The Ins and Outs of Drug-Releasing Vaginal Rings:  
A Literature Review of Expulsions and Removals

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Note to editors and reviewers: This contents section is not intended for inclusion in the published article. Instead, it has been included here to help reviewers understand the overall structure of the article.

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Article Highlights

- There is considerable interest in vaginal ring technology for sustained/controlled release of pharmaceutical drugs to the human vagina. Seven drug-releasing vaginal ring products have reached market and many other experimental devices are in preclinical/clinical development.

- Involuntary expulsions of drug-releasing vaginal rings are commonly reported in most clinical studies, irrespective of ring type and clinical indication. Up to 50% of women in some studies report at least one expulsion. Expulsions lead to reduced acceptability and adherence.

- Many factors may potentially be contributing to the incidence of ring expulsions, including: ring dimensions, the types and grades of polymers used, the mechanical characteristics of rings, location of ring insertion, changes in cervical/vaginal laxity, quantity of fluid in the vagina, concurrent use of other vaginal products, and various user/cultural practices.

- The most commonly cited reasons for voluntary ring removals include for menstruation, the desire to periodically clean the ring, and for sexual intercourse.

- Despite the continued absence of international standards for mechanical properties of drug-releasing vaginal ring products, regulatory agencies expect submission of supporting data to demonstrate that the mechanical characteristics of ring products are fit for purpose. Standardised in vitro test methods are needed to assess mechanical integrity under conditions similar to those encountered in clinical use.

- While vaginal rings generally perform well overall, further research efforts to assess, understand and ultimately address the issues around involuntary ring expulsions and voluntary ring removals are needed, with the goal of enhancing health outcomes for women.
Abstract

Introduction

There is considerable interest in vaginal ring technology for sustained/controlled release of pharmaceutical drugs to the human vagina. Seven drug-releasing vaginal ring products have reached market and have many other experimental devices are in preclinical/clinical development. Although most women who have use vaginal rings are satisfied and find them acceptable, involuntary ring expulsions and voluntary ring removals are known to occur and are widely reported in the scientific literature. There have been no previous efforts to review the historical data and understand the contributing factors leading to expulsions.

Areas covered

This article is intended to help researchers, clinicians and product developers understand the pertinent factors and issues around ring expulsions and removals, and to inform new research aimed at optimising the design of new ring products. The review contains four sections: (i) introduction to vaginal ring technology; (ii) a discussion of the anatomical, physiological, device, and user factors potentially affecting ring expulsion; (iii) a literature review around involuntary ring expulsions; (iv) a literature review around voluntary ring removals; and (v) concluding remarks and opinions.

Expert Opinion/Commentary

Further research is needed to better understand the factors contributing to involuntary ring expulsions and removals so that rings can be designed from the outset to minimise rates of expulsion and to reduce removals. Determination of optimum ring dimensions and stiffness for each ring product are likely key factors, alongside better counselling around ring removal and reinsertion.

Keywords: silicone elastomer; ethylene vinyl acetate copolymers; thermoplastic polyurethanes; involuntary ring expulsion; voluntary ring removal; mechanical properties; ring dimensions; parity
1. Introduction

Vaginal rings are flexible, torus-shaped, polymeric devices for sustained or controlled release of drugs to the vagina to treat or prevent a range of clinical conditions associated with women's sexual and reproductive health [1,2,11–20,3–10]. Several seminal studies paved the way for development of the drug-releasing ring concept: (i) demonstration that the human vagina is capable of systemic absorption of drugs [21,22]; (ii) use of silicone rubbers for sustained in vivo administration of dyes and anaesthetic gases [23,24]; and (iii) the sustained controlled release of steroid molecules following their incorporation into silicone rubbers [25]. Since publication of the first patent and journal article describing the drug-releasing vaginal ring concept in 1970 [26,27], seven vaginal rings products – all releasing one or more steroid molecules – have reached market: Estring®, Progering®, Fertiring®, NuvaRing®, Femring®, Ornibel®/MyRing™ (and various alternative names in other European countries), and Annovera™ (Table 1) [28]. The estrogen replacement therapy rings Estring® and Femring® and the progestin-only rings Progering® (contraception) and Fertiring® (in vitro fertilisation) are each made from silicone elastomer, have similar dimensions, and are intended for three months continuous use with no need to remove the ring during normal use (Table 1). The combination estrogen-progestin contraceptive rings NuvaRing®, Ornibel® (manufactured from thermoplastic polymers and having a relatively thin profile) and Annovera™ (prepared from silicone elastomer) are designed to be worn continuously for three weeks and then removed for one week for withdrawal bleeding, after which either the same ring (Annovera™) or a new ring (Nuvaring®, Ornibel®) is inserted (Table 1).

Despite these recommended use regimens, both involuntary (also described in the literature as ‘inadvertent’, ‘accidental’ or ‘spontaneous’) ring expulsions and voluntary ring removals are often reported during both clinical testing and real-world use. (Expulsions are also widely reported with non-medicated vaginal ring pessaries for treatment of pelvic organ prolapse [29–31], most of which are also manufacture from silicone elastomer. Some of these ring pessaries look very similar to drug-releasing vaginal rings, while others adopt different designs.) To date, there has been no attempt to critically review the published literature on these important aspects of ring use, much less assess the different factors and reasons contributing to ring expulsions and removals. This review is intended to fill the knowledge gap, and to help researchers, clinicians and product developers understand the pertinent issues and contributing factors.
2. Factors potentially affecting ring expulsion

We have identified nine factors that likely contribute to the involuntary expulsion of rings during use: (i) differences in the dimensions of the human vagina; (ii) the dimensions of the ring device; (iii) the type and grade of the polymeric material used to manufacture the ring; (iv) the mechanical performance characteristics of the ring; (v) ring insertion procedures and the location of ring placement in the vagina; (vi) changes in cervical/vaginal laxity due to parity and age; (vii) quantity of endogenous and exogenous fluid in the vagina; (viii) concurrent use of vaginal drug products and personal lubricants, and (ix) user and cultural practices. Each of these factors is considered in turn.

2.1. Dimensions of the human vagina

The human vagina (derived from the same word in Latin meaning “sheath” or “scabbard”) is a collapsed fibromuscular tube extending from the external genitalia to the cervix. It is best considered as a potential space that undergoes considerable distension during sexual intercourse and particularly childbirth. The overall shape of the vagina and its ability to stretch are affected by the laxity (looseness) and elasticity of the vaginal tissue and its relationship to other pelvic organs (discussed in Section 2.6) [32]. Earlier scientific studies investigating the dimensions of the human vagina were often performed either using cadavers or by making three-dimensional casts in live women by injecting various moldable materials, such as wax, rapidly solidifying dental impression paste, and silicone [33–35]. Recognising that these casting methods and materials produced some degree of distension of the vagina, magnetic resonance imaging (MRI) of the live human vagina of women following administration and distribution of an aqueous vaginal gel has been reported as a means of more accurately capturing baseline dimensions [32]. In this study, significant variation in mean vaginal length (cervix to introitus) was reported across 28 women (14 nulliparous and 14 parous) aged 18–45, with a mean value of 62.7 mm. Mean vaginal width decreased from proximal vagina (32.5 mm), to pelvic diaphragm (27.8 mm) and introitus (26.2 mm). Factors such as age, height and parity (but not race) were positively associated with differences in baseline vaginal dimensions.

Corroborating quantitative data from a more recent MRI study has demonstrated considerable variation in vaginal shape, axis and dimension as measured in 80 healthy women aged 28–70
years with different sizes and body types [36]. The variations in vaginal dimensions could not be correlated with body size (e.g. height, BMI) or other demographic variables. The highly variable anatomical data, and most notably in the measurement of vaginal width, suggest that the one-size-fits-all approach to selecting the dimensions of a vaginal ring product may not be ideal in terms of increasing user comfort and acceptability and reducing rates of involuntary expulsions.

2.2. Ring dimensions

Given the variation in baseline vaginal dimensions, it is somewhat surprising that a once-size-fits-all approach is still widely adopted for many vaginal products [37,38], including drug-releasing vaginal rings. Despite having slightly different dimensions, each of the marketed vaginal rings is designed and manufactured in a single size (Table 1). This contrasts with many cervical caps and diaphragm products that are often available in a range of different sizes. Of course, unlike vaginal rings, the barrier contraceptive products need to fit tightly around the cervix in order to function as an effective barrier preventing sperm crossing the cervix and uterus and accessing an egg in the fallopian tube. Also, vaginal ring pessaries – used for urinary incontinence or for vaginal/pelvic organ prolapse – are available in different sizes, with external diameters typically ranging from 38–127 mm [39–42].

Historically, drug-releasing vaginal rings have been developed and tested having a wide range of dimensions (Figure 1). The two parameters than define any torus are the external (ED; also known as ‘overall’ diameter) and the cross-sectional diameter (CSD). The earliest ring prototypes – containing 2 g of the contraceptive progestin medroxyprogesterone acetate – were relatively large at 10 mm CSD and between 70 and 80 mm in ED, although thinner 7 \times 75 \text{ mm} ring profiles with lower loadings of this steroid (50–400 mg) were also evaluated (Figure 1) [27,43,44]. These relatively large ring sizes were necessary at that time, since the silicone elastomer was then molded around a stiff and flat metal spring, similar to that used in some diaphragms [45]. However, in early clinical studies and particularly with nulliparous women, reports of erosion/ulceration of the vaginal tissue and general discomfort were common and attributed to excessive pressure exerted by the relatively stiff metal rings [27]. It was concluded that any possible advantage offered by the rigid spring component in these rings in helping vaginal retention (no partial or complete involuntary expulsions were recorded in the subjects) was offset by the mucosal erosion/ulceration associated with their use. It was also conceded that the possibility of users experiencing some expulsions with
smaller rings without a metal spring would be preferable to the possibility of tissue damage.

