



Original research article

Post-use ring weight and residual drug content as potential objective measures of user adherence to a contraceptive progesterone vaginal ring



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ABSTRACT

Objectives: The primary aim was to investigate post-use ring weight as a potential measure of cumulative adherence to a progesterone-releasing vaginal ring.

Study design: We weighed and quantified residual progesterone in 115 vaginal rings following 90-day use by participants in an acceptability trial conducted in Nigeria, Senegal and Kenya. The primary objective was to correlate residual progesterone content with post-use ring weight. Secondary objectives included correlating ring weight with putative duration of ring use, and, where participants used two rings consecutively in the study, correlating residual content between these paired rings.

Results: Mean ring weight and progesterone content of used rings was 8.62 ± 0.24 g and 1245 ± 245 mg respectively, versus 9.37 ± 0.02 g and 2058 ± 21 mg for control rings. Most used rings (90.4%) had residual progesterone levels less than 85% of the nominal loading. Linear regression showed a strong positive linear trend between residual progesterone content and post-use ring weight for all rings ($r^2=0.82$). Duration of ring use was inversely associated ($p=.00020$) with ring weight.

Conclusions: Post-use ring weight is highly correlated with residual progesterone content, a benchmark objective cumulative measure of adherence, and thus potentially useful as a surrogate objective measure of cumulative adherence to a progesterone-releasing vaginal ring.

Implication statement: For vaginal rings containing a high initial drug loading and releasing a relatively large fraction of the initial loading during clinical use, post-use ring weight may offer a simple and inexpensive alternative to residual content testing for accurate monitoring of user adherence.

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1. Introduction

It has long been assumed that use of long-acting vaginal rings for drug delivery leads to increased product adherence, acceptability and efficacy compared with conventional short-acting vaginal formulations. This assumption is particularly prevalent in the HIV microbicide and multipurpose prevention technology fields, which are heavily focused on new vaginal ring technologies [1–6]. Based on adherence data from other clinical indications [7–9], including hormonal contraception for which depot injections, sub-dermal implants, transdermal patches and vaginal rings are available [10,11], the case for sustained/controlled drug delivery is generally well made and widely accepted. However, a major challenge in vaginal ring product development remains the accurate measurement of adherence in late stage clinical trials [3,12,13], as recently highlighted by the results of the dapivirine ring trials

demonstrating increased efficacy in women showing high levels of adherence [14,15].

Historically, assessment of user adherence to vaginal rings has relied almost exclusively on self-report measures. However, these are highly subjective and prone to error, due to participants misreporting use, staff errors in data collection, and lack of clarity about what is being measured [3,13,16–21]. Driven by the need for more accurate and reliable measures of adherence, alternative methods for quantitatively measuring adherence are being considered, including drug analysis in hair or dried blood spots and temperature-monitoring vaginal rings [22–25]. In general, these methods can be classified as either point or cumulative measures of adherence [22]. Several investigators have reported measurement of the quantity of drug remaining in a vaginal ring following clinical use (known as ‘residual drug content’) as an indicator of cumulative ring use [1,15,26–28]. For example, residual levels of etonogestrel and ethinyl estradiol in Nuvaring®, a combination contraceptive ring, provided objective measures of ring use, with 69–81% of the initial 11.7 mg etonogestrel loading and 79–93% of the initial 2.7 mg ethinyl estradiol loading recovered from the rings after use

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[26]. In contrast, no clear relationship was observed between residual dapivirine content and dapivirine plasma concentration for a dapivirine-releasing ring [28]. This may be due to the relatively low fraction of dapivirine released from the ring (approximately 4 mg of the 25 mg initial loading), coupled with significant intra-subject variability in drug release from the device and subsequent drug pharmacokinetics [27].

