Published in final edited form as:

Contraception. 2018 May ; 97(5): 415–421. doi:10.1016/j.contraception.2017.12.011.

Factors associated with non-adherence to instructions for using the Nestorone®/ethinyl estradiol contraceptive vaginal ring

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Abstract

Objectives—We sought to identify factors associated with non-adherence to instructions for using a novel contraceptive providing 1-year of protection.

Study design—Data from a multi-country Phase 3 trial of the Nestorone® (segesterone acetate)/ethinyl estradiol (NES/EE) CVR were analyzed. Participants were instructed to use the CVR over 13 cycles and follow a 21/7 regimen. Their reports of CVR removals >2 hours outside scheduled removal periods served as a proxy for non-adherence. We used multivariate logistic regression to determine factors associated with such use.

Results—Of 905 participants, 120 (13%) reported CVR removals >2 hours. Removals for washing (OR 3.96, 95% CI 2.50–6.27) or sexual intercourse (OR 3.19, 95% CI 2.03–4.99), and finding CVR insertion difficult (OR 2.80, 95% CI 1.36–5.80) were factors associated with removals >2 hours. Lower educational attainment also predicted ring removal >2 hours (OR 3.23, 95% CI 1.55–6.75). Women residing in Europe or Australia were less likely to remove the ring for >2 hours compared with women in the US (OR 0.44, 95% CI 0.24–0.83 and OR 0.13, 95% CI 0.02–0.98, respectively). Participants who reported removals >2 hours were more likely to discontinue CVR use (OR 1.93, 95% CI 1.24–2.95), report dissatisfaction (OR 2.20, 95% CI 1.32–3.69), and become pregnant during the study (OR 4.07, 95% CI 1.58–10.50).

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Clinical Trial Registration Number: NCT00263341.

Disclosures

CSV has served on the Medical Advisory Boards for Merck and Bayer, and has given ad hoc invited lectures for Merck and Bayer. The other authors have no conflicts of interest to disclose.

Conclusions—Removing the CVR for washing and before intercourse are factors associated with non-adherence to ring use. These are important topics for counseling women who are considering or using vaginal rings, including the NES/EE CVR.

Keywords

Contraception; vaginal ring; adherence; acceptability

1. Introduction

Efforts to increase global access to contraception have led to overall decreases in unintended pregnancy rates, yet 40% of pregnancies worldwide continue to be unintended [1]. In the United States contraceptive failures account for 41% of unintended pregnancies [2], and occur mainly with user-dependent methods [3,4]. Long-acting reversible contraceptives (LARCs) eliminate the user dependence variable and can greatly reduce unintended pregnancy rates [4]. When cost, access and knowledge barriers are removed, a majority of women who have chosen LARCs report high satisfaction and continuation rates [5].

Access to LARCs, however, requires the availability of skilled providers for insertions and removals and entails high up-front costs. These barriers contribute to underutilization of LARCs, especially in low resource settings [6,7]. Targeted investments and initiatives to increase LARC uptake in low-income countries have generally shown high user satisfaction and continuation rates [8,9], but such measures have not yet yielded significant increases in LARC use or to changes in the contraceptive method mix [6].

Recently, vaginal rings have gained increasing attention as a promising technology to diversify and add to the method mix for both contraceptive use and prevention of sexually transmitted infections (STIs) [10]. Contraceptive, microbicide, and multipurpose vaginal rings are new developments that may allow women to have control over pregnancy timing and prevention of STI transmission. These products may even be useful for women in settings where they have limited power to negotiate the terms of sexual relationships [11].

In this context, the Population Council developed a contraceptive vaginal ring (CVR) containing Nestorone® (segestosterone acetate) and ethinyl estradiol (NES/EE) and is reusable for 1-year. The ring releases 150 mcg of NES and 15 mcg of EE daily and is designed for use on a 21/7 day regimen for 13 cycles. It does not require skilled providers for insertion or removal, does not require refrigeration, and may have global appeal for women who value using one device for a longer period of time while remaining in control of their contraception. Results of an acceptability study of the NES/EE CVR indicated that women were highly satisfied with this contraceptive method and found it easy to use [12].

As a user-dependent method, however, the NES/EE CVR requires adherence to instructions for use to maintain contraceptive effectiveness. Accordingly, we sought to evaluate factors associated with non-adherence. We also explored the extent to which non-adherence predicts method dissatisfaction, early discontinuation, and pregnancy.