As a consequence, the spring-free design was subsequently adopted for all future drug-releasing ring devices, facilitated by significant improvements in silicone elastomer formulations and use of alternative thermoplastic materials.

Developments during the 1970s and 1980s focused on silicone elastomer rings – primarily for hormonal contraception and estrogen replacement therapy in Western countries – mostly having EDs and CSDs ranging from 50–61 and 5–9.5 mm, respectively (Figure 1).

Exceptionally, much smaller contraceptive silicone elastomer rings releasing megestrol acetate were also being developed in China at this time, measuring just 45 × 4 and 40 × 4 mm [46,47]. Rings having significantly thinner CSDs (3.0, 3.5 and 4.0 mm, each with 54 mm ED) were also used for ethylene vinyl acetate (EVA) copolymers (see Section 2.3), a type of thermoplastic elastomer material with greater rigidity than silicone elastomer [48,49].

According to the data presented in Figure 1, there is no correlation observed between ring dimensions and expulsions. However, for further insight, studies testing different dimensions of rings fabricated from the same polymer material would be useful.

2.3. Types and grades of polymeric materials used to manufacture vaginal rings

To date, three different types of polymer have been used for the manufacture of marketed vaginal rings – silicone elastomers (also known as ‘silicone rubbers’), ethylene vinyl acetate (EVA) copolymers, and thermoplastic polyurethanes (TPU) (Table 1, Figure 2). These polymers can exhibit very different physical and mechanical properties, reflecting the diversity of polymer composition, cure chemistries, grades, and formulations. Of these polymers, only silicone elastomers and EVAs directly contact the vaginal mucosal tissue; the thermoplastic polyurethane contained in Ornibel® is only used for formulation of the drug-loaded core and is surrounded by a drug-free, rate-controlling EVA membrane. However, other experimental rings described in the literature do include TPU materials in mucosal contact [50–54], and TPUs are otherwise used in short-term implantable devices, including dialysis devices, feeding tubes, intra-aortic balloon pumps, and surgical drains [55]. A small number of other polymeric materials have also previously been considered for vaginal ring manufacture [56–62].

Silicone elastomers
Silicone elastomers are synthetic, chemically crosslinked, non-biodegradable, highly elastomeric, thermosetting polymer systems that are formulated as complex multi-component mixtures [1]. By adjusting the type and concentration of the various components, including the mechanical fillers used to improve their physical and mechanical characteristics [63], suppliers can offer a broad range of grades varying in their viscosity, cure temperature, Shore hardness and mechanical properties.

Different types of silicone elastomers can be used for ring manufacture, although they are generally selected from medical or drug delivery grades conforming to USP Class VI / ISO 10993 specifications. Liquid silicone rubbers (LSRs) and room-temperature vulcanised (RTV) silicone rubbers that are capable of being injection molded are most common; the viscosities of the supplied components can vary substantially. High consistency silicone rubbers (HCRs) are also available, although their components parts have much higher viscosities compared to LSRs and RTVs. Of the marketed vaginal rings, only Estring® is made from a HCR (Silastic® Q7-4735, Table 1).

Silicone elastomers for use in ring manufacture can also vary in their cure chemistries. The most common are condensation-cure systems (Femring® and the cores of Annovera™) and addition-cure systems (Estring®, Progering®, Fertiring® and the body of Annovera™) (Table 1) [1]. Condensation-cure systems are cured at relatively low temperatures (<100 °C), making them particularly suitable for drugs that melt or degrade at higher temperatures. However, the tin catalyst used can be poisoned by certain chemical functional groups found in drug molecules. Addition-cure silicone elastomer systems are generally cured at higher temperatures (120–180 °C) and are compatible with a wider range of drug chemistries, although reaction and binding has been observed with drug molecules containing certain unsaturated moieties [64–66]. Other cure systems are also available from silicone suppliers, including those catalysed by peroxide species and UV light. However, these have not been used widely for drug delivery devices, due to the increased potential for drug degradation, processing/manufacturing constraints, or lack of appropriate material grades.

Once cured to form the final product, the different silicone elastomer grades and types used to manufacture vaginal rings are chemically very similar, since the primary chemical unit is polydimethylsiloxane (Figure 2) [1]. However, differences in composition of the supplied silicone elastomer formulation – including cure chemistry, cross-linking density, type and
molecular weight of the various polydimethylsiloxane components, the inclusion of fillers, etc. [1] – leads to different mechanical properties of the final ring product, which can potentially impact performance in clinical use, including retention and expulsion of the device.

Ethylene vinyl acetate copolymers

As with silicone elastomers, thermoplastic EVAs have a long history of use in sustained and controlled release drug delivery applications [49]. The NuvaRing® concept (and the similarly conceived subdermal contraceptive implants Implanon®/Nexplanon®) was largely fashioned after the success of early EVA sustained/controlled release drug delivery products developed by the Alza Corporation, most notably the ocular implant Ocusert® (1974) and the intrauterine device Progestasert® (1976) [67]. In fact, Alza Corporation applied for and owned several early patents around the application of EVA polymers to drug-releasing vaginal ring devices [62,68,69].

EvAs are hydrophobic, non-biodegradable, thermoplastic copolymers synthesized by high pressure free radical polymerisation of ethylene (ethene) and vinyl acetate and having a vinyl acetate content ranging from 1–40% (Figure 2). Their thermal, mechanical, drug permeability and other properties are primarily dependent on the ratio of ethylene to vinyl acetate residues in the polymer [49]. Since EVAs are generally stiffer than silicone elastomers, ring devices fabricated from EVAs tend to have thinner CSDs, typically 4–4.5 mm (Figure 1, Table 1).

NuvaRing®, the only vaginal ring product on the market constructed solely of EVA, is prepared by co-extrusion of two different EVA materials: a 3.98 mm CSD drug-loaded core prepared from 28% vinyl acetate EVA and drug-free sheath of thickness 110 μm prepared from 9% vinyl acetate EVA [70].

Thermoplastic polyurethanes

Polyurethanes (TPUs) are thermoplastic polymers suitable for injection molding, extrusion and 3D-printing of drug delivery devices [71]. They are beginning to emerge as useful materials for fabrication of vaginal rings, particularly given the broad range of properties available by manipulating their chemical composition (Figure 2) [50,52–54,72–76]. The drug-loaded core component of the combination contraceptive vaginal ring Ornibel® contains a TPU material (Table 1). Like EVAs, rings made from TPUs are generally thinner than those made from silicones due to their increased stiffness of the polymer.
2.4. Mechanical performance of rings

Although it has long been known that the dimensions of vaginal ring products and the nature of the polymeric materials used in their construction contribute to the final mechanical properties, only limited discussion and testing of these factors have been described in the literature [77]. Instead, most developers are content to ensure that their ring products have similar mechanical performance specifications to those of existing marketed ring products. There have been no reports of attempts to characterise and optimise mechanical performance with the aim of reducing expulsion rates or enhancing user acceptability.

The mechanical tests of most significance to drug-releasing vaginal rings include various compression, tensile and twist tests (Figure 3) [77], the results of which will primarily depend upon the ring dimensions, drug loading and type/grade of polymer/s used in their manufacture. In vitro mechanical tests and data should have clinical significance, and needs to demonstrate to regulatory bodies the mechanical integrity, safety and reliability of the final ring product [78].

2.5. Ring insertion and location of ring placement in the vagina

Although custom plastic applicators have previously been reported in the patent literature for ring insertion and/or removal [79,80] and are commonly used for vaginal application of gels, creams and some diaphragm products, their use has not been reported in any ring clinical study and they are not normally used or supplied with any marketed ring product. However, Merck do offer insertion applicators for use with Nuvaring upon request [81].

The vagina is an elastic muscular canal that connects the uterine cervix to the skin. The proximal end (entrance) of the vaginal canal is the vulva and the distal end of the canal (internally) is the vaginal fornix. The part of the uterus known as the uterine cervix protrudes into the vaginal canal. Since the vaginal canal is elastic, it can usually stretch to easily accommodate insertion of the ring device. The insertion guidelines for both marketed and investigational vaginal rings invariably require the women to squeeze the ring into a figure-of-eight shape using the thumb and index finger and to manually insert the ring as high as possible in the vaginal canal; the upper third portion is wider than the lower portions of the vaginal (Table 2, Figure 4). In this location, the ring should settle into place, feel comfortable during use, and expulsions are less likely [82,83]. There is no danger that a vaginal ring can
be pushed into the uterus since the cervical canal is much too narrow (< 8 mm) for ring passage in non-pregnant women [84]. The ring is generally retained in the upper segment of the vaginal canal around the cervix (the vaginal vault) where it can be easily retrieved by finger insertion (Figure 4).

Assessment of the placement of NuvaRing® in vivo using magnetic resonance imaging (MRI) has demonstrated that the ring eventually resides in a partially compressed oval shape (length minus width was ~5–7 mm) within the transverse plane of the vagina (in the X-Z plane, parallel to the ground) [85]. In most instances, the ring sits over the cervix. If the ring was positioned lower in the vagina, ambulation led to its repositioning at the cervix. These in vivo imaging data suggest that the ring must cause the vaginal width to distend beyond normal baseline vaginal dimensions (Section 2.1) [32]. Similar MRI studies have not been reported for silicone elastomer rings.