Progering®, a progesterone-releasing vaginal ring approved in Chile, Dominican Republic, Peru, Bolivia, Ecuador, Guatemala, Panama and Honduras, is used by breastfeeding women to extend the contraceptive effectiveness of lactational amenorrhoea [29–32]. Fabricated from silicone elastomer and containing ~2 g (22.5% w/w) micronized progesterone dispersed throughout its volume, a single Progering® device is intended for continuous use for up to 3 months, although removal for up to 2 hours for intercourse or cleaning is permitted. The relatively high drug loading in Progering® (compared with the low milligram drug quantities contained in the dapivirine-releasing ring and Nuvaring®), coupled with its relatively large daily release rate of progesterone (initially 22 mg/day, declining to 6 mg/day after 90 days; historically described as a ‘10 mg/day’ ring in the literature) and long duration of use [33], offer the possibility of accurately assessing adherence through measurement of residual drug content and/or post-use ring weight. We hypothesised that residual drug content, and by implication adherence, could be correlated with post-use ring weight. Here, we report the measurement and correlation of residual progesterone content and post-use ring weight for 115 Progering® devices used as part of an acceptability study in Kenya, Nigeria, and Senegal [34]. In an exploratory study involving a small number of rings, we also attempted to correlate the thickness of the drug depletion zone with both ring weight and residual drug content. Neither ring weight nor drug depletion zone thickness has previously been considered as a measure of user adherence to a vaginal ring device.

2. Materials and methods

2.1. Details of clinical study

The Population Council conducted an acceptability study of Progering® in Kenya, Nigeria, and Senegal in preparation for introduction of Progering® to these markets [34]. Rings for the study were manufactured (Batch G3585) by Grunenthal Chilena Ltda. (Santiago, Chile), and supplied by the Population Council (New York, USA). The study was approved by the Population Council's Institutional Review Board and ethics committees in Kenya, Nigeria and Senegal (see [34] for details). As part of the study, women used Progering® for one or two 90-day cycles and completed questionnaires reporting ring expulsions and removals. Used rings ($n=115$) were returned to the facility, cut, cleaned as per the site protocol regarding clinical product returns (including washing with bleach in some cases) and stored until the final study monitoring visit. Rings were subsequently shipped to Queen's University Belfast for analysis of residual content; this analysis was not part of the acceptability study.

2.2. Measurement of ring weights and visual inspection of rings

Used and control rings were weighed using a 4-decimal point balance. Visual assessment of ring discolouration was conducted as described in the Supplementary Information (Section S.2). Rings were subsequently cut using a scalpel into ~35 individual discs of thickness ~4 mm prior to solvent extraction.

2.3. Residual progesterone content

Residual progesterone content in the used rings was determined using a solvent extraction method. Ring sections were transferred to 250 mL glass flasks and 200 mL acetone (Sigma-Aldrich, Gillingham,

UK) added before placing in an orbital shaking incubator (Unitron HT Infors, 60 rpm, 37 °C, 25 mm throw). Solvent extraction was performed for a minimum of 24 h. Control rings were also extracted for reference. After allowing flasks to cool to room temperature, a 1 mL sample of the acetone extraction solution was diluted to 100 mL with a mixture of 1:1 water:acetonitrile (HPLC-grade water from a Millipore Direct-Q 3 UV Ultrapure Water System, Watford, UK; acetonitrile from Sigma-Aldrich, Gillingham, UK) and analysed by HPLC.

2.4. Quantification of progesterone content in rings using HPLC

Samples were analysed on a Waters HPLC system (Waters Limited, Herts, UK) consisting of a 1525 Binary HPLC pump with an inline degasser AF unit, 1500 column heater, 717plus autosampler and a 2487 dual wavelength absorbance detector. Samples were injected onto a BDS Hypersil C18 column (150 × 4.6 mm, 3 µm particle size; Apex Scientific, Kildare, Ireland) maintained at 45 °C and separated using a mobile phase comprising acetonitrile (66%) and a 9:1 mixture of water/acetonitrile (34%). Progesterone was detected at 260 nm with a retention time of ~3.4 min. All progesterone concentrations were determined using a calibration curve of progesterone standards (Bim Safrim Group, Puteaux, France) run with the samples on the day of analysis. Injector precision was <2% for each set of samples analysed. Weighted linear regression on the combined calibration curve samples gave a regression r^2 value of 0.99. The limit of quantification, calculated using the standard deviation of the residuals, was 0.67 µg/mL. No sample concentrations determined in the analysis were below 20 µg/mL.

2.5. Digital microscopy

In an exploratory study, sectioned samples of six rings used by Senegalese women and two control rings, selected to cover the range of measured ring weights, were viewed using a Keyence VHX-700F series Digital Microscope (Keyence Limited, UK) fitted with an RZ 100–1000× wide-range zoom lens and ring illumination standard light. Progesterone depletion zone thickness was measured using the microscope software.