2. Methods

2.1 Study design and population

This study draws on data collected during a Phase 3 clinical trial of the NES/EE CVR and from a previously published acceptability study conducted within that trial [12]. The trial was conducted at 12 sites in the US, Latin America, Europe and Australia from 2006 to 2009. Participants were healthy, sexually active women 18–40 years old. Exclusion criteria included medical contraindications to combined hormonal contraceptive use; body mass index $>29 \text{ Kg/m}^2$; cystocele, rectocele or any uterine anatomical abnormality; use of monthly injectable contraceptives within 2 months of study initiation or DMPA use within 6 months; and history of sterilization. The study protocol was approved by the Population Council's Institutional Review Board and each site's Ethical Committee.

Participants provided informed consent and were taught how to use the CVR. For each of 13 cycles during which they were enrolled in the study, they were instructed to keep the ring in place during 21 full days, and to remove it for a 7-day interval. During this interval they were told to wash the ring with warm water and mild soap and store it in a provided case. They were advised not to remove the ring during the 21 days of use, but if they did remove it they were instructed to reinsert it within 2 hours.

An acceptability questionnaire was administered to trial participants at the beginning of the third study cycle (time 1) and again after 13 cycles or at study discontinuation (time 2). The questionnaire was developed based on a theoretical model of NES/EE CVR acceptability encompassing four domains (ease of use, side effects, expulsions or feeling the ring, and sexual activity) that could affect overall satisfaction, adherence to instructions, and method continuation [12].

2.2 Outcomes

The primary outcome was ring removal >2 hours during the 21 days when the CVR was to be in place, a surrogate marker for non-adherence to CVR use. Acceptability questionnaire respondents were asked: "in the first 3 weeks of your last cycle, how many times did you take the ring out and leave it out for more than 2 hours?" We considered women to be "ring removers" if their response to this question was anything other than 0, either at time 1 or at time 2 or both. To evaluate potential factors associated with ring removal >2 hours, responses to the acceptability questionnaire within the domains of ease of use, expulsions, sexual activity, and side effects served as covariates. We drew additional covariates from the clinical trial database, including demographic variables and the desire for pregnancies following study completion.

Associations among ring removals >2 hours and dissatisfaction with the CVR, early discontinuation and unplanned pregnancy were secondary outcomes. Data for participants' level of satisfaction were obtained from the acceptability questionnaire, while method continuation and pregnancy data (as measured by pregnancies occurring during or within 7 days of last ring use) were obtained from the clinical trial database.

2.3 Statistical analysis

Responses at time 2 were used in the analysis unless the participant only completed the questionnaire at time 1, in which case time 1 responses were used. We used Pearson's Chi-square and t-tests for categorical and continuous variables respectively to compare demographic characteristics as well as acceptability questionnaire responses of ring removers and non-removers. To assess factors associated with ring removal >2 hours, we used a stepwise logistic regression model with backward selection. All variables with $p < 0.25$ in the Chi-square analyses were initially included in the model. Variables with the highest p value were sequentially removed from the model, which was repeated until all variables were significant with $p < 0.05$.

To test whether ring removal >2 hours is associated with dissatisfaction, early discontinuation, and pregnancy, we constructed three additional multivariate logistic regression models using dissatisfaction, early discontinuation and pregnancy as outcomes, and ring removal >2 hours as a covariate. We included demographic variables (marital status, education, race, ethnicity, parity, and desire for children in the future) as covariates in the models.

There were 102 women who completed the survey at time 1 only. In order to assess the robustness of our model that had included these 102 participants, we conducted a sensitivity analysis. We compared the original model results with the odds ratios from a model that did not include these 102 subjects.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used to quantify the magnitude and direction of associations. The level of significance was 5%. All analyses were performed using SAS 13.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

Of 1135 participants enrolled in the study, 1036 completed acceptability questionnaires (91%). We excluded participants from the analysis if they discontinued the study for non-ring-related reasons (84) or were lost to follow-up (47). We analyzed questionnaires for 905 participants, 706 (78%) of whom completed the clinical trial and 199 (22%) who discontinued the study early due to ring-related reasons. Of the 905 participants included, 803 (88.7%) completed the survey at time 1 and time 2, while 102 (11.3%) completed the survey at time 1 only. Of the 102 who completed the survey at time 1 only, 84% discontinued the study early due to ring-related reasons or pregnancy (e.g., 11.8% for repeated ring expulsions, 7.8 % for pregnancy, 6.9% for nausea, 5.9% for vaginal discharge). Of the 803 who completed the survey at time 1 and time 2, 16% discontinued the study early due to ring-related reasons or pregnancy (e.g., 2.2 % for pregnancy, 1.1% for repeated ring expulsions, 1.1% for unscheduled spotting, and 0.9% for vaginal discharge).