Even though the ring resides around the cervix, expulsion can occur during sexual arousal since the vaginal vault undergoes physical transformation known as tenting or ballooning [86,87]. Just prior to coitus there is increased muscular tension in the body that draws the uterus upwards resulting in more space in the vaginal vault. There are also increased secretions from the vaginal wall, the cervix, and from the two Bartholin glands located at the entrance to the vagina) that keep the vagina lubricated during arousal and reduce friction during penetration. Depending upon the extent of these physical changes, which vary widely between women, the ring may be expelled. After sex, the vaginal canal rapidly returns to its previous size. If the ring has been expelled, it can be reinserted in accordance with specific product instructions (Table 2).

2.6. Changes in vaginal laxity due to parity and age

Increased laxity and decreased elasticity of the vaginal walls are common in both parous and post-menopausal women. In parous women, the biomechanics of vaginal delivery result in significant stretching of the cervicovaginal musculature due to degradation of the collagen and elastin fibres in the tissue [88], while in post-menopausal women atrophy of the vaginal tissue is caused by declining levels of circulating estrogen [89]. The strength and elasticity of fibromuscular tissues in the vaginal wall is often measured using various ex vivo and in vivo methods which evaluate stretching of these tissues [90], with ex vivo, uniaxial tensile testing being most prevalent [91,92]. While tensile testing studies provide specific values for tissue
modulus and loading before failure, they are not representative of the true forces generated within the vaginal canal itself. The data from such analyses is useful in quantifying the effects of age, pregnancy, prolapse and menopause on the rigidity of vaginal tissue [93–96].

Parity refers to the number of previous pregnancies of >20 weeks duration and is generally classified into four groups: nulliparity (never having carried a pregnancy beyond 20 weeks), primiparity (one birth) multiparity (two or more births), and grand parity (five or more births) [97]. In the context of this review article, we are primarily interested in ‘vaginal parity’, referring to the number of vaginal births, since this may impact vaginal laxity and, in turn, the incidence of involuntary ring expulsions. That the odds of pelvic organ prolapse are significantly increased after a single vaginal birth compared to nulliparity is potential supporting evidence for this hypothesis [98]. Although vaginal delivery is known to impact the laxity of the vaginal introitus and the strength of the pelvic floor muscle [99–102], there are no reports in the literature of its effects on the musculature of the mid-vagina or close to the cervix, the most common and preferred location for ring placement [85]. Clinical studies testing vaginal rings are often conducted with women of different parity. Literature reports on the influence of parity on involuntary ring expulsions are not definitive. Some studies have reported increased ring expulsions with parity (with women of parity 2 or greater having discontinuation rates due to expulsions 2.4 times greater than those of lower parity) [103], while others have reported no correlation [104]. However, there were huge differences in the number of subjects involved in these trials (1005 vs 24 women, respectively). More recently, in a Phase 3 study of the Annovera™ ring (Table 1), no parity differences were noted among women who experienced complete expulsions, although partial expulsions were more likely among nulliparous and younger women (<20 years) [105].

2.7 Quantity of fluid in the vagina – endogenous / menstrual / ejaculate

The quantity of vaginal fluid – comprising contributions from vulvar secretions, transudate through the vaginal walls, exfoliated cells, cervical mucus, and endometrial and oviductal fluids [106,107] – may also play a role in involuntary ring expulsions, particularly with the increased production of vaginal fluid/secretions/exudate that occurs during sexual stimulation [108,109], during menstruation [110], and with vaginal infection [111]. However, there are no reports in the literature dealing with this issue in the context of ring expulsions. Typical daily production of vaginal fluid is ~6 g/day, with approximately 0.5– 0.75 g present in the vagina at any one time [107]. It is also plausible that deposition of ejaculate in the vagina
during intercourse could lead to increased rates of post-coital involuntary ring expulsion – particularly during subsequent toileting, straining or squatting – due to increased liquid volume and lubricity. Again, this issue has not been addressed in the scientific literature.

2.8. Concurrent use of vaginal drug products and personal lubricants

Vaginal application of semi-solid products – such as suppositories, gels and creams for either medication or lubrication – while using a vaginal ring could potentially impact rates of involuntary expulsion by reducing frictional forces at the ring/tissue interface. Rather surprisingly, there is no supporting literature on this topic, and only a small number of studies reporting concurrent use of a ring device and other vaginal drug or lubrication products [112,113]. Women are often permitted to make use of certain (mostly aqueous-based) vaginal medications and personal lubricants during concurrent ring use. However, there is a risk of increased release and/or systemic absorption of the drugs in the ring, particularly with oil or silicone-based vaginal products (which are usually contraindicated with ring use) [112,113].

2.9. User practices

User practices that involve physical straining or exertion while the ring is in place – such as defaecation, urination, squatting, strenuous activity, lifting heavy objects, intercourse, and practices around menstruation – can result in involuntary ring expulsions [114–119]. For example, in certain countries and cultures, a squatting posture is adopted either when resting/sedentary or when using a toilet or pit latrine [120]. Although squatting itself involves higher levels of low level muscle activity compared to sitting [121], it likely needs to be combined with straining of the muscles to produce sufficient force to expel a vaginal ring. Rings tend to rest horizontally on the pelvic floor muscles and most instances of ring expulsion are attributed to opening or avulsion of the levator ani muscle [11,122]. However, some studies have reported partial or full expulsion while sleeping [117], perhaps pointing to poor fit or placement rather than muscle exertion as the cause. Specific articles reporting the contribution of user practices to ring expulsions are highlighted in the subsequent literature reviews.

3. Review of literature on involuntary ring expulsions

In this section, we have collected and reviewed data around involuntary ring expulsions as reported in patient information leaflets for marketed rings and in published journal articles of
clinical studies dating back to the 1970s. Unfortunately, many early clinical studies on vaginal rings did not make any direct reference to involuntary ring expulsions, instead capturing and reporting these events under the general categories of ‘use-related problems’, ‘problems with ring use’, or similar [123,124]. Some early studies – particularly those testing larger/stiffer ring designs or performing evaluations in relatively small numbers of subjects – reported no involuntary expulsions [27,125,126]. The sections that follow focus on literature that makes specific reference to either partial or complete involuntary expulsions.

3.1. Patient advice in the event of involuntary ring expulsion

Both under clinical testing conditions and real-world use, ring users are invariably instructed to re-insert rings that are involuntarily expelled. That information, supplied in the accompanying patient information leaflets, is summarised in Table 2 for marketed vaginal rings. The consequences for not re-inserting a ring soon after an expulsion are clearly more significant for contraceptive ring users since efficacy is dependent upon maintaining systemic drug concentrations to successfully inhibit ovulation. The importance of quickly re-inserting a ring after expulsion will also be paramount for future users of antiretroviral-releasing rings for HIV prevention [114,127]. Data from acceptability studies with several different vaginal rings showed that women who felt the ring coming out were more likely to discontinue use [103,104,115,128,129].

3.2. Drug-free rings

Many ring development programs begin with clinical testing of a drug-free ring (also known as a ‘non-medicated’ ring, although commonly – and often erroneously – also referred to as a ‘placebo’ ring) for the purposes of evaluating initial user acceptability or preferred ring dimensions. For rings that required only relatively small quantities of drug to be incorporated in the final product (<5% w/w), the mechanical performance characteristics for drug-free rings are likely to be similar to drug-loaded rings. However, for higher drug loadings, this may not be the case, particularly when solid drug particles in the ring act similar to a mechanical filler [63,130].

Spencer et al. reported the results of a pilot study to assess acceptability of and tolerance to a placebo silicone elastomer vaginal ring (58 mm ED, 7.6 mm CSD) over 28-day use in 24 hysterectomised postmenopausal women aged 37–74 years (mean age 54) [104]. All the women were taking estrogen replacement therapy for at least two years prior to the study and...
were asymptomatic. Women were instructed that rings could be removed for defecation and intercourse, although rings were to be re-inserted afterwards as soon as possible. Five (21%) women withdrew from the study due to either repeated involuntary expulsion of the ring, mostly due to either micturition/defecation or significant discomfort during use. No correlation between expulsion rates and either parity or vaginal/pelvic pathology was noted, although the length and width of the vaginal vault were not measured. Some women removed the ring during the study for reasons including personal discomfort and partner discomfort during intercourse. For the eight women who completed the study and who also reported voluntary temporary removal of the ring for reasons other than personal discomfort, the reasons included: patients own wish (n=7 removals); micturition/defecation (n=130 removals); and prior to intercourse (n=24 removals). Involuntary partial or complete ring expulsions were experienced by twelve women and were mostly associated with micturition and defecation. Overall, just over half of women reported some discomfort with the placebo ring, with two-thirds rating the intravaginal ring acceptable. Unlike other clinical studies assessing estrogen-releasing rings, the women in this study were already receiving estrogen replacement therapy via other means, and therefore not seeking relief from symptoms of urogenital atrophy; this may skew their experiences with this ring device. It is interesting to note that some women in this study found the placebo ring difficult to reinsert after removal or expulsion due to it being too flexible. It is still not known to what extent ring dimensions and flexibility impact user acceptability and comfort, although it is generally considered that less flexibility and relatively larger ring diameters may be beneficial. Also, for post-menopausal women with vaginal atrophy, it is acknowledged that reduced vaginal dimensions and increased vaginal laxity associated with the condition may influence the incidence of involuntary ring expulsions.