2.6. Statistical analysis

The primary outcome was to correlate post-use ring weight with residual progesterone content. Simple linear regression was performed with ring weight as the independent variable and residual progesterone content as the dependent variable. Secondary outcomes included comparisons of ring weight with duration of ring use in a subset of rings (determined as the number of days between study visits), and where available, correlation of residual progesterone content of two rings used consecutively by a single participant. Exploratory secondary analyses involved correlation of ring weight and progesterone content with depletion zone thickness.

3. Results

3.1. Sample characteristics

We collected 115 rings in total from participants at three clinical sites in Nigeria, Kenya and Senegal. Thirteen women returned a single ring, and 51 women returned two rings following two consecutive cycles of use. We also analysed six unused rings from the same manufacturing batch as controls. A visual assessment of ring discolouration of used rings is presented in Supplementary Information (Section S.3 and Fig. S.1).

Table 1

Mean residual progesterone (P) content for all used rings by country of clinical trial site with unused controls as a comparator, subgroups of rings containing greater than 85%, and less than 85% residual P content are also defined. All values represent means \pm standard deviations.

Country	All rings				Rings with >85% residual content				Rings with <85% residual content			
	No. rings	P content (mg)	% P recovery ¹	Ring weight (g)	No. rings	P content (mg)	% P recovery ¹	Ring weight (g)	No. rings	P content (mg)	% P recovery ¹	Ring weight (g)
Unused	6	2058 \pm 21	100%	9.37 \pm 0.02	–	–	–	–	–	–	–	–
Kenya	4	1197 \pm 47	58.2%	8.55 \pm 0.03	0	–	–	–	4	1197 \pm 47	58.2%	8.55 \pm 0.03
Nigeria	69	1215 \pm 217	59.0%	8.62 \pm 0.23	4	1942 \pm 99	94.4%	9.33 \pm 0.11	65	1171 \pm 121	56.9%	8.58 \pm 0.14
Senegal	42	1299 \pm 289	63.1%	8.62 \pm 0.29	7	1894 \pm 74	92.0%	9.20 \pm 0.07	35	1180 \pm 112	57.3%	8.51 \pm 0.11
Total ²	115	1245 \pm 245	60.5%	8.62 \pm 0.24	11	1911 \pm 83	92.9%	9.25 \pm 0.10	104	1175 \pm 116	57.1%	8.55 \pm 0.14

¹ Mean % recovery values were calculated relative to the mean progesterone content for the unused control rings, i.e., 2058 mg.

² Total number of used (i.e. clinical) rings; this does not include unused control rings.

3.2. Post-use ring weights

Unused control rings ($n=6$) had a mean \pm SD ring weight of 9.37 \pm 0.02 g (Table 1). Post-use ring weight for used rings ($n=115$) was 8.62 \pm 0.24 g (Table 1). There were no significant differences between the mean ring weight of used rings by country (Table 1). A plot of ring weight against the putative duration of ring use, based on the interval between clinical visits, is presented in Fig. 1 for participants who completed all of the acceptability study ($n=92$ rings). Regression analysis indicated an inverse relationship ($p=.00020$).

3.3. Residual content analysis

Unused control rings had a mean residual progesterone content of 2058 \pm 21 mg (99.2 \pm 1.0% relative to a mean content assay of 2074 mg for the ring batch; Table 1). The mean residual progesterone content for used rings ($n=115$) was 1245 \pm 245 mg (60.5 \pm 11.9% of control ring values), with no significant differences across the three clinical sites (Table 1). Of these, 104 rings contained between 45.9 and 72.4% of mean content assay value, and the remaining 11 rings contained >85% (Table 1).

3.4. Correlation of ring weight and residual content

In the primary outcome measure, a strong linear correlation ($r^2=0.82$) was observed between measured residual progesterone content and post-use ring weight for all rings (Fig. 2A). Rings from Nigeria ($n=69$, Fig. 2B) showed the greatest dispersion about the regression line, compared to rings from Senegal (Fig. 2C) and Kenya (Fig. 2D). In