Ring removal >2 hours was reported by 120 participants (13.3%). In the Chi-square analysis, ring removal >2 hours was significantly associated with educational attainment ($p < 0.001$), race ($p < 0.001$), ethnicity ($p < 0.001$), study region ($p < 0.001$), parity ($p = 0.004$), previous

vaginal ring ($p=0.007$) or tampon use ($p<0.001$). There were no differences in terms of age, marital status, and desire for future pregnancy (Table 1).

Table 2 displays the Chi-square analysis of acceptability questionnaire responses. In terms of sexual activity, reports of feeling the ring during sex ($p=0.012$), removing the ring during sex ($p<0.001$), and effects of the ring on a partner's sexual pleasure ($p=0.002$) were associated with ring removal >2 hours, while sex frequency, sexual pleasure, or CVR expulsions during intercourse were not. Ring removal >2 hours was associated with removing the ring to wash it ($p<0.001$) and feeling the ring while wearing it ($p=0.002$). There was no association with participants' reports of side effects and ring removals >2 hours.

Results of a multivariate model to identify factors associated with ring removal >2 hours are shown in Table 3. Removing the ring to wash it (OR 3.96, 95%CI 2.50–6.27) or prior to intercourse (OR 3.19, 95%CI 2.03–4.99), and finding the ring difficult to insert (OR 2.80, 95%CI 1.36–5.80) were associated with CVR removal >2 hours. Lower educational attainment, i.e. having completed grade school only compared to college, was also associated with ring removal >2 hours (OR 3.23, 95%CI 1.55–6.75). Women residing in Europe or Australia were less likely to remove the ring for >2 hours compared with women in the US (OR 0.44, 95%CI 0.24–0.83 and OR 0.13, 95%CI 0.02–0.98, respectively).

Table 4 shows the association between ring removal >2 hours and method dissatisfaction, early discontinuation, and pregnancy. Ring removers were significantly more likely than non-removers to be dissatisfied with the ring (OR 2.20, 95%CI 1.32–3.69), to discontinue the method prior to termination of the study (OR 1.93, 95%CI 1.24–2.95), and to become pregnant during the study (OR 4.07, 95%CI 1.58–10.50).

The sensitivity analysis yielded minimal changes in the ORs displayed in tables 3 and 4 (sensitivity analysis data not shown).

4. Discussion

In this study, we examined factors associated with non-adherence to instructions for use of a novel CVR reusable for up to 1-year, as measured by ring removals >2 hours outside scheduled removal periods. We found that 13% of women reported such removals, and those who did had almost twice the odds of being dissatisfied with the ring and discontinuing its use early. They also had four times the odds of becoming pregnant during the study. These findings are similar to continuation data for NuvaRing® users indicating that women who temporarily removed that ring were more likely to discontinue its use [13].

Removing the ring for washing was the factor most significantly associated with non-adherence to the CVR use instructions. It is well known that women have varied ideas and practices regarding vaginal hygiene, and that these likely affect their experiences using vaginal products [14–18]. For some women, ring removals for washing may be related to perceptions about the ring's effect on cleanliness and vaginal health. In a dapivirine vaginal ring trial for HIV prevention, for example, the most commonly cited reason for removing the ring was to clean it, even though participants had been advised to keep the ring in. While reported ring removals were uncommon among women in that study, they increased over

time, perhaps reflecting users' concerns about undesirable effects on vaginal hygiene over time [19]. In a phase 1 trial of a multi-drug HIV prevention ring, 18% of 48 participants expressed concerns about the ring being "dirty", and some wanted to obtain a new one, particularly after menses [20]. Although we did not ask women directly about their reasons for washing the ring frequently, it is likely that ring removals for washing in this study occurred for reasons similar to those cited in microbicide studies. Results from this NES/EE CVR study and the microbicide studies suggest that for some women, perceptions of a vaginal ring's effect on vaginal health and cleanliness may be an essential component of use.

