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Vaginal delivery of contraceptives

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Although a steady increase in contraceptive use has been observed both in developed and less-developed countries, the large number of unplanned pregnancies may indicate that the contraceptive needs of a significant percentage of couples have so far not been met. Several new contraceptive products have reached the market during the last 2 years. Among these is a new contraceptive vaginal ring, which has become available for prescription. This new female method has been developed to expand the contraceptive choices available to couples. This review will address the specifics of the vaginal route for delivering contraceptive steroids and describe the various systems available or under evaluation.

Keywords: contraceptive steroid, contraceptive vaginal ring, controlled-release, dual protection, long-acting system, vaginal delivery

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1. Introduction

The anatomy of the vagina and vascular supply makes this organ an ideal route of drug administration in the woman [1]. Contraceptive steroids are particularly suitable for delivery through the vaginal epithelium, which allows quick absorption, unaffected by gastrointestinal disturbances and steady drug levels in the systemic circulation. Formulations of contraceptive steroids from the vaginal route have been studied in the form of gels, tablets and rings.

The vaginal delivery of contraceptive hormones was initially conceived and executed by several groups over the past decades (**Table 1**). Several steroids were tested and showed efficacy in suppressing ovulation when administered from vaginal rings [2-18].

The delivery of steroids by the vaginal route offers many advantages that have led to continued research for refining the delivery method. Steroid absorption through the vaginal mucosa is rapid and initial studies placing oral contraceptive formulations (OCs) in the vagina proved to be successful in suppressing ovulation. Appropriate formulations were developed for this purpose and contraceptive vaginal rings (CVRs) were designed to deliver low doses of steroid at a constant release rate. The advantages of the long-acting delivery systems such as vaginal rings are perceived by the women who participated in clinical studies as a method directly controlled by the user herself, with easy insertion and removal. In addition, there is no daily attention to the system and compliance is higher than with daily intake of an oral tablet.

In spite of early successful trials, the use of soft and flexible silicone rings for vaginal delivery of contraceptive levels of hormones is only now reaching the market and gaining clinical acceptance. The Population Council's progesterone-releasing ring, manufactured by Silesia SA in South America is on the market in Chile and Peru for contraception during lactation [8,19]. More recently, Organon introduced a monthly ring delivering etonogestrel (ENG) and ethinyl oestradiol (EE; Nuvaring®) in Europe, the US and other countries [15,20]. The Population Council is also developing a ring releasing a non-androgenic progestin, Nestorone® and EE, which is designed to be effective for 1 year [16-18].

Although the use of oral tablets is as affective as the vaginal route [21], it was not an appropriate formulation for contraception, the technology for the design and formulation of vaginal rings has been perfected, which should facilitate its wide availability

Table 1. Steroids tested in contraceptive vaginal rings.

	Steroids	Ref.
Progestin-only	MPA	[2]
	NET	[3]
	Norgestrienone	[4]
	LNG	[5]
	Nestorone®	[6]
	Progesterone	[7,8]
Progestin combined with E_2	MPA + E_2	[9]
	Megestrol Ac + E_2	[9]
	NET + E_2	[10]
	LNG + E_2	[11]
Progestin combined with EE	NET Acetate + EE	[12,13]
	Etonogestrel + EE	[14,15]
	Nestorone + EE	[16,18]

E_2: Oestradiol; EE: Ethinyl oestradiol; LNG: Levonorgestrel; MPA: Medroxyprogesterone acetate; NET: Norethisterone.
Adapted from ALEXANDER NJ, BAKER E, KAPTEIN M, KARCK U, MILLER L, ZAMPAGLIONE E: Why consider vaginal drug administration? *Fertil. Steril.* (2004) **82**:1-12 [1].

in the future. In addition, gels for vaginal application containing combinations of microbicides for the purpose of preventing sexually transmitted infections (STIs) and either steroid- or spermicide-based contraceptives are under development for a dual protection [22,23].