As part of early development activities that ultimately led to the contraceptive NuvaRing®, Roumen et al. published two articles reporting the clinical acceptability of drug-free prototypes. In the first, three different 60 × 5 mm rings (Table 1) – differing only in their stiffness (stiffness ratio: 5.2 : 3.0 : 1.0; presumably achieved using different polymer grades having different Shore Hardness values) and consisting of two Silastic® silicone elastomer tubes connected via glass joints [131] – were tested in 6 nulliparous and 24 parous women [132]. Stiffness values were determined by measuring compressional force at a fixed velocity (the distance was not reported), in a similar fashion to the method described recently [77]. Although the article describes use of diary sheets to capture frequency of expulsion, no
involuntary expulsion data is explicitly presented beyond a passing reference to one woman who discontinued due to frequent expulsions. Instead, the authors concluded that there were no differences in acceptability (and presumably also in the expulsion rate) due to ring stiffness. The second article reported a study conducted among 20 healthy women testing non-medicated EVA rings having 54 mm ED and different CSDs (3.0, 3.5 and 4.0 mm) [48]. The grade of EVA used to fabricate the rings was not specified in the article. The two different grades of EVA used in the marketed NuvaRing® (9% and 28% vinyl acetate content) have markedly different mechanical characteristics such that using one or the other in this study would have been expected to impact ease of insertion, ease of removal, ring expulsion, and overall user acceptability. Nonetheless, results from the study demonstrated no significant differences between the three ring types except for an increased sensation of expulsion with the ring having the smallest CSD. However, there was a notable trend towards higher number of subjects removing the ring and increased number of total removals with the 4.0 mm ring. Expulsion was reported once during intercourse with the 3.5 mm ring. Insertion and removal of the rings were judged to be easy by the majority of women. As an interesting aside, the authors reveal in the article that this new EVA ring was developed as an alternative to a previously developed silicone elastomer ring device, prompted by the fact that the supplier of the silicone elastomer tubing and adhesive no longer supplied the material for human use.

3.3. Progesterone and progestogen-only rings

Megestrol acetate

One of the earliest continuous-use progestogen-only ring prototypes – a silicone elastomer tube filled with megestrol acetate and then joined to form a ring having dimensions 40 × 4 mm (Figure 1) – was developed in China [15,46,47]. To date, this represents the smallest ring external diameter to have been tested in humans, presumably reflecting the relatively small height/body size of Chinese women [133]. The small ring size may also explain the 26% of women in the study who experienced ring expulsions, which was the primary reason for study discontinuation in almost one quarter of cases [128].

Following the abandonment of medroxyprogesterone acetate, progesterone and norethisterone (also known as norethindrone) in early studies of progestogen-only rings due to excessive menstrual problems and relatively high pregnancy rates [43], the World Health Organization's (WHO) Special Programme of Research in Human Reproduction focused
instead on development of a ring device releasing the synthetic progestogen levonorgestrel (also known as D-norgestrel) at a constant low dose rate of 20 μg/day. In an early Phase III study involving 108 healthy parous women and designed to investigate contraceptive effectiveness, acceptability, and adverse effects over 1 year of use, 49 women (45%) experienced expulsions and five discontinued use of the ring because of repeated expulsions [134]. Fifty-nine of the 74 expulsion events (79.7%) occurred during either defecation or urination, and most occurred during the early stages of the trial. 

One of the most comprehensive journal articles describing involuntary ring expulsions was published in 1990 by Koetsawang et al. [103] as part of the WHO research program to develop a levonorgestrel-releasing vaginal for contraception [129,135–142]. The paper investigates the relationships between self-reported ring expulsions, voluntary ring removals and the demographic characteristics of 1005 women from 19 countries using a continuous-use core-type silicone elastomer vaginal ring releasing 20 μg/day levonorgestrel over four consecutive 90 day periods [103]. This levonorgestrel ring was relatively large (55.6 × 9.5 mm; weight 11 g), similar to the dimensions of the marketed products Estring® (55 × 9.0 mm) and Progering®/Fertiring® (58 × 8.4 mm) (Table 1). The Silastic 382 silicone elastomer material from which the ring was constructed has a reported Shore A hardness value of ~45 [143–145], entirely similar to values reported previously for Estring® and the Silastic Q7-4735 elastomer used in its manufacture [77,146]. Most of the 57 discontinuations due to involuntary ring expulsion (equivalent to a 7.1% one-year discontinuation rate) occurred within the first three months, with significant heterogeneity between women from different countries (1.7–22.9%; Europe < China < Latin America < Africa < Asia). Analysis suggested that parity – but not age, weight or ponderal index – was a contributing factor, leading to increased expulsion. The number of expulsions per woman ranged from 0–10; 771 women (76.7%) experienced no expulsions, 150 women (14.9%) one expulsion, and one woman reported 10 expulsions. Of the 417 ring expulsion events (83%) for which circumstances were noted, contributing associations were made with defecation (57%), urination (12%), menstruation (17%), strenuous activity (5%), intercourse (2%) and other (7%). Although menstrual disturbance was the principal reason for discontinuation (17.2%) in another WHO study [129], 57 women (5.6%) discontinued use of the ring due to involuntary expulsions. 26 women discontinued for repeated expulsions and 31 following a single expulsion, and most of these expulsions occurred before six months of use.
Clinical assessment of the same 20 μg/day levonorgestrel ring in a UK cohort of the multicentre multinational trial noted that 20 of the 150 subjects (13%) reported between one and seven involuntary ring expulsions during the study period [142]. 33% of expulsions were associated with defaecation and 15% with menstruation. Expulsion appeared to be more common in older and heavier women of high parity, although significant differences were not measured due to the small numbers of expulsion events within each sub-group.

_Progesterone / Progering®_

Progering® is a marketed matrix-type silicone elastomer vaginal ring (dimensions: 58 mm ED, 8.4 mm CSD, Figure 1) providing continuous release of progesterone over three months for contraception in lactating women (Table 1) [116,147–155]. The total number of involuntary ring expulsions was not routinely reported in clinical studies of early core-type prototypes of the silicone elastomer progesterone ring, which were relatively large (61 × 9 mm and 58 × 8.8 mm). Instead, it was simply noted that expulsion was never a reason given by women for discontinuation [156]. In a later study, comparing a smaller version of the progesterone-releasing ring (59 × 8.4 mm) and a copper intrauterine device, frequent involuntary ring expulsions occurred in 6% of women, and led to a termination rate of 8.1 per 100 after 12 months [154]. By comparison, complete or partial expulsion of the IUD occurred in 0.8 and 3.7% of users, respectively, giving a one-year termination rate of 5.6 per 100.

Reporting on clinical studies conducted in Chile, Massai et al., noted Progering® discontinuation rates of 11.5% and 17% due to expulsion/uncomfortable use and lack of compliance by users (e.g. having the ring out of place for more than 48 h, failure to replace the ring at the scheduled time, or losing the ring), respectively [153]. The investigators also reported a much lower 2% discontinuation rate with an alternative segesterone acetate (Nestorone®) ring having the same dimensions tested as part of a pilot study in 50 nursing women over one year. In an earlier qualitative acceptability study with 78 participants who used the PVR, most women described positive aspects of using the ring, e.g. comfort, ease of insertion and removal, user control, safety, no negative effect on sex life, and prolonged amenorrhoea. A few women reported negative experiences, including expulsions. One woman felt the PVR slipping out regularly, including while walking such that she had to “squeeze her legs together really hard to make it go back in” [157].


In a six month study (two 30-day cycles) assessing acceptability of Progering® among 174 women in Kenya, Nigeria and Senegal, 13% of women reported one or more expulsions [116]. Ring expulsions were four times higher among women who did not complete both cycles. At the 3-month follow-up, 51% reported that they felt the ring slipping; this declined to 39% at 6 months. Of the women who were unlikely to recommend the product, 38% cited expulsion as a reason for their reluctance. Eight women discontinued use of the ring due to expulsions. Reports of feeling the ring slipping declined as the length of PVR use increased, which suggested the importance of counselling women, especially at the outset, about correct placement of the ring high in the vagina to reduce/avoid feeling of slippage. It appears that women may become more adept at ring placement with time and experience.

Results from a more recent non-randomized open label postpartum contraceptive study conducted in India and testing the Progering® and an IUD revealed a 12-month discontinuation rate of 19.7 per 100 women versus 2.7 among IUD users (p<0.001) due to ring expulsions. Women who lost the ring in that study – mainly due to the use of Indian-style squatting toilets – did not receive a replacement and had to be discontinued [119].

**Progesterone / Fertiring®**

Fertiring® is similar in dimensions and design to Progering® except for a lower initial drug loading of 1000 mg (Table 1). However, there are no reported studies on expulsion rates with this ring device.

### 3.4. Estrogen-only rings

**Estradiol / Estring®**

Despite the considerable early focus on development of contraceptive rings, the first vaginal ring product to reach market in 1992 was the estradiol-releasing ring Estring® for treatment of local symptoms associated with urogenital atrophy [11,126,158–162]. In a 12-week clinical study testing two ring prototypes offering different daily doses, four of 24 post-menopausal women reported that the ring occasionally fell out during straining, although re-inserting was rated easy [158]. Also, Smith et al. [162] reported 18 occasions of Estring® falling out during use, most occurring during the first 24 weeks and attributed to toilet straining by patients with utero-vaginal prolapse or constipation. Women did not consider ring reinsertion difficult.
Estradiol-3-acetate rings / Femring®

As part of a multicentre study evaluating the efficacy, safety and acceptability of a vaginal ring releasing estradiol-3-acetate (which is rapidly hydrolysed to estradiol, the naturally circulating estrogen [163,164]), Al-Azzawi et al. reported four discontinuations due to an "inability to hold the vaginal ring in place" [165]. 159 women were enrolled in the study with 48 discontinuations in total.