Awareness or sensations of the ring in the vagina during sexual intercourse may also play a role in ring removal. Most NES/EE CVR and NuvaRing users do not report any interference of the CVR with their sexual experiences [12,19], but a minority of women do. In this study, we found that removing the ring before sex was a significant factor associated with keeping the ring out for >2 hours. Similarly, among NuvaRing users who reported temporary ring removal, interference with intercourse was commonly cited [13]. Thus, while only a minority of users find that vaginal rings interfere with sex, these women are likely to remove the ring, and, based on our study results, to keep it out for periods longer than recommended to maintain contraceptive efficacy.

Women may be removing the ring to cleanse themselves prior to intercourse. They may also be concerned about its physical interference with intercourse or about their partner's reaction. In a survey exploring Portuguese women's perceptions of vaginal products, 40% felt their partner's opinion of the products was important, and potential interference with intercourse was considered a disadvantage for use of any vaginal product [21]. It is well established that partner support influences contraceptive use [22–24]. The presence of a physical product in the vagina - a space viewed by some women as "shared" with a partner [18] adds additional complexity to this negotiation.

The potentially complex relationship between CVR use, vaginal hygiene and sexual function may be perceived by some women more than others. In our study, reduced educational attainment was a predictor of non-adherence to the CVR use instructions, a finding consistent with results from prior studies describing lower education and limited understanding of instructional materials as predictors of inconsistent or incorrect oral contraceptive use [25–27]. Young age, black race, Hispanic ethnicity, multiparity and lower socioeconomic status have also been associated with reports of non-adherence [27], higher contraceptive failure rates [24], and higher Pearl indices [28]. Associations between ring removal and race, ethnicity, and parity were not significant in our study. However, women in study sites in Europe and Australia were less likely to report ring removals >2 hours than women in the US. Similar results were observed in NuvaRing clinical trials with more temporary ring removals reported among participants in North America than in Europe [29]. Of interest was the finding that experiencing side effects was not related to ring removal >2 hours. As previously reported, however, side effects were related to overall satisfaction [10].

Limitations of this study include reliance on self-reported measures of non-adherence to method use instructions, which is subject to social desirability bias [30]. Real-life user data would more closely reflect typical use, but such data are not yet available for this

investigational product. Additionally our study excluded women with a BMI > 29, suggesting that our findings may not necessarily apply to overweight or obese women. Another limitation is lack of data collected in the acceptability or Phase 3 study to clarify the reasons why women who removed the ring did not reinsert it within 2 hours, e.g. forgetting to re-insert the ring versus choosing not to or being unable to do so. Further research utilizing qualitative methods may reveal additional information to guide counseling for prospective users.

A major strength of our study is its analysis of specific factors associated with non-adherence to instruction for use for the NES/EE CVR. The study was conducted in multiple countries, and had a large sample size with a low rate of lost to follow-up. The effects found in the multivariate models showed minimal changes in the sensitivity analysis, indicating robustness of the models. These features increase the generalizability of our findings, which may be applicable to other vaginal ring products, including antimicrobial and multipurpose rings designed for contraception and prevention of sexually transmitted infections [31,10]. While individual vaginal ring products have unique features (such as size and texture), they share certain characteristics such as the need to insert the product in the vagina and the feeling of having it in the vagina. That some of our findings parallel previous findings from NuvaRing and dapivirine studies suggests similar factors may be influencing acceptability and adherence to use instructions for a variety of vaginal ring products.

In conclusion, while most users of the NES/EE CVR reported satisfaction and adherence to ring use [12], this analysis yielded important new insights. Removing the ring for washing and before intercourse are factors associated with non-adherence, which in turn are associated with method dissatisfaction, discontinuation, and an increased risk of pregnancy. Clinicians should provide anticipatory guidance to women considering a vaginal ring, with a focus on how the ring feels in the vagina and during sex. Inquiring about vaginal hygiene practices is also important. Users need reassurance that the ring does not increase the incidence of vaginal infections [32] and does not need frequent washing. Asking about a user's overall experience with a vaginal ring, including ring removals, will help to identify women who need additional counseling and support. These strategies are likely to maximize the impact of this novel contraceptive vaginal ring and of other promising vaginal ring technologies.

