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Comparison of self-reported female condom failure and biomarker-confirmed semen exposure ☆,☆☆



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ABSTRACT

Objective: To investigate whether rates of self-reported Woman's Condom (WC) clinical failure and semen exposure from a functionality study are comparable to results from a contraceptive efficacy substudy.

Study design: We structured our comparative analysis to assess whether functionality studies might credibly supplant contraceptive efficacy studies when evaluating new female condom products. Couples not at risk of pregnancy in the functionality (breakage/slippage/invagitation/penile misdirection) study and women in the contraceptive efficacy study completed condom self-reports and collected pre-coital and post-coital vaginal samples for up to four uses of the WC. Both studies used nearly identical self-report questions and the same self-sampling procedures and laboratory for prostatic specific antigen (PSA), a well-studied semen biomarker. We compared condom failure and semen exposure proportions using generalized estimating equations methods accounting for within-couple correlation.

Results: Ninety-five (95) efficacy substudy participants used 334 WC and 408 functionality participants used 1572 WC. Based on self-report, 19.2% WC (64 condoms) clinically failed in the efficacy substudy compared to 12.3% WC (194 condoms) in the functionality study ($p=.03$). Of the 207 WC efficacy uses with evaluable post-coital PSA levels, 14.5% (30 uses) resulted in semen exposure compared to 14.2% (184 uses) of the 1293 evaluable WC functionality study uses.

Conclusions: When evaluating the ability of an experimental condom to prevent semen exposure, the rate of clinical condom failure reported by participants risking pregnancy in an efficacy substudy was significantly higher than the rate reported by participants not risking pregnancy in a functionality study. The rate of semen exposure, assessed by an objective biomarker was nearly identical for the two studies.

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Implications: Our results suggest that an objective marker of semen exposure in functionality studies could provide a reasonable alternative to contraceptive efficacy studies in evaluating risk of unintended pregnancy and inferring protection from sexually transmitted infection than condom failure rates based on self-report.

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1. Introduction

Despite the public health importance of developing a variety of female condom products to counter both unintended pregnancy and sexually transmitted infection (STI) transmission, only four female condom products are widely available in multiple markets around the world, having received WHO/UNFPA prequalification and the European Union's CE marking [1,2]. Only one of these products, the FC2, is FDA approved and available for sale in the United States. While FDA approval of a new male condom product is contingent on successful completion of a large functionality (breakage and slippage) study demonstrating non-inferiority compared to a predicate condom, a new female condom product requires a large scale contraceptive efficacy study prior to market approval [3]. The rationale for this expensive requirement, which impedes additional female condom products from becoming available in the United States. [4], stems from the variations and complexities in female condom design that can lead to failure modes other than breakage and slippage.

Regulators have laid the groundwork for female condom functionality studies by defining additional failure modes which include invagination (condom pushed into the vagina) and misdirection (condom bypassed by penis) [5]. Concerns remain about how accurately participants can discern multiple failure modes and the degree to which these failure modes reflect actual risk of unintended pregnancy or STI transmission. The incorporation of quantifiable semen exposure measurement within functionality studies is a viable response to these concerns [6–10]. Prostate specific antigen (PSA), is a reliable biomarker of semen exposure [7–20]. Studies have demonstrated the utility of collecting pre-coital and postcoital vaginal samples which can be stored at room temperature and later assayed for PSA following well-established laboratory procedures [21–23]. Comparative studies have shown that semen exposure estimates are more consistent than self-collected failure reports across different study populations [18]. Furthermore, semen exposure estimates are more directly related to the risk of STI transmission than pregnancy rates [8].

Whether a study population not at risk of pregnancy in a functionality study (breakage/slippage/invagination/penile misdirection) would be representative of a study population at risk of pregnancy in a contraceptive efficacy study requires further investigation. Functionality studies would not be an acceptable substitution for efficacy studies if participants not at risk of pregnancy experienced lower condom failure rates and/or semen exposure rates than participants at risk of pregnancy.

Close collaboration between CONRAD and the National Institute of Child and Human Development (NICHD) on their respective studies of the Woman's Condom (WC) allowed for the use of nearly identical report forms, and identical sample collection and laboratory testing procedures to estimate female condom failure rates and biomarker-confirmed semen exposure estimates based on PSA results. Our objective was to determine whether the self-reported condom failure and semen exposure rates were comparable between a functionality study and a contraceptive efficacy substudy of the WC.