3.5. Progestogen+estrogen rings

Prior to development of Annovera™ (segestosterone acetate + ethinyl estradiol contraceptive vaginal system; Table 1), the Population Council had focused its efforts on development of several prototype combination rings co-releasing levonorgestrel and estradiol [118,166–172]. As part of a clinical study among Indian women testing a relatively large 61 × 9.5 mm silicone elastomer shell-type ring releasing levonorgestrel + estradiol [172] (Table 1), Mehta et al. reported 16 incidences of involuntary ring expulsion [118]. Of the 17 women (54%) who did not complete the study, three discontinued due to frequent ring expulsion, and two of these women lost rings using the toilet. The authors suggested that squatting to use the toilet (as is common in Indian culture) and laxity of the vaginal musculature due to repeated childbearing were contributing factors.

Sivin et al. reported a large multinational clinical study assessing one-year use of various three-layered shell-design silicone elastomer contraceptive vaginal rings [169]. Rings were designed to release 250–290 μg/day levonorgestrel and 150–180 μg/day estradiol, and had EDs of 50 or 58 mm. 15% of women using the 58 mm ring and 21% using the 50 mm reported involuntary ring expulsion at some time during the course of use, although expulsion seldom led to termination. In a follow-on study, 10% of users reported involuntary ring expulsions, mostly during defecation but also after straining/exertion, while walking or sitting [168]. In a study involving 18 healthy Indian women aged 25–35 years and testing two types of shell-type silicone elastomer rings (50 × 9 and 60 × 9 mm) co-releasing levonorgestrel and estradiol over 35 days, a total of four involuntary ring expulsions were reported [170]. This relatively high rate of expulsions was attributed by the authors to high parity, inadequate puerperal rehabilitation, and squatting to use the toilet.

Norethindrone acetate + ethinyl estradiol
Almost 30% of 159 US and Australian women aged 18–37 reported involuntary ring expulsion as part of a 6-month clinical study evaluating a contraceptive vaginal ring releasing 20 μg estradiol and 1 mg of norethindrone acetate daily [173,174]. Two women experienced more than six expulsions, and three women discontinued on account of the issue. Most expulsions occurred during either defecation or tampon removal. Few women were concerned about expulsion, and no rings were lost because of unnoticed expulsion. In subsequent studies across three international clinical sites, problems with ring expulsion (four episodes in one woman) and slippage (five episodes in one woman) were reported by the authors as “surprisingly infrequent” (no breakdown data provided), although one woman did expel and lose a ring [175,176].

Etonogestrel + ethinyl estradiol ring / NuvaRing®

NuvaRing® – and its generic/bioequivalent competitor products Ornibel® / MyRing® / EluRyng® / SyreniRing® marketed across Europe – are unusual among marketed vaginal rings in that they are fabricated from thermoplastic polymers (EVA and TPU) rather than thermosetting silicone elastomers (Table 1, Figure 1, Figure 2). The difference in mechanical performance between these materials means that the thermoplastic rings have a CSD of just 4.0 mm compared with 7.6–9.0 mm for the various marketed silicone elastomer rings (Table 1). This reduced CSD is necessary to ensure that the device is sufficiently flexible/compressible for ease of insertion and user comfort. A ring device manufactured from the same (or similar) materials as NuvaRing® but having dimensions similar to those commonly used in silicone elastomer rings would be relatively inflexible and could possibly cause erosion and ulceration of the vaginal tissue, as reported for the earliest vaginal ring prototypes comprising a stiff metal spring over-molded with a silicone sheath [27].

As with other marketed vaginal rings, ring expulsions are widely reported for NuvaRing®, although these expulsions are often captured under the catch-all category of ‘device-related events’ [177–185]. In a small crossover study comparing NuvaRing® and oral contraceptive use, nulliparous women were not able to force expulsion of the ring (presumably by straining) [179]. Further, 16% (4/24) of the male partners in the study who reported ten or more coital events with the ring in place reported that the ring was sometimes expelled during coitus.
A study involving 1,130 Dutch women reported that 6% of women experienced involuntary ring expulsion [182]. Significantly higher expulsion rates (20.4%) were reported in a subsequent clinical study, which the authors attributed to potential differences in the populations studied or the definitions used (e.g. complete vs. partial expulsions) [178].

As part of two large trials conducted in North America and Europe to assess user acceptability of NuvaRing®, 821 women (35.4%) prematurely discontinued participation. Of those women who disliked the ring and discontinued, 21 women (6%) stated the reason for discontinuing as the tendency for the ring to fall out [184].

Following the expiration of the NuvaRing® patent in 2018, several generic or pharmaceutically bioequivalent products have since reached market. The Ornibel® vaginal ring releases the same two active agents – etonogestrel and ethinyl estradiol – at the same rates as NuvaRing® but differs in its use of a polyurethane drug-loaded core (rather than a 28% vinyl acetate EVA copolymer) and a 28% vinyl acetate EVA copolymer membrane (rather than a 9% vinyl acetate EVA copolymer membrane) (Table 1). As part of a crossover-design clinical study to compare the pharmacokinetics, safety and acceptability of Ornibel®, compared to NuvaRing®, only one of the 40 subjects reported involuntary ring expulsion during the two 28-day periods of ring use [177]. However, rings were inserted by the investigators in a clinical setting. The mechanical properties of Ornibel® may also be different from those of NuvaRing® given that both the core and membrane polymers are different (Table 1); however, experimental mechanical data have not been reported.

As part of a study assessing intermittent versus continuous use of NuvaRing® in Rwandan women, involuntary ring expulsions occurred in 14% of ring use periods, and most commonly occurred during or after sex, during urination, or during defecation [181]. At the ring removal visits scheduled at the end of each cycle, single ring expulsions were reported at 51 of the 416 visits, while 2–4 expulsions were reported at seven visits. Most women reinserted the ring at home after rinsing with water only (no women reported using soap), and usually within three hours of expulsion (although occasionally within 3–12 hr). Others had to attend the clinic to have the ring reinserted or replaced. Most subjects reported that they could feel the ring coming out and could act to avoid it becoming fully expelled.

Segesterone acetate + ethinyl estradiol rings / Annovera™
Annovera™ is a contraceptive vaginal system (CVS) releasing segesterone acetate (SA; Nestorone®) and ethinyl estradiol (EE). This silicone elastomer ring body of the CVS measures 56 × 8.4 mm and contains two channels into which silicone elastomer drug-loaded rod-shaped cores and then sealed [66]. One core contains SA only and the second core contains both SA and EE. The size and length of the cores including the silicone elastomers used are shown in Table 1. The system is effective for 13 consecutive cycles with women following a 21-day-in/7-day-out regimen [186] (Table 1).

During the two pivotal Phase 3 Annovera™ trials that included 2096 women with evaluable diary data that recorded expulsions events, 52.8% reported at least one complete (24.6%) or partial expulsion (44.0%) [105]. Although discontinuations due to expulsion were relatively low (1.4%), 25% of women experienced complete expulsions at some point during the trials with most reported in the first cycle of use. Further analysis of these data showed that in 21,842 treatment cycles eligible for expulsion analysis, complete expulsions occurred in 1509 (7.0%) of cycles and partial expulsion in 4259 (19.5%) cycles. There were no parity differences among women who experienced complete expulsions, although incomplete expulsions were more likely among nulliparous and younger women (<20 years).

Data from an acceptability study conducted with 905 women enrolled in one of the Annovera™ Phase 3 trials (an international study conducted in Latin America, the US, Europe and Australia) revealed that not feeling the CVR while wearing it and not experiencing expulsions were pivotal factors relating to overall satisfaction and method continuation [115].

3.6. Antiretroviral rings

Dapivirine

A placebo silicone elastomer ring having the same dimensions and properties as the dapivirine ring (Table 1) has been tested [127] as part of a series of studies investigating acceptability of vaginal rings among African women [127,187,188]. 6 of 154 (3.9%), 7 of 155 women (4.5%), and 3 of 149 women (2.0%) self-reported involuntary ring expulsions at the Week 4, 8 and 12 follow-up visits, respectively. The main contributing factors for rings being expelled included menses, defaecation, and urination. At Week 4 and final Week 12 of the study, 11.7 and 7.2% of the 157 participants, respectively, expressed concerns about the ring being involuntarily expelled, demonstrating that women became increasingly reassured
with continued ring use. Concerns over the possibility of expulsion were minimised by providing explanations using a pelvic model of how the ring is located within the vagina [187].

Tenofovir + Levonorgestrel

As part of an outpatient, randomized, partially blinded, placebo-controlled, parallel study testing three 90-day intravaginal ring devices – one delivering ~10 mg/day tenofovir, a second additionally delivering ~20 μg/day levonorgestrel, and a placebo ring – only one of the fifty healthy 18–45 year old women who completed the study self-reported a ring expulsion event, and that was due to bowel movement [189]. Each ring measured 55 mm in ED and comprised (i) a drug-free, hydrophilic, polyurethane tube (5.5 mm CSD, 0.7 mm wall thickness), (ii) a drug-free or drug-loaded semi-solid core for the placebo and tenofovir rings, respectively, and optionally (iii) a 2 cm core comprising levonorgestrel dissolved in a solid hydrophobic polyurethane. These tenofovir ± levonorgestrel rings have dimensions different from the two marketed thermoplastic vaginal rings (NuvaRing® and Ornibel®, both 54 × 4.0 mm) [177]. Also, although the authors claim that the test rings have similar flexibility to NuvaRing®, no supporting data or article citation is provided.