Acknowledgments

We would like to acknowledge the following individuals for their contribution to the conduct of the clinical trial: All Principal Investigators from the 300B study including: Dr. Daniel Apter, Dr. Luis Bahamondes, Dr. Horacio Croxatto, Dr. Gyorgy Bartfai, Dr. Melissa Gilliam, Dr. Antonia Nicosia, Dr. Philip Darney, Dr. Jody Steinaur, Dr. Christina Gemzell, Dr. Ian Fraser, Dr. Edith Weisberg, Lic. Vivian Brache, Dr. David Portman, Dr. Erica Banks, Dr. Maria Jose Miranda, and the late Dr. Daniel Mishell. Special thanks to Population Council members Dr. Barbara Mensch, Dr. Paul Hewett, Stan Mierzwa, Dr. Regine Sitruk Ware, Dr. Kevin Roberts, and Heather Sussman.

Funding source

This study was supported by the National Institute of Health/NICHD [grant #: 3RO1HD047764-02S2]; and the US Agency for International Development (USAID) [grant #: GPO-A-00-04-00019].

References

1. Sedgh G, Singh S, Hussain R. Intended and unintended pregnancies worldwide in 2012 and recent trends. *Stud Fam Plann.* 2014; 45:301–14. [PubMed: 25207494]
2. Sonfield, A., Gold, RBHK. *Moving Forward: Family Planning in the Era of Health Reform.* New York: Guttmacher Institute; 2014.
3. Polis CB, Bradley SE, Bankole A, Onda T, Croft T, Singh S. Typical-use contraceptive failure rates in 43 countries with Demographic and Health Survey data: summary of a detailed report. *Contraception.* 2016; 94:11–7. [PubMed: 27018154]
4. Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. *N Engl J Med.* 2012; 366:1998–2007. [PubMed: 22621627]
5. Peipert JF, Zhao Q, Allsworth JE, Petrosky E, Madden T, Eisenberg D, et al. Continuation and satisfaction of reversible contraception. *Obs Gynecol.* 2011; 117:1105–13.
6. United Nations, Department of Economic and Social Affairs, Population Division. *Trends in Contraceptive Use Worldwide 2015 (ST/ESA/SER.A/349).* 2015. Available at: <http://www.un.org/en/development/desa/population/publications/pdf/family/trendsContraceptiveUse2015Report.pdf>
7. Blumenthal PD, Voedisch A, Gemzell-Danielsson K. Strategies to prevent unintended pregnancy: increasing use of long-acting reversible contraception. *Hum Reprod Updat.* 2011; 17:121–37.
8. Hubacher D, Olawo A, Manduku C, Kiarie J, Chen PL. Preventing unintended pregnancy among young women in Kenya: prospective cohort study to offer contraceptive implants. *Contraception.* 2012; 86:511–7. [PubMed: 22633247]
9. Blumenthal PD, Shah NM, Jain K, Saunders A, Clemente C, Lucas B, et al. Revitalizing long-acting reversible contraceptives in settings with high unmet need: a multicountry experience matching demand creation and service delivery. *Contraception.* 2013; 87:170–5. [PubMed: 23153895]
10. Thurman AR, Clark MR, Hurlburt JA, Doncel GF. Intravaginal rings as delivery systems for microbicides and multipurpose prevention technologies. *Int J Womens Heal.* 2013; 5:695–708.
11. Peitzmeier SM, Tomko C, Wingo E, Sawyer A, Sherman SG, Glass N, et al. Acceptability of microbicide vaginal rings and oral pre-exposure prophylaxis for HIV prevention among female sex workers in a high-prevalence US city. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV.* 2017:1–5.
12. Merkatz RB, Plagianos M, Hoskin E, Cooney M, Hewett PC, Mensch BS. Acceptability of the Nestorone(R)/ethinyl estradiol contraceptive vaginal ring: development of a model; implications for introduction. *Contraception.* 2014; 90:514–21. [PubMed: 24993487]
13. Novak A, de la Loge C, Abetz L, van der Meulen EA. The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability. *Contraception.* 2003; 67:187–94. [PubMed: 12618252]
14. Martin Hilber A, Hull TH, Preston-Whyte E, Bagnol B, Smit J, Wacharasin C, et al. A cross cultural study of vaginal practices and sexuality: Implications for sexual health. *Soc Sci Med.* 2010; 70:392–400. [PubMed: 19906477]
15. McKee MD, Baquero M, Anderson MR, Alvarez A, Karasz A. Vaginal douching among Latinas: practices and meaning. *Matern Child Heal J.* 2009; 13:98–106.
16. Brown JM, Poirot E, Hess KL, Brown S, Vertucci M, Hezareh M. Motivations for Intravaginal Product Use among a Cohort of Women in Los Angeles. *PLoS One.* 2016; 11:e0151378. [PubMed: 26967165]
17. Vallely A, Fitzgerald L, Fiya V, Aeno H, Kelly A, Sauk J, et al. Intravaginal practices and microbicide acceptability in Papua New Guinea: implications for HIV prevention in a moderate-prevalence setting. *BMC Res Notes.* 2012; 5:613. [PubMed: 23116431]
18. Francis JK, Fraiz LD, Catallozzi M, Rosenthal SL. Qualitative Analysis of Sexually Experienced Female Adolescents: Attitudes about Vaginal Health. *J Pediatr Adolesc Gynecol.* 2016; 29:496–500. [PubMed: 27133374]
19. Nel A, Bekker LG, Bukusi E, Hellström E, Kotze P, Louw C, et al. Safety, Acceptability and Adherence of Dapivirine Vaginal Ring in a Microbicide Clinical Trial Conducted in Multiple Countries in Sub-Saharan Africa. *PLoS One.* 2016; 11:e0147743. [PubMed: 26963505]