2. Properties of the vaginal epithelium

The delivery of products from the vagina is a convenient and effective route of administration in women. The vagina is lined with a nonkeratinised squamous epithelium that absorbs small molecules such as steroids very easily. Several types of medications have been administered from the vagina including misoprostol, analgesics, steroids and antiviral agents [1]. As the bioavailability is often increased from this route of absorption, lower doses can be administered from the vagina for the same general effect. The absorption is made via the circulation by a complex network of arteries and veins; the venous drainage from the upper part of the vagina is linked to the inferior vena cava [1].

De Ziegler *et al.* [24] described a first uterine pass effect for progesterone, showing that concentrations of the steroid were much higher in the endometrium than in the circulation when progesterone cream was applied in the vagina. A direct transit from the vagina to the uterus has been assessed in experimental studies testing the absorption of progesterone in women undergoing hysterectomy and a direct transport of the steroid has been attributed to the particularly rich arterial local network [25].

3. Contraceptive vaginal rings

3.1 Design

Several technologies have been engineered for the sustained release of steroids. The 1-year ring being developed by the Population Council is a doughnut-shaped device composed of a soft and flexible inert silicone elastomer. Although sizes vary for the different rings designed so far, they are generally in the range of 58 mm in diameter with a cross section of ~ 8.4 mm. The hormone(s) ensuring the contraceptive effect are mixed with a medical grade elastomer to form cores that are implanted in the body of the ring and from there are released slowly and constantly from the silastic. The steroids are absorbed from the vaginal epithelium and subsequently passed into the general circulation. Other rings are designed as a mix of steroid and elastomer matrix injected in the ring body. Alternatively, rings may contain steroid(s) homogeneously disseminated through the core of the ring or in a circular system throughout the centre of the doughnut [1,8,17].

Nuvaring® is 54 mm in diameter with a 4-mm cross-sectional diameter. In the current ring a new material, the ethylene vinyl acetate copolymer has replaced the silastic elastomer. All vaginal ring systems, however, operate similarly, with slow release of the drug from the device through vaginal tissue and extended release for prolonged activity. Depending on the type of ring used, steady release of hormones may occur over a period ranging from 3 weeks to 1 year. The Population Council's version of a 1-year oestrogen/progestin ring contains the fourth-generation progestin Nestorone plus the synthetic oestrogen EE. The steroids are contained in cores implanted in the ring, one containing Nestorone alone and the other containing both hormones (**Figure 1**). The current rings are very flexible and can be easily inserted and removed by the woman herself. Once inserted, the ring fits in the upper vagina, and by contact with the walls of the vagina delivers the steroids into the systemic circulation. Other forms of long-term contraception, such as implants and intrauterine devices (IUDs), must be inserted by medical providers and thereby prevent the woman from controlling her own contraceptive method. With this new method using a vaginal ring, a woman may easily learn ring insertion and removal techniques to begin or discontinue hormonal contraception in a single session. Most women find the ring to be a simple and convenient method of birth control [1,26].

3.2 Steroids used in vaginal rings for contraception

The main contraceptive effect, suppression of ovulation, is ensured by the progestin component contained in the ring. The progestins suitable for this effect are potent anti-ovulatory agents. Two testosterone-derived progestins, levonorgestrel and ENG, and the progesterone-derived molecule Nestorone are able to suppress ovulation when delivered at very low doses [27,28]. This property makes long-acting delivery feasible as the reservoir fits into delivery systems of reasonable size such as gels, patches and implants or rings [28]. Nestorone (16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3,20 dione) is a progestational agent derived from 19-norprogesterone. It has no oestrogenic or androgenic actions and is 10-fold as potent as levonorgestrel on the endometrium and twice as potent as levonorgestrel in suppressing ovulation.

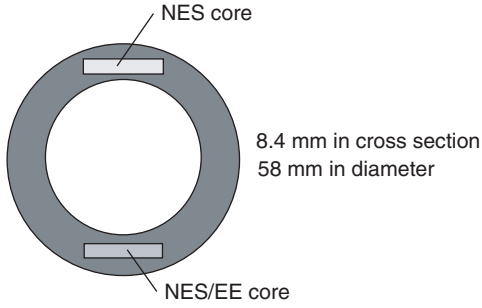

Figure 1. Schematic design for the 1-year Nestorone®/ethinyl estradiol contraceptive vaginal ring under development by the Population Council.
EE: Ethinyl oestradiol; NES: Nestorone.