2. Materials and methods

2.1. Study design

We report on two studies which evaluated the WC. The CONRAD functionality study was a randomized, open-label, crossover

study of clinical condom failure and vaginal semen exposure which compared the WC with the FC2 condom. Participating couples completed a self-report of clinical failure and collected a pre-coital vaginal swab and postcoital swabs from the vagina and condom interior after each of four condom uses of both condom types. California Family Health Council (CFHC) conducted this study in 2010–2011.

The NICHD contraceptive efficacy study was a phase III multi-center, open-label, non-comparative trial of the WC. Seven of 11 study sites (two managed by CFHC), participated in a nested substudy in which participants completed a self-report of clinical failure and collected a pre-coital vaginal swab and postcoital swabs from the vagina and condom interior after the first four uses of the WC (study conducted in 2011–2012).

Participants in both studies recorded each study condom use on a condom self-report form on which they recorded the circumstances of condom use, how the condom performed, and whether they collected swabs (Supplement Sections 6 and 7). All participants provided written informed consent in conformance with 21 CFR Part 50.25 [24]. Institutional Review Boards associated with the respective study sites approved the studies.

2.2. Study population

Participants in both the functionality and efficacy studies were sexually active, between the ages of 18 and 45, in monogamous relationships of at least 3 months, and reported themselves at low STI risk. Couples in the functionality study were required to use effective back-up contraception such as a hormonal method, IUD or sterilization to prevent pregnancy. Women in the efficacy study had no known factors impairing their fertility and depended solely on the WC to prevent pregnancy.

2.3. Study products

The WC (Shanghai Dahua Medical Apparatus, Shanghai, China) consists of a 0.03-mm-thick pliable plastic pouch that easily conforms to the shape of the vagina. It is 22.7 \pm 0.25 cm (9.0 \pm 0.1 in.) long and has a flexible soft outer ring designed to hug the external genitalia. Foam shapes on the outside of the pouch cling lightly to vaginal walls to stabilize the device. The insertion capsule made from dissolvable polyvinyl alcohol (PVA) is similar to the PVA used in C-Film (Apothecus Pharmaceutical Corporation, New York, NY). Since the WC is not pre-lubricated, participants were instructed to use only a study-provided water based personal lubricant which has been shown not to interfere with the PSA assay used in this study [25] (Supplement Section 1).

2.4. Swab collection

Participants in both the functionality study and efficacy substudy collected vaginal and condom samples using Falcon Swubes[®] (Becton Dickinson and Company) [26]. Participants collected the pre-coital vaginal swabs immediately before any genital sexual contact and the postcoital vaginal and condom swabs immediately after removal of the WC (Supplement Sections 2 and 3).

Condom report	Used as directed		
	No use of non-study method		
	No unprotected sex between collection of precoital and postcoital swabs		
Swab collection	Precoital vaginal	Postcoital vaginal	Condom
	Swab submitted	Swab submitted	Swab submitted
	No report of collection error	No report of collection error	No report of collection error
PSA result	< 5ng/ml	22ng/ml > pre-coital result	or 22ng/ml > pre-coital result

Fig. 1. Criteria for inclusion in semen exposure analysis

2.5. Laboratory procedures

The same technician at the Center for Disease Control (CDC) followed identical laboratory procedures for both studies [22,27,28] (Supplement Section 4).

2.6. Statistical analysis

The objective of this analysis is to compare the rates of self-reported clinical condom failure and lab-confirmed semen exposure among WC users in the functionality study with comparable rates among WC users in the efficacy substudy. For functionality study results to supplant efficacy study results, it is critical that condom failure and semen exposure rates from a not-at-risk functionality study population not be lower than the rates obtained from an at-risk efficacy study population. Results included in our analysis met the criteria described in Fig. 1 [8,13,29] (Supplement Section 5).

We calculated the sensitivity and specificity of self-reported condom failure in the functionality study and efficacy substudy using PSA as the reference standard since PSA is a highly sensitive marker of semen exposure and self-reported condom failure does not directly measure semen exposure [16,18] (Supplement Section 6).