20. van der Straten A, Panther L, Laborde N, Hoesley CJ, Cheng H, Husnik MJ, et al. Adherence and Acceptability of a Multidrug Vaginal Ring for HIV Prevention in a Phase I Study in the United States. *AIDS Behav.* 2016; 20:2644–53. [PubMed: 26837628]
21. Palmeira-de-Oliveira R, Duarte P, Palmeira-de-Oliveira A, das Neves J, Amaral MH, Breitenfeld L, et al. Women's experiences, preferences and perceptions regarding vaginal products: Results from a cross-sectional web-based survey in Portugal. *Eur J Contracept Reprod Heal Care.* 2015; 20:259–71.
22. Manlove J, Welti K, Barry M, Peterson K, Schelar E, Wildsmith E. Relationship characteristics and contraceptive use among young adults. *Perspect Sex Reprod Heal.* 2011; 43:119–28.
23. Ezeanolue EE, Iwelunmor J, Asaolu I, Obiefune MC, Ezeanolue CO, Osuji A, et al. Impact of male partner's awareness and support for contraceptives on female intent to use contraceptives in southeast Nigeria. *BMC Public Health.* 2015; 15:879. [PubMed: 26358642]
24. Kost K, Singh S, Vaughan B, Trussell J, Bankole A. Estimates of contraceptive failure from the 2002 National Survey of Family Growth. *Contraception.* 2008; 77:10–21. [PubMed: 18082661]
25. Ong J, Temple-Smith M, Wong WC, McNamee K, Fairley C. Contraception matters: indicators of poor usage of contraception in sexually active women attending family planning clinics in Victoria, Australia. *BMC Public Health.* 2012; 12:1108. [PubMed: 23259407]
26. Rosenberg MJ, Waugh MS, Meehan TE. Use and misuse of oral contraceptives: risk indicators for poor pill taking and discontinuation. *Contraception.* 1995; 51:283–8. [PubMed: 7628201]
27. Westhoff CL, Torgal AT, Mayeda ER, Shimoni N, Stanczyk FZ, Pike MC. Predictors of noncompliance in an oral contraceptive clinical trial. *Contraception.* 2012; 85:465–9. [PubMed: 22079603]
28. Gerlinger C, Trussell J, Mellinger U, Merz M, Marr J, Bannemerschult R, et al. Different Pearl Indices in studies of hormonal contraceptives in the United States: impact of study population. *Contraception.* 2014; 90:142–6. [PubMed: 24813941]
29. Dieben TO, Roumen FJ, Apter D. Efficacy, cycle control, and user acceptability of a novel combined contraceptive vaginal ring. *Obs Gynecol.* 2002; 100:585–93.
30. Stuart GS, Grimes DA. Social desirability bias in family planning studies: a neglected problem. *Contraception.* 2009; 80:108–12. [PubMed: 19631784]
31. Villegas G, Calenda G, Ugaonkar S, Zhang S, Kizima L, Mizenina O, et al. A Novel Microbicide/Contraceptive Intravaginal Ring Protects Macaque Genital Mucosa against SHIV-RT Infection Ex Vivo. *PLoS One.* 2016; 11:e0159332. [PubMed: 27428377]
32. Huang Y, Merkatz RB, Hillier SL, Roberts K, Bliethe DL, Sitruk-Ware R, et al. Effects of a One Year Reusable Contraceptive Vaginal Ring on Vaginal Microflora and the Risk of Vaginal Infection: An Open-Label Prospective Evaluation. *PLoS One.* 2015; 10:e0134460. [PubMed: 26267119]

Implications

Findings from this study may be useful in guiding counseling for current and prospective vaginal ring users. Anticipatory guidance should focus on how the ring feels in the vagina and during sex. Asking about ring removals may help identify women who are at increased risk for having an unplanned pregnancy.

