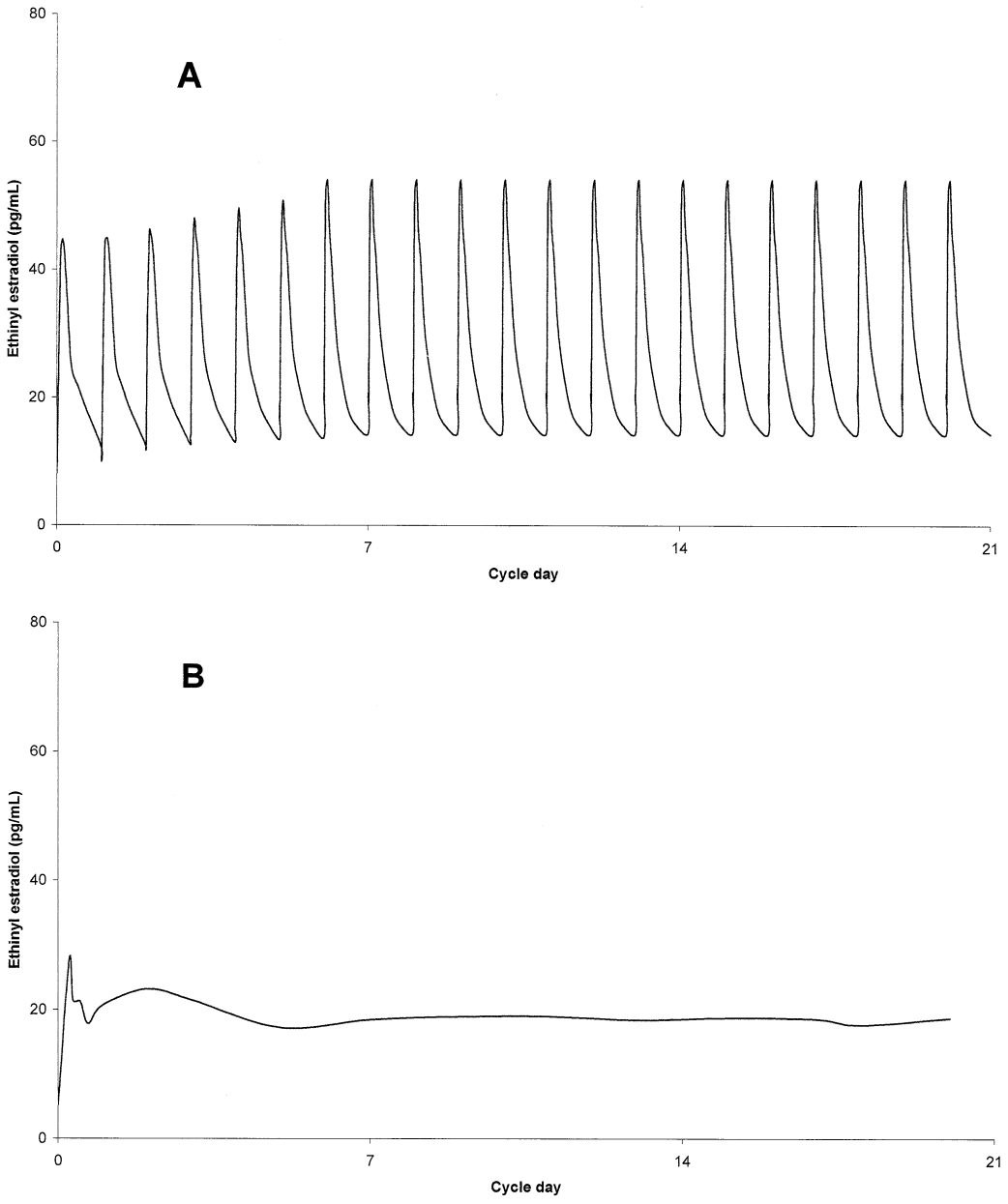
A number of compounds have been shown to have greater effects when administered vaginally as compared with other routes. For example, misoprostol has been used effectively for cervical ripening and labor induction (61). Misoprostol administered vaginally has been shown to be more effective and to have fewer side effects than misoprostol administered orally. Another example is indomethacin for the treatment of preterm labor, which appears to be superior when used intravaginally as opposed to an intrarectal plus oral regimen. Delivery was delayed by more than 7 days in 78% of women who received the drug intravaginally compared with 43% who received the same dose rectal-orally ($P=.03$) (14). Furthermore, the interval from treatment to delivery was 26.5 days versus 12.6 days, respectively ($P=.007$). Overall, the women allocated to the intravaginal route had statistically significantly better outcomes, as evidenced by improved birth weight (2.3 vs. 1.9 kg) ($P=.001$), less need for mechanical ventilation (1.4 vs. 5.3 days) ($P=.02$), and decreased time for the infants in the neonatal intensive care unit (3 vs. 9 days) ($P=.001$).