ENG is derived from levonorgestrel but is less androgenic and its ovulatory suppressive effect is close to that of Nestorone [27,28]. The three progestins permeate the vaginal mucosal membranes easily and a very low dose is sufficient to suppress ovulation [5,6,20].

The use of Nestorone may afford greater benefit than the other progestins used so far as this progestin exhibits significantly less binding to androgen receptors (and, thus, substantially less androgenic activity) than levonorgestrel [28]. Furthermore, because it is not orally active, it is unlikely to pass to infants through breast milk when nursing mothers use Nestorone-containing vaginal rings, subdermal implants, gels or patches.

In addition to the progestin, an oestrogen is contained in the combination rings. It increases the contraceptive efficacy of the progestin by a synergistic effect on ovulation inhibition and maintains the endometrial development contributing to a regular withdrawal bleeding pattern. Older versions of Population Council rings used oestradiol [10,11]. However, EE has a more potent effect on the suppression of gonadotropins and a low dose can be combined with the progestin to ensure both effective contraception and a regular bleeding pattern [18,29,30].

4. Efficacy of contraceptive rings

4.1 Progestin-only vaginal rings

Progesterone-only rings have been most widely used, and one is currently available to women in Chile and Peru [8,23]. This ring releases progesterone 10 mg/day, the natural hormone, and is intended for contraceptive use exclusively by breastfeeding women. The steroid is inactivated rapidly when absorbed orally and exposure of the newborn through breast milk is avoided. In addition, progesterone acts on the pituitary and prevents ovulation, supporting and extending the physiological anovulation experienced by breast feeding women [8]. In lactating women, the natural progesterone-only ring is as effective at preventing pregnancy as the copper T IUD and is equally safe for infant health and weight [19]. Another ring, releasing a very low dose of Nestorone for 6 – 12 months, has been tested in breastfeeding women [8,30]. With the Nestorone-only ring, ovulation was inhibited (progesterone levels < 10 nmol/l) in most subjects with doses as low as 50 µg/day (**Table 2**) [6].

Table 2. Nestorone contraceptive rings: percentage of cycles without luteal activity*.

Nestorone delivery	50 µg/day	75 µg/day	100 µg/day
Percentage of cycles without luteal activity	97.5	97.4	98.8

*Luteal activity is defined as progesterone Š10 nmol/l or 3 ng/ml.
Adapted from BRACHE V, MISHELL DR, LAHTEENMÄKI P et al.: Ovarian function during use of vaginal rings delivering three different doses of Nestorone®. Contraception (2001) 63:257-261 [6].

Table 3. Contraceptive efficacy and ovulation inhibition of the vaginal rings currently approved* or in development.

Type	Duration of use (months)	% Ovulation inhibition	Ref.
Etonogestrel/EE*	1	98 – 99	[30]
Nestorone	6	97.5 – 98.8	[6]
Nestorone/EE	12	~ 88 – 98	[17]

*NuvaRing® approved worldwide.
EE: Ethinyl oestradiol.

4.2 Combined oestrogen-progestin rings

Combination contraceptive rings will have greater application to the general population of women seeking to prevent pregnancy. With the recent worldwide approval of a combination ring containing ENG/EE, this regimen is available to a large population of women. The Population Council has also developed vaginal rings that release a combination of progestin and oestrogen: a ring releasing norethindrone acetate and EE was initially developed for 3 months and later reformulated for 12 months use [12,13]. This formulation was discontinued due in part to an unacceptable incidence of ovulation, as well as nausea. Another ring combining Nestorone and EE that is in development appears to be effective for 12 months [17,18]. A long-term contraceptive method that will remain active for prolonged duration would be of particular value for use in developing countries.