The rates of self-reported condom failure (CFF) and semen exposure (SEF) in the functionality study were deemed “not appreciably lower” than the rates of self-reported condom failure (CFE) and semen exposure (SEE) in the efficacy substudy if the lower bounds of the 90% confidence interval for (CFF-CFE; SEF-SEE) were greater than -0.03 (-3%), the margin used in both the CONRAD functionality study and NICHD substudy. We used generalized estimating equations (GEE) methods to perform tests of noninferiority, accounting for within-couple correlation. Missing outcome data were assumed missing completely at random. The model used an identity link function and independence working correlation matrix. The output was a 90% confidence interval around the dif-

Table 1
Demographic characteristics and sexual/contraceptive histories of participants at enrollment in two studies of a female condom^{1, 3, 4, 5}

Characteristic	Functionality Study	Efficacy Substudy
	n(%)	n(%)
Total participants	408	95
Social/demographic/physical		
Female age (median)	25	28
Race/Ethnicity ¹		
Asian/Pacific Islander	34 (8.3)	11 (11.6)
Black	45 (11.0)	40 (42.1)
White	193 (47.3)	42 (44.2)
Hispanic	75 (18.4)	21 (22.1)
Native American	4 (1.0)	4 (4.2)
Other/Multiple	57 (14.0)	10 (10.5)
Some college or above	360 (88.2)	75 (78.9)
Not married	286 (70.1)	66 (69.5)
Current smoker	48 (11.8)	19 (20.0)
Current alcohol drinker	359 (88.0)	48 (50.5)
BMI (lb*703/in ²) (median) ²	24	27
Sexual activity/contraceptive use		
Lifetime sexual partners (median)	5	5
Used hormonal method in past 6 months	NC ³	21 (22.1) ⁴
Currently using hormonal method	270 (66.2) ⁵	NC ³
Previous experience using female condom	28 (6.9)	18 (18.9)

¹ Multiple responses allowed in Efficacy Study.

² Calculated from height and weight measures.

³ Not collected from study participants.

⁴ Includes oral contraceptives, patch, implant, vaginal ring, emergency contraception.

⁵ Includes oral contraceptives, injectables, and patch.

Table 2
Evaluable condom self-reports and swab sets in two studies of a female condom

	Functionality Study		Efficacy Substudy	
	n	%	n	%
Total condom self-reports submitted	1582		353	
<i>Disqualifications based on self-report</i>				
Used for anal intercourse	1	0.1	1	0.3
Used non-study lubricant	4	0.3	11	3.1
Not used for vaginal intercourse	0	0.0	1	0.3
Total evaluable condom self-reports	1577		340	
<i>Disqualifications based on swabs (multiple reasons possible)</i>				
Precoital vaginal swab not collected or interpretable	10	0.6	18	5.3
Postcoital vaginal swab not collected or interpretable	16	1.0	22	6.5
Postcoital condom swab not collected or interpretable	33	2.1	21	6.2
Precoital vaginal sample ≥ 5 ng/ml PSA ¹	56	3.6	34	10.0
Unprotected intercourse between collection of precoital and postcoital swabs ²	42	2.7	14	4.1
Non-study method use between collection of precoital and postcoital swabs ³	NA	NA	16	4.7
Neither vaginal nor condom postcoital sample ≥ 22 ng/ml > precoital sample ⁴	162	10.3	53	15.6
Total evaluable swab sets	1293		207	

¹ Indicative of semen exposure from previous act of intercourse.

² Swabs not disqualified if unprotected intercourse only occurred after a condom failure.

³ Swabs not disqualified if non-study method use occurred after a condom failure.

⁴ No possibility of semen exposure due to insufficient amount of semen.

ference in the semen exposure rates from the two studies. For all other comparisons, we evaluated statistical significance at $p < .05$.

3. Results

All 490 couples in the functionality study and 154 efficacy sub-study participants agreed to complete a condom self-report and collect samples in conjunction with four condom uses. Table 1 presents demographic characteristics for the 408 female functionality study participants and 95 efficacy sub-study participants who completed at least one condom self-report. Table 2 provides a breakdown of condom self-reports and swab sets used in the analysis, as well as the reasons for the exclusion of results from the analysis. The percentage of uses excluded from the analysis was higher in the efficacy sub-study than in the functionality study for all categories.

3.1. Condom functionality measures

One hundred twenty-four (32%) couples in the functionality study and 25 (35%) participants in the efficacy sub-study who contributed at least one evaluable swab set reported one or more

female condom failure modes while using the WC. Table 3 presents the frequencies of these failure modes (penile misdirection, invagination, completely slipping out of the vagina while not clinging to the penis, clinical breakage) for both studies. While none of the individual failure modes were statistically different ($p < .05$) between the two studies, the total clinical failure was significantly higher in the efficacy sub-study (19.2%) compared to the functionality study (12.3%) ($p < .03$), reflecting the cumulative effect of the higher incidence of failure reported by efficacy sub-study participants for each of the failure modes compared to functionality study participants.