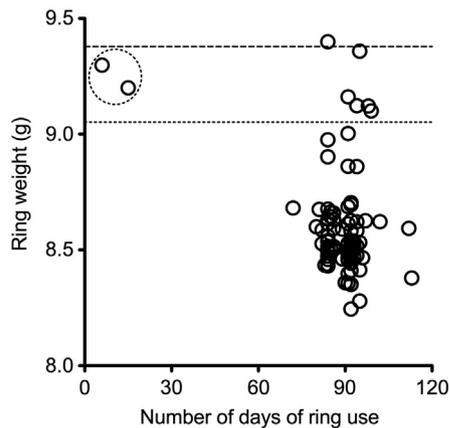


Fig. 1. Plot of ring weight vs. theoretical number of days of ring use for $n=92$ rings (calculated as the time between the first and second clinic visit per ring and assuming full ring use in this interval). The top line in the graph marks the approximate unused ring weight (9.37 g) while the lower line marks the approximate ring weight at 85% residual progesterone. The two values encircled represent participants who discontinued ring use early (after 6 and 15 days respectively).

a secondary outcome measure for participants using two rings consecutively, a plot of residual progesterone content for Ring 1 vs. Ring 2 is presented in Fig. 3. For most ring pairs, a high degree of correlation was observed between the two measurements. The mean difference between residual progesterone content values for Ring 1 vs. Ring 2 was 133.3 \pm 190.9 mg. We noted four cases of discordant results, where the difference between recovered progesterone values was >600 mg (represented by points far from the central regression line, Fig. 3). Excluding these values, the mean difference in residual content values between matched pairs was 82.6 \pm 73.6 mg.

3.5. Digital microscopy

Representative photographs showing cross-sectional samples of a control ring and three of the Senegalese rings (selected to cover the range of ring weights measured in this study) are displayed in Fig. 4 (A–D). Each used ring sample clearly shows a progesterone depletion zone of varying thickness adjacent to the ring surface. The thickness of the progesterone depletion zone in this sample of used rings correlates strongly with residual progesterone content ($r^2=0.97$; Fig. 4E) and post-use ring weight ($r^2=0.98$; Fig. 4F).

4. Discussion

In the primary outcome measure, a strong correlation was observed between ring weight and residual progesterone (Fig. 2). Therefore, assuming residual progesterone content to be the current benchmark measure of ring use/adherence, post-use ring weight may be useful as a surrogate measure of adherence. Several lines of evidence point to this correlation being directly related to ring use. First, the observed mean weight loss is inversely associated with the duration of ring use (Fig. 1). Second, assuming a nominal initial ring weight of 9.37 g and content of 2058 mg, the observed weight loss matches the putative progesterone loss (Table 1). Third, the weight differences between control and used rings (-0.8 g) cannot be attributed to loss of other components from the ring, since the rings do not contain other leachable excipients. Finally, this weight change matches the overall average ‘10 mg/day’ release rate over 90 days mentioned in the literature [33]. Therefore, we can confidently attribute any differences in weight to release of progesterone during clinical use.

Also, the limited number of self-reported ring removals and expulsions (Supplementary Information, Table S.1) cannot alone explain the variations in residual progesterone observed. Rather, the wide variation in residual progesterone content measured for individual rings (range 945–2058 mg; 45–100% of the control value) may be attributed to very significant differences in user adherence not captured by self-report.

Residual content of ring samples from Nigeria (Fig. 2B) showed greater dispersion about the regression line than the Senegalese or Kenyan samples (Fig. 2C and D). We attribute this to incomplete progesterone extraction from a small number of rings from Nigeria, which came to light only after analysis was complete. This accounts for the