Vicriviroc (MK-4176) and MK-2048

Liu et al. have reported a Phase 1 28-day study testing two different antiretroviral-releasing EVA rings in 19 HIV-uninfected women – a low dose combination ring containing vicriviroc (VRC, MK-2048, 91 mg) and MK-2048 ring (10 mg) and a higher dose formulation (182 mg VCV + 30 mg MK-2048). Two participants reported ring expulsions, including one with recurrent expulsions thought to be related to anatomic issues (e.g. small vaginal surface area or suboptimal smooth muscle tone) [190].

In further testing of this VRV+MK-2048 prototype ring (a 48-subject Phase I trial to evaluate the safety, pharmacokinetics and pharmacodynamics of vaginal rings; dimensions 54 × 4 mm; similar to NuvaRing® and Ornibel®, Table 1), twelve women (25%) reported a single partial or complete involuntary expulsion of the ring, while two women (4.2%) reported two or more expulsions [191,192]. Expulsions generally occurred during menses, while urinating or during a bowel movement, and most participants were able to reinsert the ring immediately.
3.7. Other rings

As part of a Phase II clinical study testing a silicone elastomer oxybutynin-releasing vaginal ring for treatment of overactive bladder, involuntary ring expulsions (referred to as "accidental fallout" in the article) were self-reported by 28, 24 and 18% of women in the placebo, 4 mg daily, and 6 mg daily ring groups [193]. All rings had the same dimensions, presumably 58.3 mm ED and ~6 mm CSD, based on information gleaned from a supporting patent application [194].

4. Review of literature on voluntary ring removals

4.1. Advice regarding voluntary ring removals

In most clinical testing and real-world scenarios, users of vaginal ring products are permitted to remove them for relatively short periods of time [195–197]. Voluntary ring removal is generally permitted for: (i) sexual activity (particularly intercourse), (ii) cleaning of the ring, (iii) vaginal bleeding and menses. For contraceptive rings, temporary removal is typically permitted for up to two or three hours; of course, longer removal periods may compromise contraceptive efficacy [157,175,184,185,196]. Unsurprisingly, women have different views on the ability or need to remove rings. Some women greatly valued the degree of user autonomy and control afforded by the method, while others were concerned about making the ring ineffective or forgetting to replace it [157]. Other women believed that it was not hygienic to keep the ring inserted in the vagina for long periods without periodic cleaning [123].

4.2. Drug-free rings

In clinical tests of a non-medicated silicone elastomer vaginal ring, 8 of 30 women (27%) prematurely removed their ring for ring-related reasons and did not complete the 3-cycle study [132]. Four of these women (3 nulliparous and 1 parous) removed the ring on the first day of the study, citing pain, foreign body feeling or frequent expulsions. The number of removals and complaints diminished markedly during the study period, presumably due to women growing accustomed to use of the ring device.

4.3. Progestogen-only rings

*Levonorgestrel*
In a large multicentre clinical trial of a levonorgestrel-releasing ring conducted by the WHO, 121 women (12%) reported voluntary removal of the ring on 201 different occasions [103]. The reasons for ring removal included various method-related reasons (medical and non-medical) and those unrelated to the method. The most commonly reported reasons for ring removal were vaginal discharge/irritation, curiosity, to clean the ring, pain, and bleeding. Another article from this series of WHO studies noted that 57.0, 18.6, 12.9 and 11.3% of voluntary removals occurred within the first three months, during months 4–6, during months 7–9, and during months 10–12 of ring use, respectively, a clear trend suggesting that women grow accustomed to the ring with time [129].

52 of 150 women (35%) self-reported voluntary removal of a levonorgestrel-releasing ring during 12 months of use in a UK clinical study to assess efficacy and acceptability [142]. Most ring removals occurred during the first four weeks of the study, and the most common reason for removal was vaginal discharge and irritation. 32 women removed the ring only once, while the remaining 20 women removed the ring 3–6 times.

**Progesterone**

Sivin et al. reported that 9.4% of users removed a progesterone vaginal ring (PVR) – intended for continuous use except for removal up to two hours for intercourse and cleaning – for more than 24 hr [154]. The investigators deemed extended removal as having compromised efficacy and it was defined as a criterion for terminating study participation. In the study conducted in India that compared safety and efficacy of the PVR and IUD plus duration of lactation amenorrhea and infant growth, 18 of 459 postpartum women using the PVR terminated for self-removal of the ring for > 2 hr. The mean duration of ring removal was 46 hr. The reasons most often reported for these ring removals were menses, having sex, defecation and other reasons [119].

**4.4. Estrogen-only rings**

**Estradiol-3-acetate / Femring®**

In a US-based study involving healthy postmenopausal women treated for 13 weeks with either the 50 or 100 μg per day estradiol Femring® products (Table 1) or a placebo vaginal ring, less than 25% of women reported removing the vaginal ring during the treatment period (respectively, 81%, 92%, and 84% of women kept the rings in place); those who did generally found them easy to remove and reinsert [198].
4.5. Progestogen+estrogen rings

**Levonorgestrel + estradiol**

In a study to assess the acceptability of a levonorgestrel + estradiol contraceptive vaginal ring in Brazil and Dominican Republic, 33% of women removed the ring on non-scheduled occasions, beyond the instructions to only remove the ring once a month [123]. Moreover, 73% of users additionally used soap, detergent and/or a brush to wash the ring following removal, despite instructions to use water only. Thirteen percent and 10% of users removed the ring sometimes or always for intercourse, respectively, which the authors attributed to complaints from partners. The study results suggest that greater user acceptability of this ring – and presumably other rings more generally – might be achieved by permitting ring removal for intercourse and periodic washing with at least soap and water. In another study, 10% and 70% of women using a levonorgestrel+estradiol silicone elastomer contraceptive ring (shell design; 58 mm ED) reported always and never removing the ring for intercourse, respectively [199].

**Norethindrone + ethinyl estradiol**

Planned temporary removal of a contraceptive ring releasing norethindrone and ethinyl estradiol has been investigated as part of a study to evaluate the effect of different initial insertion regimens on side effects (primarily transient post-insertion nausea and vomiting related to the initial high burst of ethinyl estradiol from the ring) [173]. In Regimen 1, subjects inserted the ring between 5 and 7 pm on the first day, removed it at bedtime, and then reinserted it the next morning. In Regimen 2, the ring was inserted between 5 and 7 pm and then left in place. In Regimen 3, the ring was inserted at bedtime between 10 pm and midnight. Thereafter, for all regimens, women left the ring in place for three weeks, removed it for seven days, and reinserted it for a further three weeks according to the regimen to which they had been assigned. A new ring was used for each 2-month period. Differences in the incidence of side effects were not observed. Voluntary removals of the ring outside the initial insertion regimen were also reported, although this was mostly due to the different instructions given at the two centres regarding removal of the ring for intercourse [174].

**Etonogestrel + ethinyl estradiol / NuvaRing®**

As part of a questionnaire-based acceptability study for the combined contraceptive vaginal ring NuvaRing®, Novak et al. captured self-reported information on the reasons why users
removed rings during the study period [184]. Less than 40% women reported removing the ring during the ring cycles, despite being permitted to do so for up to 3 hr. Of those women who completed the study, 1046 (69.7%) reported that they never temporarily removed the ring compared with 334 (51.8%) of those who prematurely discontinued. For women who completed and had temporarily removed the ring, 212 (14.1%) did so because of interference with intercourse and 64 (4.1%) because the ring fell out. The main reasons for temporarily removing the ring for discontinuers were interference with intercourse [91 women; 14.1%], the ring fell out [37 women; 5.7%] and discomfort [32 women; 5.0%]. In a smaller study involving 16 healthy Dutch women with the aim of assessing the effects of an extended 35-day NuvaRing® use regimen on ovarian function, temporary ring removal by some women reduced self-reported cumulative ring exposure from the maximum 6,720 hr (8 users per group × 35 days × 24 hr) to 6,704 (Group 1) and 6,715 hr, respectively [200]. Bjarnadóttir et al. also reported that ~90% of women did not temporarily remove NuvaRing® during six cycles of ring use [185]; of the 10% who did remove the ring, cumulative removal time was 2–4 hr per 3-week cycle.

In a 1-year multicentre Phase III clinical study of the combined contraceptive NuvaRing®, the incidence of cycles in which women extended the ring-free period beyond one week was 4.8% (which can increase the risk of pregnancy), while shortened ring-free periods occurred in 4.9% of cycles [196]. Slightly more temporary ring removals occurred with North American women compared to European women.

As part of an observational study involving 1,130 women recruited by 257 general practitioners in The Netherlands, Roumen et al. reported that 14% of users removed NuvaRing® at least once for intercourse during the first three months of use, with 4% regularly or always removing the ring. Women voluntarily removed the ring for reasons other than intercourse; hygiene (4%), inconvenience (4%), and curiosity/uncertainty (4%) were the reasons most frequently reported [182].

**Segesterone acetate + ethinyl estradiol rings / Annovera™**

Data from the Phase 3 Annovera™ acceptability study revealed that 120 of the 905 participants (13%) reported removals >2 hr [201]. Women cited several reasons for these removals including washing the ring, sexual intercourse, and finding CVR insertion difficult. Women residing in Europe or Australia were less likely to remove the ring for >2 hr compared with
women in the US. There was a greater overall likelihood of ring removal > 2 hr among women with lower educational attainment. Women who reported removals >2 hr were more likely to discontinue using Annovera™, report dissatisfaction and become pregnant during the study.

4.6. Antiretroviral rings

Dapivirine

In a 2012 study to assess safety and acceptability of a placebo version of the dapivirine ring intended to be worn for 12 weeks of continuous use, 120 women (82%) self-reported never having removed the ring voluntarily [127]. When the ring was removed, it was for defecation, urination, during menses, or during sex (sometimes at the partner’s request).