HISTORY OF VAGINAL RING DEVELOPMENT

Vaginal rings to deliver hormones for contraception or hormone therapy were developed to deliver hormones at uniform concentrations and over a longer period of time; they allow lower doses to be used, and can still be user controlled. Development began in 1966, after the demonstration that hormones could diffuse through Silastic® (polysiloxane; Dow Corning, Midland, MI) tubes or solid discs at constant rates (62). Since then, vaginal ring technology has progressed with the development of flexible polysiloxane and then ethylene vinyl acetate copolymer (EVA) rings.

FIGURE 1

Systemic levels of ethinyl estradiol during use of an (**A**) oral contraceptive pill, (**B**) contraceptive vaginal ring, (**C**) contraceptive patch. (Data on systemic levels extrapolated [56–58].)



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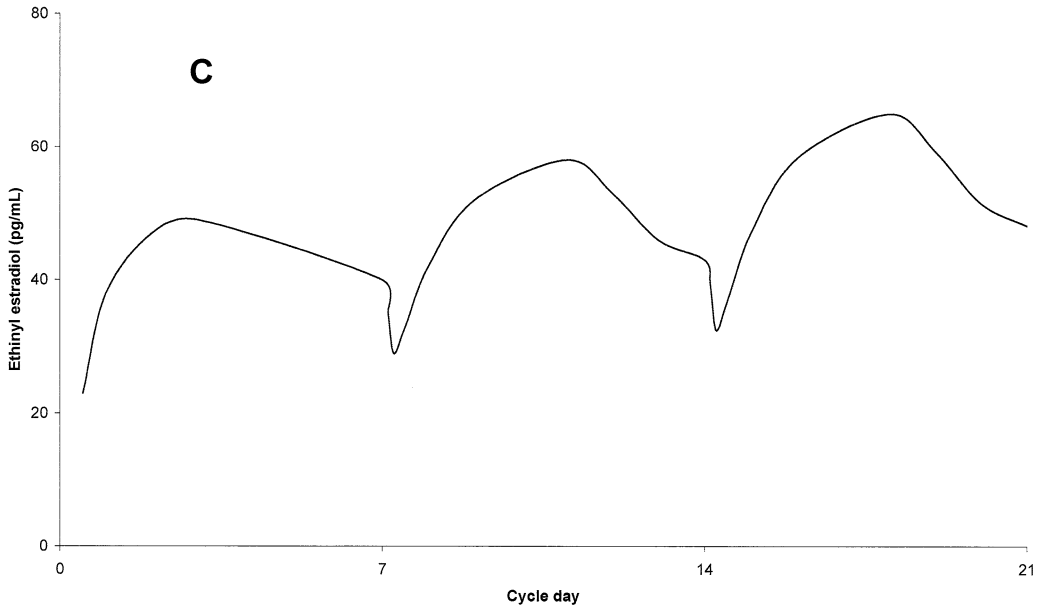
Both of these materials are flexible, inert, and nonirritating. Contraceptive rings have been extensively studied in recent years, both for the delivery of progestogens alone or in combination with estrogen (63, 64) (Table 4). Rings for noncontraceptive use have been evaluated for delivery of estrogen for postmenopausal hormone therapy (65), and a danazol ring has been studied for the treatment of deep pelvic endometriosis (66).