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Table 1

Demographic and background characteristics by adherence to instructions for using the NES/EE CVR

	Ring removers (n=120)	Non-removers (n=785)	Total (n=905)	P value
Age (mean/SD)	26.1 (5)	26.9 (5.1)	26.8 (5.1)	0.15 *
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	
Marital status				0.64
Not married	85 (70.8)	572 (72.9)	657 (72.6)	
Married	35 (29.2)	213 (27.1)	248 (27.4)	
Education				<0.001
College	32 (26.7)	312 (39.7)	344 (38.0)	
Some college	24 (20.0)	203 (25.9)	227 (25.1)	
High school graduate	39 (32.5)	209 (26.6)	248 (27.4)	
Grade school	25 (20.8)	61 (7.8)	86 (9.5)	
Race				<0.001
White	81 (67.5)	644 (82)	725 (80.1)	
Black	8 (6.7)	38 (4.8)	46 (5.1)	
Mixed race	22 (18.3)	51 (6.5)	73 (8.1)	
Other	9 (7.5)	52 (6.6)	61 (6.7)	
Ethnicity				<0.001
Not Hispanic/Latino	43 (35.8)	470 (59.9)	513 (56.7)	
Hispanic/Latino	77 (64.2)	315 (40.1)	392 (43.3)	
Study Region				<0.001
US	37 (30.8)	249 (31.7)	286 (31.6)	
Latin America	62 (51.7)	228 (29.0)	290 (32.0)	
Europe	20 (16.7)	250 (31.9)	270 (29.8)	
Australia	1 (0.8)	58 (7.4)	59 (6.5)	
Parity				0.004
0	61 (50.8)	505 (64.3)	566 (62.5)	
1	59 (49.2)	280 (35.7)	339 (37.5)	
Previous vaginal ring use				0.007
No	109 (90.8)	634 (80.8)	743 (82.1)	
Yes	11 (9.2)	151 (19.2)	162 (17.9)	
Previous tampon use				<0.001
No	45 (37.5)	169 (21.6)	214 (23.8)	
Yes	75 (62.5)	612 (78.4)	687 (76.2)	
Desire for future pregnancy				0.38
No	40 (33.3)	214 (27.3)	254 (28.1)	
Yes	59 (49.2)	424 (54)	483 (53.4)	
Unsure	21 (17.5)	147 (18.7)	168 (18.6)	

NES/EE CVR: Nestorone®/ethinyl estradiol contraceptive vaginal ring

Ring removers: Women who removed the ring and kept it out for >2 hours

* Based on unpaired t-test. All other p values based on Pearson's Chi Square test.

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Table 2

Associations between NES/EE CVR acceptability domains and ring removal

	Ring removers (n=120)	Non-removers (n=785)	Total (n=905)	P value*
Sexual domain	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	
Feel ring during sex				0.012
Never	71 (59.2)	550 (70.6)	621 (69.1)	
Ever	49 (40.8)	229 (29.4)	278 (30.9)	
Partner feels ring during sex				0.10
Never	41 (34.2)	332 (42.6)	373 (41.5)	
Ever	68 (56.7)	404 (51.9)	472 (52.5)	
Don't know	11 (9.2)	43 (5.5)	54 (6.0)	
Change in frequency of sex				0.42
No change or increased	101 (86.3)	647 (83.4)	748 (83.8)	
Decreased	16 (13.7)	129 (16.6)	145 (16.2)	
Change in sexual pleasure				0.38
No change or increased	105 (89.0)	662 (86.0)	767 (86.4)	
Decreased	13 (11.0)	108 (14.0)	121 (13.6)	
Ring affects partner sexual pleasure				0.002
Never	79 (65.8)	622 (80.0)	707 (78.0)	
Ever	25 (20.8)	92 (11.8)	117 (13.0)	
Don't know	16 (13.3)	65 (8.3)	81 (9.0)	
CVR expelled during sex				0.24
Never	109 (90.8)	730 (93.7)	839 (93.3)	
Ever	11 (9.2)	49 (6.3)	60 (6.7)	
CVR removed before sex				<0.001
Never	64 (53.3)	613 (78.9)	677 (75.5)	
Ever	56 (46.7)	164 (21.1)	220 (24.5)	
Ease of use domain				
Removal to wash				<0.001
Never	32 (26.7)	508 (65.8)	540 (60.5)	
Ever	88 (73.3)	264 (34.2)	352 (39.5)	
Ring is easy to insert				0.10
No	13 (10.8)	52 (6.7)	65 (7.2)	
Yes	107 (89.2)	727 (93.3)	834 (92.8)	
Ring is easy to remove				0.07
No	18 (15.0)	75 (9.6)	93 (10.3)	
Yes	102 (85.0)	706 (90.4)	808 (89.7)	
Easy to remember to remove ring				0.87
No	14 (11.2)	88 (11.3)	102 (11.3)	
Yes	105 (88.8)	693 (88.7)	798 (88.7)	
Easy to remember to reinsert ring				0.72
No	11 (9.3)	65 (8.3)	76 (8.5)	