3.2. Semen exposure measures

The rates of semen exposure were nearly identical for the two studies (Table 3). Likewise, quantitative PSA results for the pre-coital and postcoital vaginal samples and the sample from the interior of the used condom were similar for both studies (Table 4).

In Table 5, we compare the rate of semen exposure following a reported condom failure or performance problem for the two studies. We also include the median PSA results for condom failure modes and performance problems collected in the functionality

Table 3
Self-reported condom failure events and semen exposure in two studies of a female condom, by failure mode

Event Type	Functionality Study			Efficacy Substudy			P-Value
	Uses with reported events ⁷	% (95% CI)	Total uses ⁸	Uses with reported events ⁷	% (95% CI)	Total Uses ⁸	
Misdirection ¹	59	3.8 (2.7–4.9)	1570	19	5.7 (2.7–8.7)	333	0.23
Invagination ²	115	7.3 (5.6–9.0)	1570	37	11.0 (6.3–15.7)	336	0.15
Complete slip out ³	13	0.8 (0.4–1.3)	1577	7	2.1 (0.6–2.5)	340	0.18
Clinical breakage ⁴	40	2.5 (1.6–3.5)	1577	11	3.2 (1.1–5.4)	339	0.55
Total clinical failure ⁵	194	12.3 (10.3–14.4)	1572	64	19.2 (13.3–25.0)	334	0.03
Semen exposure ⁶	184	14.2 (11.7–16.7)	1293	30	14.5 (8.4–20.6)	207	NS ⁹

¹ Penis was inserted between condom and the vagina.

² Open end of the condom was pushed completely into the vagina.

³ Slipped completely out of vagina during intercourse while NOT clinging to the penis.

⁴ Broke during vaginal intercourse or removal of the condom from the vagina.

⁵ Includes penile misdirection, complete invagination, complete slip out while not clinging to penis or clinical break.

⁶ Difference between pre-coital and postcoital vaginal PSA result ≥ 22 ng/ml.

⁷ Event occurred one or more times.

⁸ Excludes uses where event occurrence is unknown due to missing data.

⁹ Not statistically significant: $p > .05$.

Table 4
PSA results in two studies of a female condom, by swab source

Swab Source	n	Functionality Study					n	Efficacy Substudy				
		<1 ng/ml	1–4 ng/ml	5–22 ng/ml	23–99 ng/ml	≥100 ng/ml		<1 ng/ml	1–4 ng/ml	5–22 ng/ml	23–99 ng/ml	≥100 ng/ml
		%	%	%	%	%		%	%	%	%	%
Precoital vaginal	1293	98	2	—	—	—	207	94	6	—	—	—
Postcoital vaginal	1293	75	7	4	4	10	207	63	15	8	4	10
Postcoital condom	1287	2	1	1	2	95	207	1	0	0	4	94

study but not the efficacy substudy. Clinical breakage resulted in the highest rate of semen exposure among the failure modes (76%) and the second highest median PSA result (5225 ng/ml). Penile misdirection had the second highest probability of semen exposure (32%) and the highest median PSA result (8175 ng/ml), followed by invagination (29%) with a lower PSA result (2648 ng/ml). Surprisingly, slipping out of the vagina while clinging to the penis, which is *not* defined as a failure mode, was much more likely to result in semen exposure (17%) than slipping out of the vagina while *not* clinging to the penis (0%), which is defined as a failure mode [5]. Slipping out of the vagina while clinging to the penis also resulted in a median PSA result of 4691 ng/ml, comparable to PSA results of clinical breakage (5225 ng/ml).

3.3. Sensitivity and specificity of self-reported clinical failure using PSA level as the reference standard

Since the PSA is a highly sensitive marker of semen exposure and measures semen exposure directly, we used PSA as the reference standard for calculating the sensitivity and specificity of self-reported condom failure as an indicator of semen exposure. The sensitivity is the probability that a condom failure would be self-reported when the PSA level indicated semen exposure and the specificity is the probability that a condom failure was not self-reported (when the PSA level actually did not indicate semen exposure). Thus, the sensitivity and specificity estimates presented

in [Table 6](#) quantify the loss of information about semen exposure when relying on self-reports of condom failure.

While the specificity of failure self-reports was high in both studies (93% functionality, 85% efficacy), the sensitivity was low, especially in the efficacy study (45% functionality, 23% efficacy). The sensitivity and specificity of condom self-reports were consistently higher in the functionality study than in the efficacy substudy.