CONTRACEPTIVE VAGINAL RINGS

Contraceptive rings do not act as a physical barrier to sperm, but rather prevent pregnancy by hormonal mechanisms, either suppression of ovulation or changes to cervical mucus. These rings, unlike the cervical cap or diaphragm, do not have to be fitted or placed over the cervix. The ring is simply inserted into the vagina. The only requirement for

FIGURE 1 Continued.



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correct placement is contact with the vaginal epithelium. Contraceptive hormones are absorbed through the vaginal epithelium into the systemic circulation.

The earliest vaginal ring developed for contraception was the progestogen-only medroxyprogesterone acetate ring (67). Other progestogens have been investigated, such as norethindrone and norgestrel (64), but perhaps the best studied have been the levonorgestrel ring developed by the World Health Organization (68–70) and the Population Council's progesterone-releasing ring (71–73). As with most

TABLE 4

Research on vaginal rings used for contraception or estrogen therapy.

Type of ring	Hormone type and dose per day or dose per ring	Study author and year published
Contraceptive; progestin-only	50, 100, 200, or 400 mg of medroxyprogesterone acetate/day	Mishell 1970 (76)
	50 or 200 μg of norethindrone	Landgren 1979 (77)
	50 mg of norgestrienone/ring	Toivonen 1979 (78)
	20 μg of levonorgestrel	WHO 1990 (68)
	50, 75, or 100 μg of nestorone/day	Brache 2001 (79)
	5 to 15 mg of progesterone/day	Diaz 1991 (80)
Contraceptive; combined	700 μg of medroxyprogesterone acetate and 200 μg of estradiol/day	Ahren 1983 (75)
	1.9 mg of megestrol acetate and 200 μg of estradiol/day	Ahren 1983 (75)
	700 μg of norethindrone and 140 μg of estradiol/day	Victor 1984 (81)
	250–290 μg of levonorgestrel and 150–180 μg of estradiol/day	Sivin 1981 (82)
	1 mg of norethindrone acetate and 20 μg of ethinyl estradiol/day	Weisberg 1999 (83)
	75, 100, or 150 μg of etonogestrel and 15 μg of ethinyl estradiol/day	Apter 1990 (84)
	120 μg of etonogestrel and 15 μg of ethinyl estradiol/day	Dieben 2002 (85)
Estrogen therapy	454 mg of estrone/ring	Sipinen 1980 (86)
	7.5 μg of estradiol/day	Eriksen 1999 (87)
	50 μg of estradiol acetate/day	Al-Azzawi 2003 (88)
Estrogen–progestogen therapy	50 mg of estradiol and 100 mg of levonorgestrel/ring	Farish 1989 (89)
	160 μg of estradiol and 10 or 20 mg of progesterone/day	Hamada 2003 (90)

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progestogen-only methods, progestogen-only vaginal rings do not completely suppress ovulation and have been associated with variable bleeding patterns (74, 75). Frequent bleeding problems were not well tolerated in women who expect regular menstrual cycles, which has led to high discontinuation rates in some studies (69, 70). The Population Council's progesterone-releasing ring has been shown to be highly effective and acceptable for lactating women with no deleterious effects on lactation, infant growth, or well-being when compared with a copper IUD (71–73).

Contraceptive ring development naturally progressed to combined rings because the estrogen component maintained the endometrium and prevented breakthrough bleeding. Several types of rings have been developed that contain a variety of progestogens and either E_2 or ethinyl E_2 (see Table 4). Rings containing norethindrone acetate (NETA) in combination with ethinyl E_2 have demonstrated good efficacy and cycle control but have been associated with a high incidence of nausea, particularly in the first cycle of use (83, 91, 92).