As part of the MTN-020/ASPIRE study, Duby et al. reported that 60% of women who were assessed qualitatively for acceptability of the dapivirine-releasing ring did not mind wearing the ring and 91% did not remove the ring during menstruation, despite strong sociocultural practices within Sub-Saharan Africa around maintaining vaginal hygiene during menses [202]. Women were instructed to leave the ring inserted “all day, every day”, and were told that “the ring should be kept inserted at all times including during menses, bathing, and sex”. At the 3-month visit, 93% of women (191/205) reported use of the ring in the past three months. Of those, 26% removed the ring at least once, although removal rates varied significantly between different countries. Nine women (5%) disclosed they removed the ring because they “had or were expecting menses”. Overall, only 4% expressed worry about wearing the ring during menses. At the product discontinuation visit, 92% (178/193) of women reported using the ring in the past 3 months. The proportion reporting any removal decreased to 14%. Overall, 91% indicated that they wore the ring during menses. Only 2 women (1%) reported that the ring ever came out on its own, during either menses or urination.

It is widely appreciated – and a lesson hard learned within the HIV microbicide field – that relying primarily on user self-report often leads to over-reporting [203–205]. Subsequent results published in 2016 from the two Phase III clinical studies of the 25 mg dapivirine ring – in which adherence (and in turn efficacy) in some groups of women was much lower than anticipated – clearly illustrate the dangers in relying too heavily on self-reporting of ring removals [206,207]. More quantitative and objective methods for measuring user adherence to rings have been considered [155,208–212].
Tenofovir disoproxil fumarate

As with contraceptive rings, rings for HIV prevention need to be worn continuously – including during menses – to ensure antiretroviral levels are maintained at sufficiently high levels for efficacy. As part of a randomized placebo-controlled trial, Watnick et al. assessed user acceptability of a polyurethane reservoir-type ring (55 × 5.5 mm; Figure 1) releasing tenofovir disoproxil fumarate in which the ring was initially correctly fitted and then removed after a 14-day continuous use period by a clinician [213]. Counter to the rationale for a long-acting microbicide ring product intended to enhance user adherence and efficacy, most women expressed a preference to remove the ring during periods of perceived low risk, such as during abstinence or menstruation.

4.7. Other rings

Oxybutynin

The concept of a vaginal ring releasing oxybutynin for treatment of urinary incontinence was first reported in 2003 [214]. More recently, as part of a Phase II clinical study of a silicone elastomer oxybutynin-releasing ring for treatment of overactive bladder, the majority of women self-reported wearing the VR during sexual intercourse [195].

5. Expert opinion

Drug-releasing vaginal rings are gaining acceptance as safe, practical and effective devices for the treatment and prevention of disease. Since the concept of a vaginal ring was first described more than 50 years ago, seven ring products have reached market (all offering sustained or controlled release of steroid molecules) and new products are being developed and considered for an increasing range of clinical indications aimed at improving women’s sexual and reproductive health.

Involuntary ring expulsions

Involuntary expulsions are commonly reported in clinical studies testing drug-releasing vaginal rings, irrespective of ring design, ring dimensions, material of construction, or stage of development, with some studies reporting ~50% of women experiencing at least one ring expulsion. Most involuntary expulsions occur with physical straining/exertion, such as associated with defaecation, urination, squatting, strenuous activity, intercourse, or practices
around menstruation. Since women who experience expulsions (partial or complete) are more likely to discontinue use (with potentially serious implications for contraceptive ring users in particular) or report poor acceptability, and in light of the limited data currently available, further research is needed to better understand the anatomical, physiological, device and human factors that likely contribute to expulsions and to develop and test new ring designs that seek to reduce the incidence of expulsions. For example, it would be helpful to gain further insight into the influence of ring dimensions, polymer type, and grade (flexibility) of polymer on ring expulsions. The limited data to date has been acquired across a myriad of different ring designs and polymers such that it is difficult to arrive at any firm conclusions without careful control of the other variables. In particular, further research is needed in countries and regions where squatting (either as a sedentary practice or when using the toilet) is common.

A wide range of external diameters and cross-sectional diameters have previously been manufactured and tested for drug-releasing vaginal rings (Figure 1). Currently, every marketed vaginal ring product is supplied in a single size format, with the implicit assumption that this one size will fit most women. From the perspective of a drug product developer, this approach is entirely practical and pragmatic, since it would be difficult and costly for a company to offer women a ring product with a choice of different dimensions and yet providing the same drug release characteristics, since ring dimensions (e.g. surface area, ring circumference, sheath thickness, core length, etc.) are critical parameters critically influencing the drug release characteristics [28]. Invariably, thermoplastic rings have a thinner profile than silicone elastomer rings, reflecting the fact these polymer materials generally less flexible/elastomeric. Furthermore, it is still not known to what extent ring dimensions and flexibility impact user acceptability, comfort and adherence. Clinical studies are needed to better understand these relationships and to help inform the design of future ring products so as to minimise the incidence of involuntary expulsion and to maximise acceptability, comfort and adherence.

Expulsions seem to occur most commonly during the early days of ring use for new users, which could reflect inadequate counselling or women’s initial inexperience with handling the ring. As such, it is important that healthcare professionals discuss this issue with prospective and ongoing users, explaining how to minimize the frequency of expulsions and how to quickly wash and reinsert the ring. There are also differences in vaginal and pelvic anatomy
that may lead to increased incidence of expulsion in some women. While several studies have assessed *in vivo* placement of thermoplastic rings (there is no such data for silicone elastomer rings), additional studies that describe ring placement in women who have pelvic variations or abnormalities are needed. The highly variable anatomy, and most notably in the measurement of vaginal width, support further clinical research to assess the impact of ring size on involuntary expulsion rates, comfort and acceptability. Although current evidence suggests no correlation between size and expulsion rate (Figure 1), the data is rather limited and there has been only one previous attempt to test rings fabricated from the same grade of polymer material across different dimensions.

**Voluntary ring removals**

The most commonly cited reasons for voluntary ring removals include for menstruation, the desire to periodically clean the ring, and for sexual intercourse. Data from at least one study suggest that women with lower educational attainment may be less likely to follow use instructions correctly and may remove the ring more frequently than advised. These data highlight the importance of tailoring counselling around correct use and addressing the specific needs of women who are considering vaginal ring use. Also, discussions about the safety of using vaginal rings over extended periods of time are important to reassure women that there is no need to remove the ring frequently for washing [115,215].

**Additional comments**

Despite the continued absence of international standards for mechanical properties of drug-releasing vaginal ring products, regulatory agencies do expect submission of supporting data to demonstrate that the mechanical characteristics of ring products are fit for purpose [71]. Standardised *in vitro* test methods are needed to assess mechanical integrity under conditions similar to those encountered in clinical use.

Women are generally permitted to use certain (mostly aqueous-based) vaginal medications and personal lubricants concurrent with ring use. However, there is limited literature on this topic, despite the potential for increased rates of involuntary expulsion. Further research is needed.

Greater user acceptability of rings might be achieved by permitting ring removal for intercourse and periodic washing with soap and water. Of course, timely reinsertions to
maintain efficacy would be essential. There also appear to be differences in adherence to ring use instructions depending on nationality of the users. For example, temporary ring removals are more often reported with North American women compared to European women.

While drug-releasing vaginal rings generally perform well in clinical use and have seen increased use and acceptance over recent years, further research efforts are needed to assess, understand and ultimately address the issues around involuntary ring expulsions and voluntary ring removals, with the goal of improving acceptability, comfort, adherence – and ultimately health outcomes – for users.

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Author Contributions
All authors contributed equally to drafting and reviewing of the manuscript.

Declaration of Interest
The authors declare no competing financial or personal interest. The drafting of the manuscript was not supported by any external funding sources.

Acknowledgements
BV and RM thank George W. Creasy M.D. (Population Council) for valuable clinical insights and information relating to the Annovera™ ring.


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Figure 1. (A) Dimensions (overall diameter vs. cross-sectional diameter) of vaginal rings, both marketed products (coloured symbols) and those previously tested in the clinic and reported in the scientific and patent literature (black symbols). Rings are further sub-classified according to polymer type – silicone elastomer (circles) and thermoplastic (squares). (B and C) Percentage of women in clinical studies reporting one or more ring expulsions as a function of overall ring diameter and ring cross-sectional diameter, respectively. Each plot symbol represents a single clinical study. The plots do not take into consideration the mechanical properties of the rings (for most, no data is available), which will likely vary considerably depending upon the grade of polymers used. Nonetheless, the plots demonstrate a general lack of correlation between ring dimensions and expulsions.
Figure 2. Chemical structures of polymeric materials used in the fabrication of drug-releasing vaginal rings. The silicone elastomer represents an addition-cure system; condensation cure systems are also known and used. The percentage of ethylene and vinyl acetate residues in the ethylene vinyl acetate copolymer can be varied to both modulate drug release rates and mechanical properties. Polyurethanes offer a broad spectrum of properties depending on the nature of the R substituents and the length of the different segments.
Figure 3. The most common mechanical tests used to characterise the mechanical properties of drug-releasing vaginal rings. The elongation test (also known as the tensile test) is used to measure two parameters – tensile extension at maximum load (mm) and maximum load at maximum tensile extension (N) – from which % elongation at break can be calculated. The static compression test involves compressing the ring to 25% of its original diameter for extended period of time (e.g. 28 days). The cyclical compression test involves compression to 25% of the original diameter and release 1000 times with recovery acceptance criteria set as at least 90% recovery of the original diaphragm diameter. The twist in compression test measures angular deformation during compression. These tests are described in detail in McCoy et al. 2019.
Figure 4. (A) General anatomical features of the human pelvic region, including the cervix and vagina, and the preferred location for ring placement adjacent to the cervix – image is free of copyright restriction [216]; (B) ‘squeeze-ring’ method for ring insertion; (C) suggested placement of Estring® in upper third of vagina (figure shows lower placement than the preferred location). Images 4B and 4C are reproduced from the patient information leaflet for Estring®.
Figure 5. X-ray images showing *in vivo* placement of (A) a vaginal ring pessary for treatment of uterine prolapse (image used under a Creative Commons License, https://radiopaedia.org, [217]), (B) Femring® (author image; image has been recoloured), and (C) NuvaRing® (image used with permission [85]).
### Table 1. Descriptions of marketed vaginal rings.