3.4. Rates of self-reported clinical failure and semen exposure

The rate of clinical condom failure based on self-report was considerably lower in the functionality study (12.3%) than in the efficacy substudy (19.2%) ([Table 7](#)). The two studies' semen exposure rates based on uses that met all evaluable criteria were nearly identical (14.2% functionality, 14.5% efficacy substudy). We did not have the statistical power to show that semen exposure in the functionality study was not appreciably lower than in the efficacy substudy.

4. Discussion

We found that the rate of self-reported clinical condom failure was significantly higher (19.2%) in the efficacy substudy compared to the functionality study (12.3%) which may reflect the difference

Table 5
Self-reported condom failure events and corresponding percent (%) semen exposure in two studies of a female condom

	Functionality Study (n=1289)			Efficacy Substudy (n=205)		Total (n=1494)	
	Self-reported events n	Semen exposure		Self-reported events n	Semen exposure % (+) ≥22 ng/ml ⁸	Self-reported events n	Semen exposure % (+) ≥22 ng/ml ⁸
		% (+) ≥22 ng/ml ⁸	Median (+) PSA (ng/ml) ⁹				
No clinical failures reported	1135	9	232	171	13	1306	9
Clinical breakage ¹	17	82	5225	4	50	21	76
Misdirection ²	15	40	8175	4	0	19	32
Invagination ³	54	31	2648	12	17	66	29
Slipped out while not clinging to penis ⁴	3	0	—	3	0	6	0
Slipped out while clinging to penis ⁵	29	14	4691	7	29	36	17
Slipped out during withdrawal ⁶	85	4	67	13	8	98	4
Total clinical failure⁷	154	53	3243	34	21	188	47

Serial dilutions on swabs >100 ng/ml were not performed in the Efficacy substudy.

¹ Broke during vaginal intercourse or withdrawal of the condom, no other functionality problem reported.

² Penis was inserted between condom and the vagina at least once, no other functionality problem reported.

³ Open end of the condom was pushed completely into the vagina at least once, no other functionality problem reported.

⁴ Slipped completely out of vagina while not clinging to the penis during intercourse at least once, no other functionality problem reported.

⁵ Slipped completely out of vagina while clinging to the penis during intercourse at least once, no other functionality problem reported (not a failure mode).

⁶ Slipped completely out of vagina during withdrawal of the penis at least once, no other functionality problem reported (not a failure mode).

⁷ One or more of the following reported: clinical breakage, penile misdirection, complete invagination, or slipped completely out of vagina while not clinging to the penis during intercourse; use not included in clinical failure estimate if information on any of the failure modes was missing.

⁸ Difference between precoital and postcoital vaginal PSA result; percentage based on self-reported events within category.

Table 6
Sensitivity and specificity of self-reported condom clinical failure using semen exposure as the reference standard in two studies of a female condom

		Functionality Study	Efficacy Substudy
A	Uses with self-reported clinical failure ¹	154	34
B	Uses with semen exposure ²	182	30
C	Uses with both self-reported clinical failure and semen exposure	81	7
C/B	Sensitivity	45%	23%
	95% confidence interval	(36–53%)	(7–40%)
D	Uses with no self-reported clinical failure	1135	171
E	Uses with no semen exposure	1107	175
F	Uses without either self-reported clinical failure or semen exposure	1034	148
F/E	Specificity	93%	85%
	95% confidence interval	(92–95%)	(77–92%)

¹ One or more of the following was reported: condom breakage, penile misdirection, complete invagination, slipped completely out of vagina during intercourse while not clinging to the penis.

² Either the condom swab PSA result or postcoital vaginal PSA result was 22 ng/ml greater than the precoital vaginal PSA result.

in the risk status of the participants by study. While participants in the efficacy study were at risk of pregnancy if the WC failed, we required participants in the functionality study to use an effective back-up method of birth control (hormonal, IUD, sterilization). This difference may have led to differences in how much care participants exercised in using condoms, as well as their attentiveness to functionality problems, acceptability of female condom use, and motivation to use the condom throughout any entire act of intercourse. These factors may have contributed to the shorter length of intercourse reported in the functionality study (13.2 min vs. 17.7 min for the efficacy substudy) and the increased propensity of functionality study participants to remove the condom before ending intercourse (8.7% functionality, 5.2% efficacy).