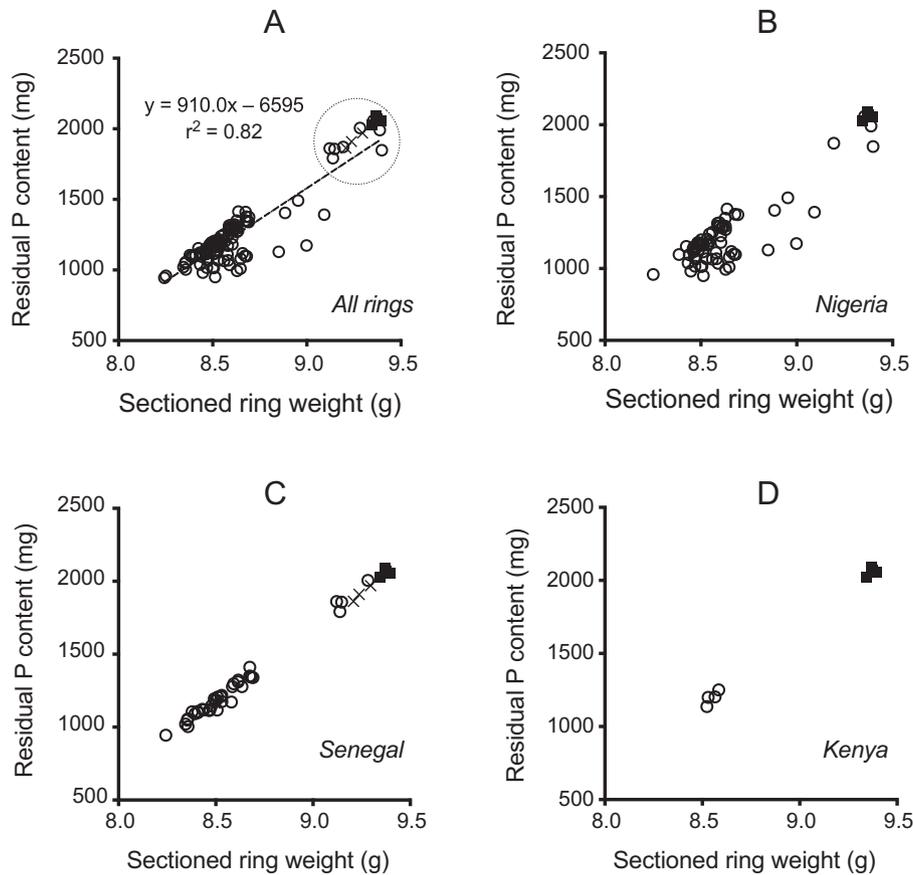


Fig. 2. Residual progesterone (P) content plotted vs. sectioned ring weight for progesterone-releasing vaginal rings following clinical use. (A) all rings across all three clinical sites ($n=115$; open circles and crosses); rings with recovery values $>85\%$ are circled; the line equation and coefficient of determination of the best fit line are also shown. Control ring data ($n=6$, filled squares) are omitted from the regression analysis; r^2 increases to 0.88 with inclusion of control rings. (B) rings from Nigeria only ($n=69$, open circles). (C) rings from Senegal only ($n=42$; open circles and crosses). (D) Rings from Kenya only ($n=4$; open circles).

lower-than-expected residual progesterone contents for some Nigerian ring samples and the associated poorer fit of data to the regression line. Although this reduced the overall coefficient of determination, the trend is robust to the influence of these values. However, the parameter estimates for the slope and intercept of the line should be interpreted with caution.

For participants who used two rings consecutively, comparison of residual progesterone content for the two rings was interpreted as a measure of consistency of use. Where participants used the two rings consistently, one would expect residual progesterone values to be similar. In Fig. 3, the cluster of data points in the lower left quadrant indicates consistent adherence use with both rings. The single data point in the upper right quadrant (with both rings having greater than 85% of the control ring loading) suggests consistently poor adherence. The four discordant cases indicate inconsistent use.

In an exploratory microscopy study involving a small number of rings, we found a strong correlation between the thickness of the depletion zone and both ring weight and residual progesterone content (Fig. 4). This is in line with well-established theoretical mechanisms describing diffusion-controlled drug release from matrix-type rings [5]. However, due to the small number of rings examined, this result should be considered preliminary. The use of depletion zone thickness as a measure of adherence is certainly interesting, but requires further study.

A potential limitation of this study is inconsistent ring cleaning procedures at different clinical sites, including use of bleach products. It is possible that differences in cleaning procedures and materials used could have an impact on the residual progesterone recovered. However, recently published work showed exposure to bleach for 1 h at 50 °C had no discernible impact on the content of a 25 mg dapivirine ring [35].

Also, we have measured almost complete progesterone recovery (>2 g) from rings from both Nigeria and Senegal. Therefore, if harsh treatments were used at either of these sites (accounting for $>95\%$ of the used rings) they did not affect progesterone levels in these rings substantially. Of note, water-based products show very limited penetration of hydrophobic silicone elastomers, such that the majority of the

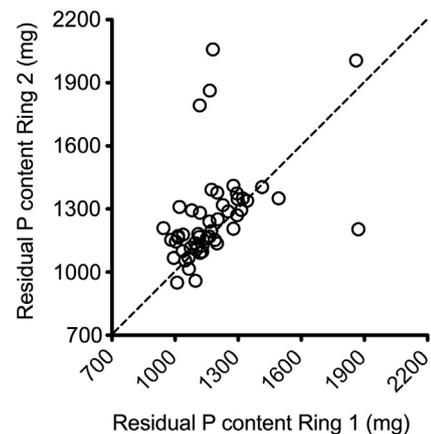


Fig. 3. Residual progesterone (P) content for first ring use (Ring 1) vs. residual P content for second ring use (Ring 2). Each plot symbol represents a single subject ($n=51$) who used two ring devices, one after the other, as part of the clinical study. Dashed line represents consistency of ring use. Clustered values located in the bottom left quadrant represent highly adherent women.