NuvaRing® (etonogestrel/ethinyl E_2 vaginal ring, Organon Pharmaceuticals USA, Inc.) is the only combined contraceptive vaginal ring currently available on the market (in the United States, Brazil, and several European countries). NuvaRing's development started with the production of various prototypes. The first was a multicompartment ring consisting of two Silastic tubes—one containing etonogestrel (ENG) and one containing ethinyl E_2 (EE)—connected with two glass stoppers (93). The glass stoppers prevented the migration of the hormones from one compartment to the other and allowed the release of each hormone to be independently altered by changing the thickness of the tube (membrane thickness) and/or the length of each hormone-containing compartment.

Dose-finding studies testing 15 μg of EE in combination with 75, 100, and 150 μg of ENG found a dose-response relationship between ENG and ovulation suppression (84). The study concluded that a ring with a daily release rate of between 100 and 150 μg of ENG and 15 μg of EE appeared to be most suitable for contraceptive purposes; subsequently, a daily release rate of 120 μg of ENG and 15 μg of EE has been and still is used. Although results with the Silastic ring were promising, NuvaRing development switched to an EVA ring design when the supplier of Silastic withdrew the material for human use.

NuvaRing releases 120 μg of ENG and 15 μg of EE and is used for 3 weeks and then removed for withdrawal bleeding. A new ring is then inserted 1 week later. The ring is 54 mm in diameter with a 4-mm cross-sectional diameter, which is similar in size to the other two vaginal rings currently on the market, Estring® (E_2 vaginal ring, Pfizer, Morris Plains, NJ) and Femring® (E_2 acetate vaginal ring, Warner Chilcott, Morris Plains, NJ). However, NuvaRing is thinner than the other two vaginal rings currently available in the United States (Fig. 2). The flexibility of these rings allows them to be easily compressed and hence easily inserted and removed by the user. Once inserted, the ring conforms to fit comfortably in the upper vagina and remains in place until removal is required.

Clinical trials for NuvaRing have shown that the ring has an excellent pharmacokinetic profile, is as effective as oral contraceptives, and is highly acceptable to women (85, 94–99). NuvaRing can also be used safely with products such as tampons, condoms, and vaginal medications (spermicides and antimycotics) if needed; studies have shown that concomitant use of these products does not affect the ring's efficacy (100–102).

RINGS FOR ESTROGEN THERAPY

Vaginal ring technology has also been used for the delivery of E_2 for estrogen therapy in postmenopausal women. As with contraceptive rings, estrogen therapy rings can be controlled by the woman herself and also require minimum attention on the part of the user compared with pills or patches. Vaginal administration of E_2 is more effective in increasing serum and endometrial levels of E_2 than the oral route (27). Several types of rings have been investigated for the treatment of menopausal symptoms. These include low-dose rings for local delivery of estrogen, higher-dose rings for both local and systemic effects, and higher-estrogen dose rings that also contain a progestogen (65). Two estrogen-releasing rings are currently available on the U.S. market, Estring and Femring.