The various formulations of vaginal rings have proven to be highly effective as contraceptives, providing excellent inhibition of ovulation [17,20,31] (**Table 3**). With proper use of the ENG/EE vaginal ring, pregnancy rates are between 1 and 2 per 100 women-years of use [20,30]. Roumen *et al.* reported only six pregnancies occurring in their population of 1145 women treated with the EE/ENG-containing ring; three of these pregnancies were in women who had clearly been noncompliant during the cycle of conception [30]. Weisberg *et al.* reported no

pregnancies in either of the two trials of the EE/norethindrone acetate ring used by 60 and 61 women, respectively [13,32].

These encouraging data are in line with other combination contraceptive methods including oral and transdermal contraceptives. However, a method avoiding a daily intake of a pill will minimise the risks of failure and may improve compliance in real-life situations. Long-acting methods requiring a health provider intervention and no other user intervention, such as IUDs and contraceptive implants, have lower failure rates of 0.1 – 0.5% in the first year of use, which is equivalent to sterilisation [33].

4.3 Contraceptive vaginal ring use schedules

The most common schedule for the contraceptive vaginal rings so far, and the one used with the recently approved ENG/EE ring, is the 3-weeks in/1-week out use schedule. With this regimen, the ring is inserted into the vagina on day five of the menstrual cycle and left in place for 3 weeks. The following week (week four) the ring is removed for withdrawal bleeding. The old ring is either discarded and a new ring (1-month ring) inserted, or the same ring (1-year ring) is reinserted after a 1-week ring-free break. It is recommended that the woman choose a specific day of the week, and hour for insertion and withdrawal of the ring, for better compliance.

Alternative schedules of vaginal ring placement have also been studied. In order to improve compliance, some investigators have utilised a calendar-based system of use from day 1 to 25 of each month [34]. In addition, an attempt to reduce the duration of the ring-off period, a 26-days in and 4-days out schedule was tested but showed no difference in the number of ovulations as compared with the 3-weeks on and 1-week off regimen (Population Council data on file). Continuous use of the ring for targeting amenorrhoea has not been extensively studied. However, another approach has been to base the insertion on bleeding signals; that is, the ring is inserted and removed only when menstrual bleeding begins. The ring remains out for 4 days, and is re-inserted at that point whether or not bleeding has stopped. This latter schedule, however, leads to irregular unpredictable bleeding patterns (Population Council data on file).

4.4 Ovulation suppression and hormonal effects of ring use

The use of safe and pliable polydimethylsiloxane carriers and the development of hormone-containing controlled-release polymers have permitted the formulation of vaginal rings that can release hormones for ≥ 1 year [31,32]. The hormonal, ovarian and bleeding patterns associated with these new contraceptives, as well as other safety features, have been evaluated in several studies.

4.4.1 Hormone levels with vaginal rings

With rings delivering Nestorone only, continuously at a rate of 50, 75 or 100 µg/day, a high rate of ovulation suppression was observed [6]. At the highest dose of 100 µg/day, only 1.2% of the cycles studied showed luteal activity, measured by progesterone levels of ≥ 10 nmol/l. The levels of oestradiol were decreased but were not less than 200 pmol/l. This indicates good suppression of the follicular maturation without hypoestrogenism.

In studies of vaginal rings containing EE and Nestorone, the ring was inserted for 3 weeks and then removed for 1 week to permit withdrawal bleeding for 13 consecutive cycles. The delivery rate of Nestorone 150 µg/day and EE 15 µg/day is very stable over 1 year, decreasing slowly with time. With this dose, encouraging results, such as a high percentage of ovulation suppression, good bleeding patterns and few side effects have been achieved [17,18]. The development of this combined ring is still ongoing.

The recently approved combination ring containing ENG (the active derivative of desogestrel [DSG]) and EE was evaluated in several clinical studies [20]. In one open-label, randomised, crossover study [35], 16 women were treated either with this ring delivering ENG 120 µg/day and EE 15 µg/day over 3 weeks for contraception, or with a combined oral contraceptive containing DSG 150 µg and EE 30 µg. The mean serum concentrations of ENG and EE were: 1578 and 19.1 pg/ml, respectively, at week one; 1476 and 18.3 pg/ml, respectively, at week two; and 1374 and 17.6 pg/ml, respectively, at week three. These serum levels were consistent with the pattern of immediate hormone elevation and slow decrease over the course of a cycle.