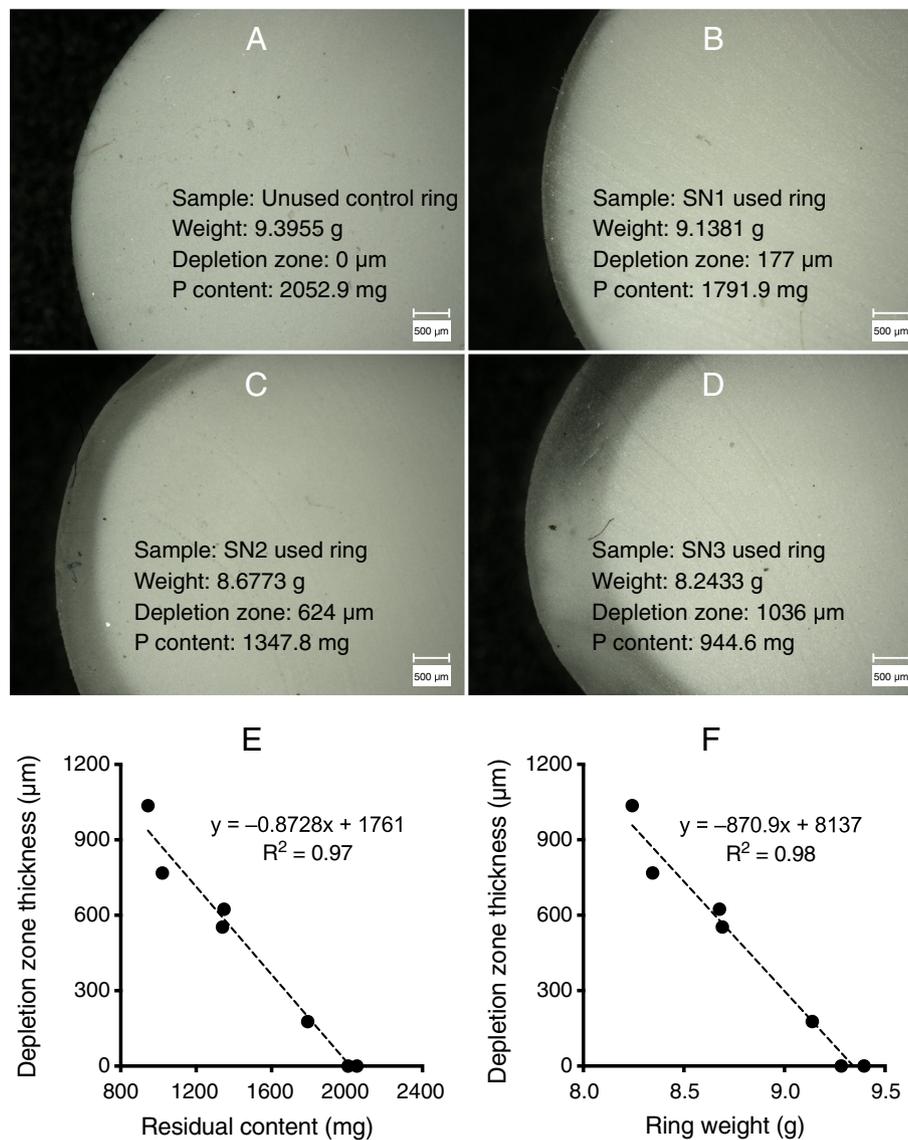


Fig. 4. (A–D) Representative digital photographs of ring cross sections (50 \times magnification) of used and unused rings ordered by size of the depletion zone with weight and residual content also included. Scatterplots showing the relationship between residual content vs. depletion zone thickness (E) and ring weight vs. depletion zone thickness (F) for the sample ring sections examined using digital microscopy are also presented.

progesterone material within a ring would not be exposed to an applied cleaning agent.