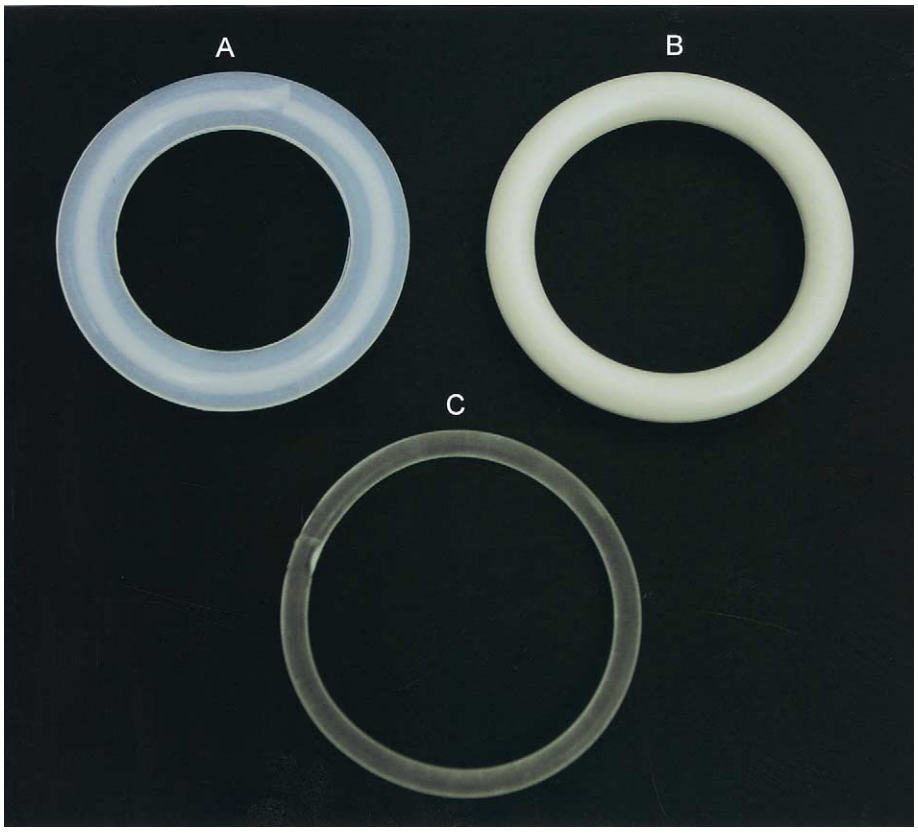
Estring, made of silicone polymers, contains 2 mg of E_2 and delivers 7.5 μg of E_2 per day. It has an outer diameter of 55 mm and a cross-sectional diameter of 9 mm. Each ring is used for up to 3 months. Estring is indicated for the treatment of urogenital symptoms associated with postmenopausal atrophy of the vagina and lower urinary tract. It has also been shown to lower vaginal pH in women with recurrent urinary tract infections (UTIs) (87).

The incidence of UTI rises with increasing age after menopause and seems to be attributable to estrogen loss and subsequent lowering of glycogen content in the vaginal epithelium (103). This effect results in a shift in vaginal flora from glycogen-dependent lactobacilli toward gram-negative bacilli, which creates a potential reservoir for UTI. Thus, a lowering of pH indicates an increase of lactobacilli in Estring-treated women, which would point toward a beneficial effect of decreasing UTI recurrence. Estring was also found to increase maturation of vaginal and urethral epithelial cells, which may also decrease the likelihood of recurrent UTIs.

Femring is an E_2 acetate vaginal ring that is self-inserted into the vagina once every 3 months. Estradiol acetate is rapidly hydrolyzed to E_2 after release from the vaginal ring. Femring is available in two strengths and delivers a steady dose of E_2 acetate at a dose equivalent to either 0.05 mg or 0.10 mg of E_2 per day over the 3-month period of use.

FIGURE 2

Vaginal rings marketed in the United States. (**A**) Estring® (estradiol vaginal ring, Pfizer). (**B**) Femring® (estradiol acetate vaginal ring, Warner Chilcott). (**C**) NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring, Organon).



Alexander. Vaginal drug administration. Fertil Steril 2004.

Femring is made of silicone elastomer and has an outer diameter of 56 mm and a cross-sectional diameter of 7.6 mm. Both doses are indicated for the treatment of both vasomotor and vaginal symptoms (88, 104). Both doses were shown to be statistically better than placebo for the relief of moderate to severe vasomotor symptoms (104). In women with vaginal atrophy at baseline, both doses improved the maturation index compared with placebo (104).

LOCAL EFFECTS OF VAGINAL RINGS

Damage to the vaginal epithelium is known to be possible through the use of tampons and pessaries. Early vaginal rings tended to be rigid and to contain a progestogen only. These rings were sometimes associated with concern about vaginal integrity, as a result of thinning of the vaginal epithelium and local pressure from the rings (105). Subsequent rings were redesigned to be thinner and more flexible and colposcopic investigations into the effects of vaginal rings on the vaginal and cervical epithelium have found no deleterious effects (106, 107).

