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Malcolm, R., McCoy, C., Murphy, D., Boyd, P., & Variano, B. (2018). Post-use ring weight, residual drug content and drug depletion zone thickness as objective measures of vaginal ring adherence. P25.16. Poster session presented at HIV Research for Prevention 2018, Madrid, Spain.

Document Version:
Peer reviewed version

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Post-use Ring Weight, Residual Drug Content and Drug Depletion Zone Thickness as Objective Measures of Vaginal Ring Adherence

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Key points

1 Accurate measurement of adherence represents a major challenge in clinical testing of vaginal ring products.

2 Post-use ring weight, residual drug content and depletion zone thickness may offer accurate methods for monitoring user adherence for vaginal rings containing a high initial drug loading and releasing a relatively large fraction of the drug in use.

3 In practical terms, ring weight measurement offers a particularly simple and inexpensive method for monitoring clinical trial product use.

Background

A major challenge in the development of microbicide-releasing vaginal rings is the accurate and reliable measurement of adherence during clinical testing. In efforts to move away from reliance on self-reported measures of adherence, there is considerable interest in the development and testing of more objective quantitative measures. Here, we assessed post-use ring weight, residual drug content and drug depletion zone thickness as potential cumulative measures of adherence to a highly-loaded progesterone-releasing ring.

Objectives

1. Visually assess ring discolouration intensity and extent
2. Measure depletion zone thickness on a selection of ring sections
3. Extract and quantify residual progesterone.
4. Link the measured progesterone levels back to the ring weights and depletion zone thicknesses

Methods

Matrix-type progesterone silicone elastomer rings (n=115) were used by breastfeeding women across three sites in Africa to extend the contraceptive effectiveness of lactational amenorrhoea. Used rings (n=115) were independently examined by three reviewers to assess the intensity and extent of discoloration. Rings were subsequently weighed and sectioned in preparation for extraction of the residual progesterone. A selection of the ring segments were analysed using digital microscopy to determine the size of the depletion zone. The residual progesterone content was subsequently assessed via solvent extraction and HPLC-UV analysis in all of the rings.

Results & Discussion

The mean ring weights of unused control rings was 9.37 ± 0.02 g. Mean ring weight of used rings was 8.6 ± 0.2 g. The ~ 0.8 g difference in weight is due to progesterone release during clinical use and correlates with the expected release over 90 days, based on the reported 10 mg/day release rate. Fig. 1A shows a plot of residual progesterone content against sectioned ring weight for all rings; rings with $>85\%$ residual content are circled. This residual value was selected to distinguish good from poor adherence, based on visual inspection of the plots. Subsets of rings from clinical sites within each country are also displayed in Fig. 1B, C & D. A strong linear correlation between ring weight and residual progesterone content is observed. Rings from Nigeria showed the greatest dispersion about the regression line (Fig. 1B), compared to rings from Senegal (Fig. 1C) and Kenya (Fig. 1D). An irrecoverable error involving incomplete progesterone extraction of n=5 Nigerian ring samples may account for lower than expected residual progesterone levels in these cases (Fig. 2B – 5 open circles plotted near the 9.0 g ring weight).