Timmer and Mulders [35] have demonstrated that the maximum concentration (C_{max}) of ENG and EE released from this ring is ~ 40 and 30%, respectively, of that observed with a combined OC (COC) containing DSG and EE. The bioavailability of ENG is higher with the CVR (103%) than with the DSG/EE COC (79%). The bioavailability of EE is similar with the CVR (55.6%) and a COC that delivers twice as much EE (53.8%) [35].

4.4.2 Bleeding patterns with vaginal rings

The Nestorone/EE combination vaginal ring has been associated with good control of menstrual bleeding [16,18]. Regular withdrawal bleeding has occurred consistently following ring removal, with little breakthrough bleeding with the ring in place. The period of menstrual bleeding is often less than the 1 week allotted for no treatment, and the need to reinsert the ring while bleeding persists is rare.

In a study of the ENG/EE ring carried out by Roumen *et al.* [30], irregular bleeding occurred at a rate of only 2.6 – 6.4% of evaluable cycles. This consisted primarily of spotting, with breakthrough bleeding reported in only 0.4 – 1.1% of cycles. Withdrawal bleeding (during the week off treatment) began early while still wearing the ring in only 5.4 – 7.7% of cycles. Only 0.6 – 2.1% of treatment cycles had no withdrawal bleeding. Finally, the mean duration of withdrawal bleeding in this study was 4.7 – 5.3 days.

5. Safety aspects of vaginal contraception

5.1 Effect of vaginal devices or gels on the vaginal mucosa

Colposcopy studies were carried out in several of the trials to determine any effect of the vaginal ring on the vaginal mucosa or on cervical cytology. Fraser *et al.* [36] studied the vaginal surface appearance in women using contraceptive vaginal rings. Colposcopic evaluations showed erythema in 4.1% and abrasions in 2.5% of the exams. However, a similar number of findings was observed in a control group of subjects who were sexually active and were using methods of contraception other than rings. Erythema was reported in 2.9% and abrasions in 1.6% of those control subjects [37]. Roumen *et al.* [30] reported a shift from normal to abnormal cervical cytology (Papanicolaou grade III – IV) in 21 of 1145 women (1.8%) receiving the ENG-containing ring. This low rate of cervical abnormalities is actually lower than the rate observed among the entire screened population (~ 2.8%) of 1200 women, suggesting that the ring is not associated with either adverse cytological effects.

Local bacterial flora and especially *Lactobacillus* helps to protect the vagina against infection and maintain the normal acidic pH. An acidic pH is also maintained by oestrogen and enables resistance to infections. Vaginal rings do not modify the vaginal flora [1]. In addition, studies conducted with Nuvaring indicated no reduction in hormone delivery with concomitant use of tampons or vaginal antifungal inserts. Those products did not reduce the efficacy of the rings [1,38].

5.2 Side effects and contraindications to the use of contraceptive vaginal ring

By and large the vaginal contraceptive rings currently approved or under investigation appear to be well tolerated. Until long-term follow-up data of vaginal ring users are available, it is widely recommended that clinicians consider all of the potential complications of combined oral contraceptives to be potential side effects of vaginal combination contraceptives. Contraindications to the use of combined rings delivering EE include a history of thromboembolic events, hypertension, gallbladder disease, hepatic adenomas or benign liver tumours.

When comparing Nuvaring to a second-generation oral contraceptive, Magnusdottir *et al.* [39] found no difference in effect on the clotting factors and similar changes were observed with the two contraceptives. Although some lipoproteins are more favourably influenced by the vaginal ring than the OC due to the less androgenic potency of the progestin, the effect of EE on the liver is the same [40,41]. Vaginal, transdermal and oral delivery of EE results in similar changes in hepatic protein and lipoprotein production. The same contraindications apply to the rings delivering EE and OCs, and the ring should not be considered as a preferred alternative to OCs for women with risk factors for cardiovascular disease.