Vaginal rings, even nonmedicated rings, are associated with an increase in vaginal secretions compared with oral or no contraceptive use (108, 109). For perimenopausal or postmenopausal women, an increase in vaginal moisture may be desirable. One study has proposed that increased secretions with ring use are the result of a weak local inflammatory effect (110). However, other studies do not support this observation, proposing instead that an estrogen effect may be responsible (29). Ring use has not been found to change the vaginal flora compared with baseline or oral contraceptive use except to increase *Lactobacillus* species (110–112).

USER ACCEPTABILITY

Suckling et al. (113) conducted a review to compare various intravaginal estrogen preparations for the treatment of vaginal atrophy in menopausal women. They identified nine comparative studies that evaluated the acceptability of vaginal estrogen preparations. Their results indicated that women favored the E_2-releasing vaginal ring for ease of use, comfort of product, and overall satisfaction. For the com-

parison of the ring versus cream, there were statistically significant differences in adherence to treatment, treatment acceptability, ease of use, and delivery system, all favoring the ring. For the comparison of the ring versus tablet, the acceptability of the ring was significantly higher.

Some of the reasons given by women for liking a contraceptive vaginal ring as opposed to oral combined contraception were effectiveness, convenience, and no requirement to take medication daily (114). The same study found that 62% of women who used a NETA/EE ring for 6 months liked the method much more than their previous method, and 92% would recommend the ring to someone else. In a large study of user acceptability (n = 2,322), 66% of participants at baseline preferred oral contraceptives but after three cycles of ring use, 81% preferred NuvaRing as their contraceptive of choice (99). Overall acceptance was high; 96% and 97% of women would recommend the ring to other women. Reasons for liking NuvaRing included not having to remember anything (45%) and ease of use (27%).

Although many women acknowledge the benefits of nonoral dosing and express a wish to have access to alternative regimens that suit their lifestyles and needs, misperceptions about the vaginal route of administration can lead to reluctance on the part of some women to use vaginally administered products. The vaginal route is still quite novel and not as well understood by women as other nonoral routes, such as the transdermal route. Women may ask if the ring will "get lost up there." Healthcare providers can help women understand vaginal anatomy and the ease of inserting and removing a vaginal ring.

Some are concerned that they will feel the ring. These concerns can be overcome by having the women insert the ring in the exam room so that they can realize that they will not feel it and that it is easy to insert and to remove. In large clinical trials of NuvaRing with over 2,000 women, 96% and 98% of women found the ring easy to insert and remove, respectively, including women who discontinued the study (85). Some women ask if their partners will feel the ring, but studies have demonstrated that most men do not feel it, and that those who do feel it usually do not mind it (85). Some women are concerned about having something in their vagina for an extended period of time but can be reassured that the ring was developed to be used in that way. Studies have also shown that women who use NuvaRing are satisfied with the method and would recommend it to other women (99).

CONCLUSIONS

Data presented in this review support the vaginal route as an acceptable and even preferable method for drug delivery, particularly for hormones, whether for contraception or postmenopausal estrogen therapy. The safety and efficacy of vaginal administration have been well established through its long and well-studied history. Drugs are easily and rapidly absorbed through the vaginal epithelium into the systemic circulation, and there are no adipose tissue or other cell layers with metabolic enzymes to traverse as with the transdermal or oral routes. The GI tract and hepatic first-pass effect are avoided. Vaginal administration allows nondaily, low, continuous dosing, which results in stable hormone levels and may, in turn, achieve a lower incidence of side effects and improve patient compliance. Vaginal ring technology makes drug administration easy and discreet for patients, giving them complete control over the method and its reversibility. Clinicians can help their patients understand these advantages and provide reassurance.

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