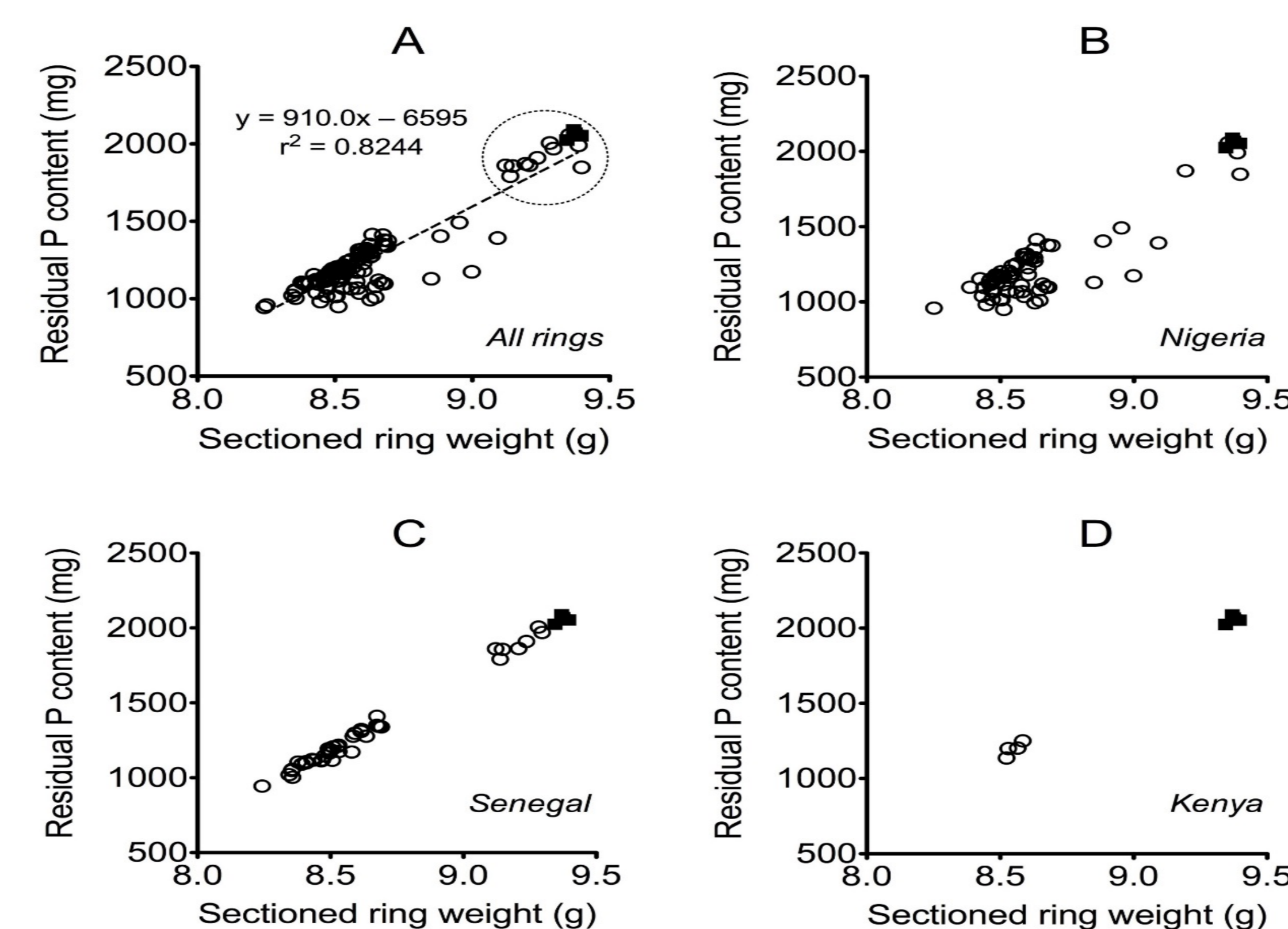


Fig. 1. Residual progesterone (P) content plotted against sectioned ring weight for rings from all study sites (A), and sites within one country, Nigeria (B), Senegal (C) and Kenya (D). Control rings (n=6, filled squares) are omitted from the regression analysis.