<table>
<thead>
<tr>
<th>Vaginal ring</th>
<th>Developer (De); Owner (O); Distributor (Di); Manufacturer (M); Marketing authorization holder (MA); Licensee (L)</th>
<th>Device type / duration of release</th>
<th>Active agent(s) (loading / release rate)</th>
<th>Polymer(s)</th>
<th>Indication</th>
<th>Ring dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estring®</td>
<td>Pharmacia &amp; Upjohn Co (De); Pfizer (O)</td>
<td>reservoir 3 months</td>
<td>17β-estradiol (2 mg / 7.5 μg/day)</td>
<td>silicone elastomer core and sheath (both Q7-4735, Dow)</td>
<td>ERT</td>
<td>Ring OD: 55 mm  &lt;br&gt; Ring CSD: 9.0 mm  &lt;br&gt; Core CSD: 2.0 mm  &lt;br&gt; Core length: 145 mm</td>
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<tr>
<td>NuvaRing®</td>
<td>Organon (De); Merck &amp; Co (O);</td>
<td>reservoir 21 days</td>
<td>etonogestrel (11.7 mg / 120 μg/day)  &lt;br&gt; ethinyl estradiol (2.7 mg / 15 μg/day)</td>
<td>28% EVA copolymer core and 9% EVA sheath</td>
<td>contraception</td>
<td>Ring OD: 54 mm  &lt;br&gt; Ring CSD: 4.0 mm  &lt;br&gt; Membrane thickness: 110 μm</td>
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<tr>
<td>Fenring®</td>
<td>Galen/Warner Chilcott (De); Millicent Pharma (O,M)</td>
<td>reservoir 3 months</td>
<td>17β-estradiol-3-acetate (12.4, 24.8 mg / 50, 100 μg/day)</td>
<td>silicone elastomer core and sheath (both MED8-6382, NuSil)</td>
<td>ERT</td>
<td></td>
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<tr>
<td>Progering®</td>
<td>Population Council (De); Silesia SA (De); Grupo Grünenthal Chile (M)</td>
<td>matrix 3 months</td>
<td>progesterone (2074 mg / ~10 mg/day)</td>
<td>silicone elastomer (MED-4211, NuSil)</td>
<td>post-partum contraception in breastfeeding women</td>
<td>Ring OD: 56 mm  &lt;br&gt; Ring CSD: 8.4 mm</td>
</tr>
<tr>
<td>Fertiring®</td>
<td>Population Council (De); Silesia SA (De); Grupo Grünenthal Chile (M)</td>
<td>matrix 3 months</td>
<td>Progesterone (1000 mg / ~10 mg/day)</td>
<td>silicone elastomer (MED-4211, NuSil)</td>
<td>IVF / hormone supplementation</td>
<td>Ring OD: 56 mm  &lt;br&gt; Ring CSD: 8.4 mm</td>
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<tr>
<td>Ornibel®, MyRing™, SyreniRing®, EluRyng™, Perlinring</td>
<td>Exelis Healthcare (D); INSUD PHARMA (O); Laboratorios León Farma, S.A. &amp; Mithra Pharmaceuticals (M); Crescent Pharma Limited &amp;Mithra (MA)</td>
<td>reservoir 21 days</td>
<td>etonogestrel (11.0 mg / 120 μg/day)  &lt;br&gt; ethinyl estradiol (3.47 mg / 15 μg/day)</td>
<td>polyurethane sheath and 28% EVA copolymer core</td>
<td>contraception</td>
<td>Ring OD: 54 mm  &lt;br&gt; Ring CSD: 4.0 mm  &lt;br&gt; Membrane thickness: 150 μm</td>
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<tr>
<td>Annovera™</td>
<td>Population Council (O,De); TherapeuticsMD (L,M)</td>
<td>reservoir 1 year</td>
<td>segesterone acetate (103 mg / 150 μg/day)  &lt;br&gt; ethinyl estradiol (17.4 mg / 13 μg/day)</td>
<td>silicone elastomer cores (x2, MED-6603 &amp; MED-6385, NuSil) and sheath (MED-4224, NuSil)</td>
<td>contraception</td>
<td>Ring OD: 56 mm  &lt;br&gt; Ring CSD: 8.4 mm  &lt;br&gt; Core CSD: 3.0 mm  &lt;br&gt; Core lengths: 11 and 18 mm</td>
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<tr>
<td>Vaginal ring</td>
<td>Advice in the event of involuntary ring expulsions</td>
<td>Advice concerning voluntary ring removals</td>
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<tr>
<td>Estring®</td>
<td>“If the ring falls out, it should be rinsed in lukewarm (not hot) water and then reinserted.”</td>
<td>• Ring should be removed if certain health conditions worsen.</td>
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<td>• It is recommended that the ring is removed when constipated or using vaginal preparations.</td>
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<td></td>
<td></td>
<td>• Ring may be removed if user or partner finds the ring uncomfortable or unacceptable during intercourse.</td>
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<td>NuvaRing®</td>
<td>“NuvaRing may accidentally be expelled from the vagina – for example, if it has not been inserted properly, while removing a tampon, during intercourse, during constipation, or if you have a prolapse of the womb. Therefore, you should regularly check whether the ring is still in your vagina (for example, before and after intercourse).” Advice is then provided to cover different periods of removal.</td>
<td>• Ring should be removed if certain health conditions appear while using NuvaRing®.</td>
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<td>• Ring should be removed if women think they are pregnant.</td>
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<td>• When a ring is used to delay the menstrual period by inserting a new ring immediately after removing the current ring, with no ring-free interval between rings [this is not the recommended regimen], the ring can be removed to start the period.</td>
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<td>Femring®</td>
<td>“If your Femring comes out of your vagina before 3 months, clean it with warm water and put it back in your vagina. Femring can come out if it is not put in far enough. Femring can come out when you are pushing hard during a bowel movement. Femring can come out if your vaginal muscles are weak. If Femring comes out often, tell your healthcare provider. Femring may not be right for you.”</td>
<td>• Femring can be left in place during intercourse. If you take Femring out during intercourse or it comes out, clean it with warm water and put it back in your vagina.</td>
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<td>Progering®</td>
<td>“The Progering® ring may occasionally fall out of the vagina. If it falls, wash with warm water and put it back before 2 hours. If it leans out, push it gently to the bottom of the vagina.”</td>
<td>“If you wish, you can remove it to wash, to have sex or to use the bathroom (in case of constipation). This withdrawal should not exceed two hours per day.”</td>
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<tr>
<td>Fertiring®</td>
<td>[Translated from Spanish] “The ring may occasionally peek out of the vagina. In these cases, gently push it all the way to the bottom of the vagina; the ring will easily accommodate. At other times, the ring may be expelled from the vagina (by defecating, mainly in cases of constipation), or the patient prefers to remove it for short periods of time (during intercourse). In these cases, the ring product may be re-introduced to the vagina after first washing it with neutral soap and water, and ensuring it does not stay out of the vagina for a period longer than two hours.”</td>
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<tr>
<td>Omibel®, MyRing™, SyreniRing</td>
<td>“[Ring] may accidentally be expelled from the vagina – for example, if it has not been inserted properly, while removing a tampon, during sexual intercourse, during constipation, or if you have a prolapse of the womb. Therefore, you should regularly check whether the ring is still in your vagina (for example, before and after intercourse). If the ring is out for less than 3 hours, it will still protect you from pregnancy. You can rinse the ring”</td>
<td>• Ring should be removed if certain health conditions appear while using [ring].</td>
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<td>• Ring should be removed if women think they are pregnant.</td>
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<td>• When a ring is used to delay the menstrual period by inserting a new ring immediately after removing the current ring, with no ring-free interval between rings [this is not the recommended regimen], the ring can be removed to start the period.</td>
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with cold to lukewarm water (do not use hot water) and put it back in.”
Advice is then provided to cover longer periods of involuntary removal.

Annovera™

“Accidental expulsion may occur while removing a tampon, during coitus, or with straining during a bowel movement. If expelled and replaced within 2 hours, contraceptive efficacy should be maintained. If expelled and not replaced within 2 hours or if more than 2 cumulative hours in 21-days of continuous use (multiple inadvertent removals or expulsions adding up to 2 hours). Back-up contraception should be used until the vaginal system has been in the vagina for 7 consecutive days.”

“You do not have to take the vaginal system out when you have sex. If you decide to remove it, remember to reinsert it within 2 hours after removing it or you may not be protected from pregnancy. However, if ANNOVERA is out of your vagina for more than 2 hours at one time or if ANNOVERA is out of your vagina at different times that add up to more than a total of 2 hours over the first 21 days of your cycle, you will need to use another method of birth control (such as male condoms or spermicide) until ANNOVERA has been in your vagina for 7 days in a row.”

ANNOVERA should be washed with mild soap and water and rinsed and patted dry with a clean cloth towel or paper towel prior to each insertion and at each removal.