Another potential limitation concerns variation between centres in local storage conditions e.g. temperature and storage times. However, the mean residual content values by country (Table 1) show that no substantial differences were observed in this study, suggesting that any storage differences between sites did not have a large effect on residual progesterone levels. Similarly, differences between ring cutting and storage times between sites are not a concern since rings were stored dry.

In conclusion, we have shown that ring weight may be a useful surrogate measurement of residual drug content in the progesterone vaginal ring, with utility as a simple and inexpensive method of measuring ring adherence. The major limitation of this strategy is that only rings containing a relatively high initial drug loading and releasing a relatively large fraction of that initial loading during clinical use are amenable to this approach. It is acknowledged that few vaginal ring devices contain such large quantities of drug as Progering®. Future work should be directed at quantifying lower limits for drug loading and drug release that would still allow this approach to be useful for adherence monitoring.

Conflicts of interest

Progering® has been developed by the Population Council in collaboration with its partners. Analysis of the Progering® vaginal rings was completed at Queen's University Belfast with funding from the Population Council. RKM and PB act as scientific consultants to the Population Council on pharmaceutical and technical aspects of vaginal ring technology. All work described here was completed within the performance roles and responsibilities of the authors as determined by their employment within Queen's University Belfast and the Population Council. There are no other competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.contraception.2019.06.013>.