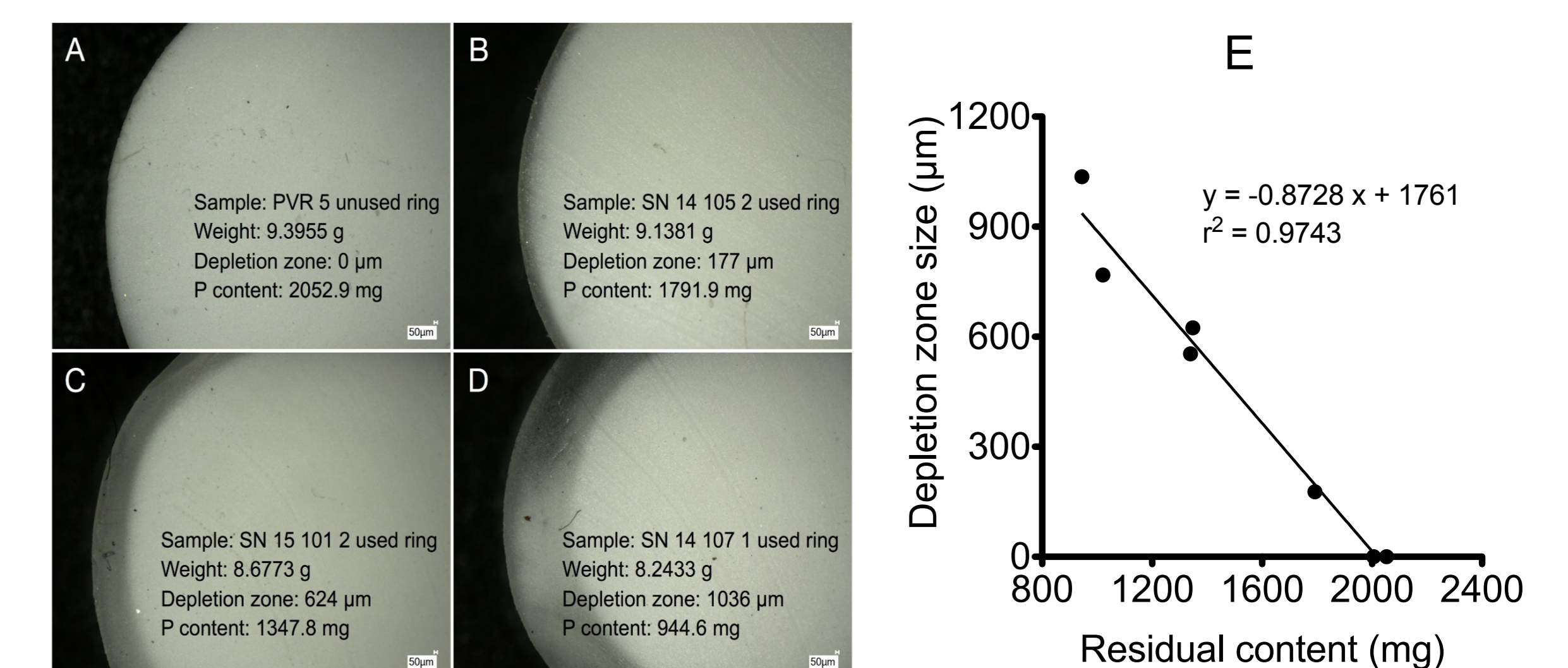


Fig. 2. Representative digital images of ring cross sections of unused A, and used, B, C and D rings ordered by size of depletion zone; E correlation of depletion zone size and residual P content.