Common side effects definitely or possibly related to treatment with vaginal rings are nausea/vomiting, headache, gastrointestinal symptoms and vaginal discharge. In general, these side effects are mild-to-moderate in nature and rarely lead to discontinuation of the medication.

5.3 Acceptability of vaginal rings

Acceptability studies [25,40] indicate that > 90% of the women who used the vaginal ring would recommend it to other women. The ease of use and no need for daily attention are the main features of the ring favoured by users. Women do not feel the ring when it is in place and most partners do not feel it during sexual intercourse [1,42].

6. Future options for vaginal delivery of contraceptive agents

6.1 Vaginal gels for contraception and prevention of sexually transmitted infections

Microbicides are being developed in vaginal gel formulations with the purpose of protecting women against STIs [43,44]. These formulations are designed to be applied before each intercourse; their efficacy is not yet demonstrated but development is ongoing. This area is the field of an intensive research and is facing several hurdles that this review does not intend to address. However, based on that field of research, another option is being studied. Possible combinations of these microbicide vaginal gels together with contraceptive agents are being actively searched in order to afford a 'dual protection' both against STIs and unwanted pregnancy. Two approaches are in the early stage of research, one using steroids delivered in the systemic circulation from the microbicide gel, which act as a delivery system thanks to its properties of retention in the vagina, and another approach using spermicides aimed at ensuring a local contraception without systemic absorption.

6.2 Vaginal delivery of spermicides in hydrogels

Saxena *et al.* [45] recently described a biodegradable vaginal device designed to deliver a nonhormonal spermicide. The body is composed of biodegradable hydrogel, which consists of a core surrounded by four concentric sheaths containing dextran, a copolymer of polylactide, and epsilon-caprolactone. The hydrogel is impregnated with iron(II) D-gluconate dihydrate, which causes complete spermiostasis due to lipid-peroxidation; ascorbic acid, which increases the viscosity of the cervical mucus; and mixtures of polyamino and polycarboxylic acids, which maintain a vaginal pH of ~ 4.5. When used in rabbits, this system produced a rapid inactivation of the sperm. Unlike the CVRs that deliver steroid hormones to the systemic circulation, this ring is designed for local delivery of a nonsteroidal spermicide.

7. Conclusion

Local delivery of contraceptive agents in the vagina is gaining acceptability and this route of administration allows an

easy absorption of steroids or other small molecules. The contraceptive ring, a doughnut-shaped drug delivery system that may remain within the vagina for weeks to months, has several unique features and advantages over other long-acting contraceptive methods. Arguably the most important advantage is that this method is under complete control of the user: a woman can easily be taught to insert and remove the flexible ring without the need for a medical office visit or insertion by medical personnel. Other methods that are controlled by the woman, such as diaphragms or spermicides, require attention at every sexual encounter or, as with birth control pills, must be taken daily for up to 3 of every 4 weeks. These challenging schedules can interfere with patient compliance and product reliability.

Future vaginal rings offer the promise of a long-acting form of contraception. Rings are being developed that can remain in place for up to 13 consecutive cycles. Their extended-release formulation allows for the delivery of relatively small daily doses of steroid into the vaginal tissue and then into the bloodstream.

The physiology of the vagina makes it an ideal route for drug delivery of various drugs and particularly steroid homones that can be self-administered and in lower doses than via the oral route.

8. Expert opinion

Several combination vaginal contraceptive rings have been found to provide excellent contraceptive efficacy and appear to be as effective as OCs in terms of pregnancy prevention. Other important benefits of vaginal rings are their ease of use, long-term schedule, which may improve compliance over OCs and user-controlled application. In clinical studies, few patients have discontinued hormonal ring therapy due to side effects, and all reported side effects have been consistent with those noted with other hormonal contraception methods.

Research on vaginal administration of biodegradable hydrogels or gels delivering a microbicide in conjunction with a contraceptive agent, either steroidal for systemic action or a spermicide for local effect, is ongoing and may offer user control for dual protection in the next decade.

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