References

- [1] Nel A, Smythe S, Young K, Malcolm K, McCoy C, Rosenberg Z, et al. Safety and pharmacokinetics of dapivirine delivery from matrix and reservoir intravaginal rings to HIV-negative women. *J Acquir Immune Defic Syndr* 2009;51:416–23.
- [2] Romano J, Malcolm RK, Garg S, Rohan LC, Kaptur PE. Microbicide delivery: formulation technologies and strategies. *Curr Opin HIV AIDS* 2008;3:558–66.
- [3] Woodsong C, MacQueen K, Amico KR, Friedland B, Gafos M, Mansoor L, et al. Microbicide clinical trial adherence: insights for introduction. *J Int AIDS Soc* 2013;16:1–9.
- [4] Malcolm RK, Edwards KL, Kiser P, Romano J, Smith TJ. Advances in microbicide vaginal rings. *Antivir Res* 2010;88:S30–9.
- [5] Malcolm RK, Boyd PJ, McCoy CF, Murphy DJ. Microbicide vaginal rings: technological challenges and clinical development. *Adv Drug Deliv Rev* 2016;103:33–56.
- [6] Malcolm RK, Fetherston SM, McCoy CF, Boyd P, Major I. Vaginal rings for delivery of HIV microbicides. *Int J Women's Health* 2012;4:595–605.
- [7] Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med* 2008;31:213–24.
- [8] Kruk ME, Schwalbe N. The relation between intermittent dosing and adherence: preliminary insights. *Clin Ther* 2006;28:1989–95.
- [9] Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–97.
- [10] Graziottin A. Safety, efficacy and patient acceptability of the combined estrogen and progestin transdermal contraceptive patch: a review. *Patient Prefer Adherence* 2008;2:357–67.
- [11] Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397–404.
- [12] McCormack SM, Gafos M, Desai M, Cohen MS. Biomedical prevention: state of the science. *Clin Infect Dis* 2014;59(Suppl. 1):S41–6.
- [13] Tolley EE, Harrison PF, Goetghebeur E, Morrow K, Pool R, Taylor D, et al. Adherence and its measurement in phase 2/3 microbicide trials. *AIDS Behav* 2010;14:1124–36.
- [14] Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med* 2016;375:2121–32.
- [15] Nel A, van Niekerk N, Kapiga S, Bekker L-G, Gama C, Gill K, et al. Safety and efficacy of a Dapivirine vaginal ring for HIV prevention in women. *N Engl J Med* 2016;375:2133–43.
- [16] Van Der Straten A, Montgomery ET, Cheng H, Wegner L, Masenga G, Von Mollendorf C, et al. High acceptability of a vaginal ring intended as a microbicide delivery method for HIV prevention in African women. *AIDS Behav* 2012;16:1775–86.
- [17] Novák a, De La Loge C, Abetz L, E a Van Der Meulen. The combined contraceptive vaginal ring, NuvaRing®: an international study of user acceptability. *Contraception* 2003;67:187–94.
- [18] Dieben TOM, Roumen FJME, Apter D. Efficacy, cycle control, and user acceptability of a novel combined contraceptive vaginal ring. *Obstet Gynecol* 2002;100:585–93.
- [19] Nel A, Kamupira M, Woodsong C, Van Der Straten A, Montgomery E, Niekerk N Van, et al. safety , acceptability and pharmacokinetic assessment (adherence) of monthly Dapivirine vaginal microbicide rings (Ring-004) for HIV. *Prevention* 2012;1089.
- [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.
- [21] Merkatz RB, Plagianos M, Hoskin E, Cooney M, Hewett PC, Mensch BS. Acceptability of the Nestorone®/ethinyl estradiol contraceptive vaginal ring: development of a model; implications for introduction. *Contraception* 2014;90:514–21.
- [22] Stalter RM, Moench TR, MacQueen KM, Tolley EE, Owen DH. Consortium for ring adherence. Biomarkers and biometric measures of adherence to use of ARV-based vaginal rings. *J Int AIDS Soc* 2016;19:20746.
- [23] Stalter RM, Tharaldson J, Owen DH, Okumu E, Moench T, Mack N, et al. Attitudes and perceptions towards novel objective measures of ARV-based vaginal ring use: results from a global stakeholder survey. *PLoS One* 2017;12:e0180963.
- [24] Liu AY, Yang Q, Huang Y, Bacchetti P, Anderson PL, Jin C, et al. Strong relationship between Oral dose and Tenofovir hair levels in a randomized trial: hair as a potential adherence measure for pre-exposure prophylaxis (PrEP). *PLoS One* 2014;9:e83736.
- [25] Boyd P, Desjardins D, Kumar S, Fetherston SM, Le-Grand R, Dereuddre-Bosquet N, et al. A temperature-monitoring vaginal ring for measuring adherence. *PLoS One* 2015;10:e0125682.
- [26] Haaland RE, Holder A, Evans-Strickfaden T, Makanga M, Oyaro B, Humwa F, et al. Residual hormone levels in used contraceptive rings as a measurement of adherence to vaginal ring use. *Contraception* 2017;95:602–4.
- [27] Spence P, Nel A, van Niekerk N, Derrick T, Wilder S, Devlin B. Post-use assay of vaginal rings (VRs) as a potential measure of clinical trial adherence. *J Pharm Biomed Anal* 2016;125:94–100.
- [28] Nel A, Bekker L-G, 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.
- [29] Carr SL, Gaffield ME, Dragoman MV, Phillips S. Safety of the progesterone-releasing vaginal ring (PVR) among lactating women: a systematic review. *Contraception* 2016;94:253–61.
- [30] Díaz S, Jackanicz TM, Herreros C, Juez G, Peralta O, Miranda P, et al. Fertility regulation in nursing women: VIII. Progesterone plasma levels and contraceptive efficacy of a progesterone-releasing vaginal ring. *Contraception* 1985;32:603–22.
- [31] Díaz S, Zepeda A, Maturana X, Reyes MV, Miranda P, Casado ME, et al. Fertility regulation in nursing women: IX. Contraceptive performance, duration of lactation, infant growth, and bleeding patterns during use of progesterone vaginal rings, progestin-only pills, Norplant® implants, and copper T 380-a intrauterine devices. *Contraception* 1997;56:223–32.
- [32] Massai R, Quinteros E, Reyes MV, Caviedes R, Zepeda A, Montero JC, et al. Extended use of a progesterone-releasing vaginal ring in nursing women: a phase II clinical trial. *Contraception* 2005;72:352–7.
- [33] Matlin SA, Belenguer A, Hall PE. Progesterone-releasing vaginal rings for use in postpartum contraception. I. in vitro release rates of progesterone from core-loaded rings. *Contraception* 1992;45:329–41.
- [34] RamaRao S, Obare F, Ishaku S, Mané B, Clark H, Liambila W, et al. Do women find the progesterone vaginal ring acceptable? Findings from Kenya, Nigeria and Senegal *Stud Fam Plann* 2018;49:71–86.
- [35] Murphy DJ, McCoy CF, Boyd P, Derrick T, Spence P, Devlin B, et al. Drug stability and product performance characteristics of a dapivirine-releasing vaginal ring under simulated real-world conditions. *Int J Pharm* 2019;565:351–7.