	Ring removers (n=120)	Non-removers (n=785)	Total (n=905)	P value*
Yes	107 (90.7)	715 (91.7)	822 (91.5)	
Side effects domain				0.31
No	103 (85.8)	635 (81.4)	738 (82.0)	
Yes	17 (14.2)	145 (18.6)	162 (18.0)	
Expulsions domain				
Feel ring while wearing				0.002
Never	66 (55.0)	540 (69.1)	606 (67.3)	
Ever	54 (45.0)	241 (30.9)	295 (32.7)	
Feel ring coming out				0.38
Never	72 (60.5)	437 (56.2)	509 (56.8)	
Ever	47 (39.5)	340 (43.8)	387 (43.2)	

NES/EE CVR: Nestorone®/ethinyl estradiol contraceptive vaginal ring

Ring removers: Women who removed the ring and kept it out for > 2 hours; CVR: contraceptive vaginal ring

* Based on Pearson's Chi square test

Table 3
Factors associated with removal of the NES/EE CVR for >2 hours (non-adherence)

	Total (905) N	Ring remover (120) n (%)	OR *	95% CI	P value
Education					0.01
College	344	32 (9.3)	ref	-	
Some college	227	24 (10.6)	1.12	0.61 – 2.06	
High school	248	39 (15.7)	1.69	0.91 – 3.14	
Grade school	86	25 (29.1)	3.23	1.55 – 6.75	
Study region					0.003
US	286	37 (12.9)	ref	-	
Latin America	290	62 (21.4)	1.15	0.65 – 2.02	
Europe	270	20 (7.4)	0.44	0.24 – 0.83	
Australia	59	1 (1.7)	0.13	0.02 – 0.98	
Ring is easy to insert					0.005
Yes	834	107 (12.8)	ref	-	
No	65	13 (20)	2.80	1.36 – 5.80	
Remove ring before sex					<0.001
No	677	64 (9.4)	ref	-	
Yes	220	56 (25.4)	3.19	2.03 – 4.99	
Remove ring to wash it					<0.001
No	540	32 (5.9)	ref	-	
Yes	352	88 (25)	3.96	2.50 – 6.27	

NES/EE CVR: Nestorone®/ethinyl estradiol contraceptive vaginal ring

N: number of participants in each category; n (%): number and percentage of ring removers in each category

* OR based on a multivariate model including the variables shown

Table 4

Association of ring removal >2 hours with method dissatisfaction, early discontinuation, and pregnancy

	N (%)	OR*	95% CI	P value
Dissatisfaction with ring				
Non-remover	102 (13%)	ref	-	-
Ring remover	25 (20.8%)	2.20	1.3 – 3.69	0.003
Early discontinuation of ring				
Non-remover	172 (21.9)	ref	-	-
Ring remover	40 (33.3)	1.93	1.24 – 2.95	0.003
Pregnancy during study				
Non-remover	10 (1.3)	ref	-	-
Ring remover	10 (8.3)	4.07	1.58 – 10.50	0.004

N (%): number and percentage of participants in each category. Ring removers: Women who removed the ring and kept it out for >2 hours

* Odds ratios based on multivariate models adjusted for marital status, education, race, ethnicity, parity, and desire for future pregnancy