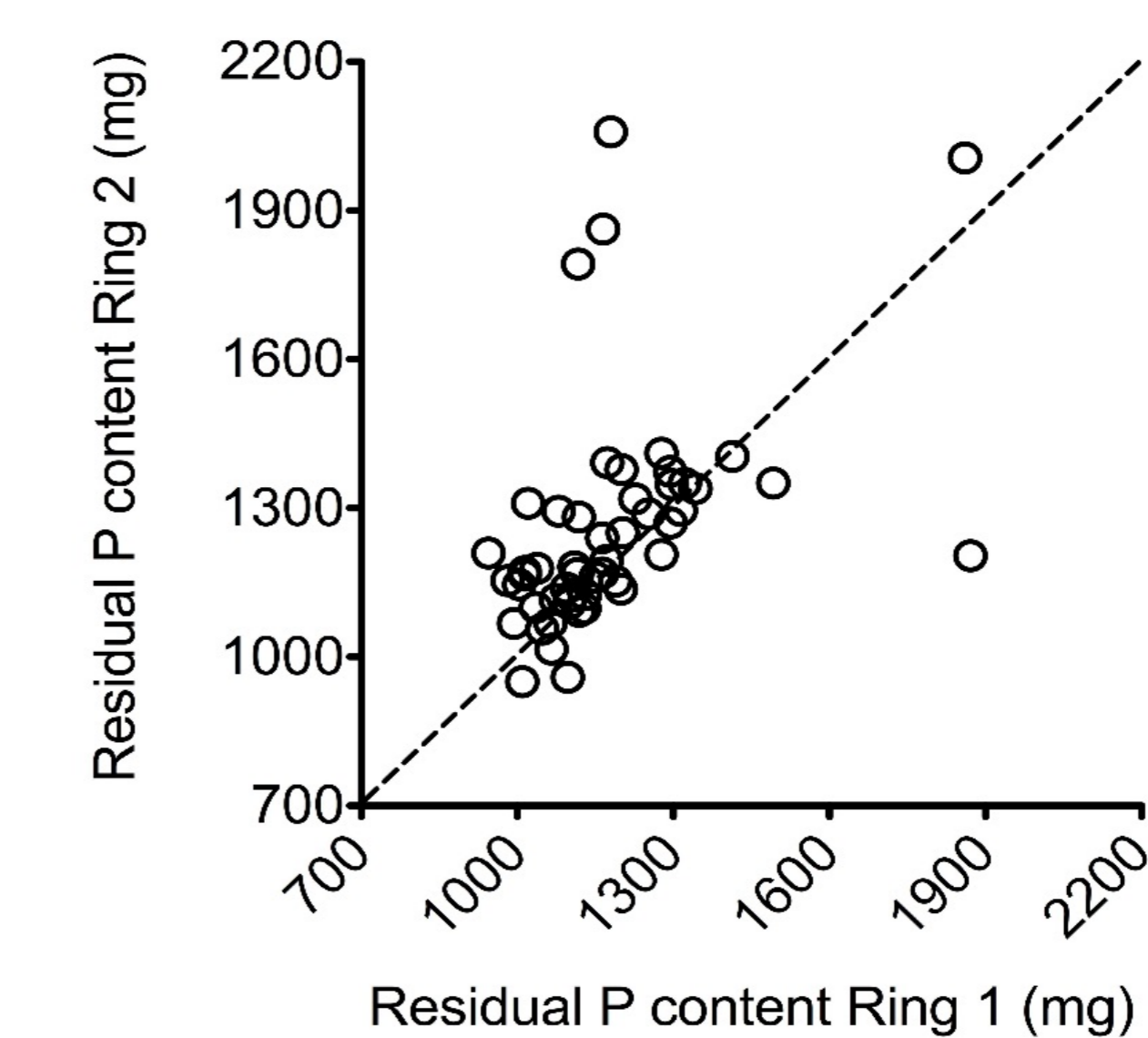


Fig. 3. Residual content for first ring use vs. residual content for the second ring use. Each plot symbol represents a single participant who used two ring devices, one after the other.

Digital photographs of representative ring cross-sections are shown in Fig. 2 A–D. A plot of the residual progesterone content against depletion zone thickness is presented in Fig. 2E, showing a strong negative correlation. 51 women in the study used two rings in succession. A plot of the residual content of the first ring versus the residual content of the second ring is displayed in Fig. 3. Here, the dashed line represents consistency of use between rings and highly adherent users are clustered in the bottom left hand quadrant of the plot. Points deviating from the line suggest discordant ring use and values closer to the top right quadrant suggest poorer adherence.