In contrast, the semen exposure rates for the two studies were almost identical (14.2% functionality, 14.5% efficacy). Previous studies have also found greater agreement between semen exposure rates than between self-reported condom failure rates. Functionality studies of the female condom which shared common protocols and procedures conducted in Brazil and Alabama, found very similar PSA postcoital levels (19% >1 ng/ml PSA Brazil, 17% >1 ng/ml PSA Alabama) but dissimilar self-reported clinical failure rates (5% Brazil, 29% Alabama) [18]. These findings strongly suggest that semen exposure might be a more consistent and objective measure of condom functionality than self-reported condom failure which relies on the ability of participants to interpret failure events during intercourse.

The low sensitivity of self-reported clinical failure (45% functionality study, 23% efficacy study) is explained by the poor correspondence between some of the clinical failure modes and semen exposure. For example, while 82% of the clinical breakages in the

functionality study and 50% of the clinical breakages in the efficacy substudy resulted in semen exposure, none of the condoms that slipped completely out of the vagina while not clinging to penis resulted in semen exposure in either study. The sensitivity of reported condom failure in the efficacy substudy was further reduced because slipping out of the vagina while clinging to the penis, resulting in semen exposure on 17% of the 36 occasions in which it was reported in the efficacy substudy, is not defined as a standard female condom failure mode [5]. Ironically, slipping out of the vagina while not clinging to the penis, which is defined as a failure mode, did not result in any semen exposure, possibly reflecting the difficulties condom users encounter detecting failure modes during intercourse. Alternatively, these results may suggest that the set of functionality problems currently defined as standard condom failure modes for female condoms merit reevaluation based on semen exposure results.

The identical study procedures and nearly identical data collection instruments used by the CONRAD functionality study and the NICHD efficacy substudy allowed us to test the feasibility of condom evaluation strategies applied to different study designs and study populations. Participants in both studies submitted swabs for a very high percentage of their reported condom uses (98% functionality, 94% efficacy). The demographic diversity of the substudy population suggests that self-collection of swabs may be feasible in various study populations.

An inherent limitation to any study based on self-reported outcomes and self-collected swabs is that the investigator cannot verify the authenticity of the data. Although our analysis includes only condom uses in which at least one of the postcoital samples was >22 ng PSA, there was no way to distinguish swabs that had been collected poorly or not at all. In a crossover functionality study randomized to order of condom use, deficient swabs evenly distributed between the different condom types would mitigate this limitation.

Another notable limitation to this comparative analysis involves the limited number of evaluable samples from the efficacy substudy. First, only 156 of the 380 participants consented to the efficacy substudy sites. Second, only 95 of the 156 consented participants ended up contributing condom self-reports with their swab sets. A substantial number of the non-contributors (34 participants) never used or reported any WC use, an indicator that WC acceptability was an issue for some participants. Furthermore, compliance with swab collection instructions was lower in the efficacy substudy than in the functionality study leading to a lower proportion of evaluable WC uses in the efficacy substudy than in the functionality study (82% functionality, 61% efficacy substudy). This was due to a variety of factors including a lower rate of swab collection, a higher incidence of precoital vaginal samples with PSA \geq 5 ng/ml, more frequent unprotected intercourse between collection of precoital and postcoital swabs and use of non-study methods. Motivational factors may account for some of these

Table 7
Test of non-inferiority ($\alpha=0.05^1$) for the probabilities of semen exposure and self-reported clinical condom failure²

Probability	Functionality Study			Efficacy Substudy			Estimate Difference	Lower bound for two-sided 90% CI	Reject Ho ³
	Uses	Events	%	Uses	Events	%			
Clinical condom failure ⁴	1572	194	12.3	334	64	19.2	–6.8	–12.0	No
Semen exposure (evaluable uses) ⁵	1293	184	14.2	207	30	14.5	–0.3	–5.78	No
Semen exposure (all uses) ⁶	1553	229	14.7	318	37	11.6	3.1	–1.24	Yes

¹ Based on the lower bound of the two-sided 90% confidence interval (CI).

² SAS GENMOD procedure, controlling for within-couple correlation and self-reported ejaculation.

³ The null hypothesis of inferiority is rejected if the lower bound of the two-sided 90% CI for delta >–3.00.

⁴ Includes penile misdirection, invagination, complete slip out while not clinging to penis or clinical break.

⁵ Difference between precoital and postcoital vaginal PSA result \geq 22 ng/ml.

⁶ Difference between precoital and postcoital vaginal PSA result \geq 22 ng/ml; includes all uses with interpretable precoital and postcoital vaginal swabs.

differences; functionality study participants agreed to test mechanical properties of a limited number of study condoms over several weeks while efficacy study participants assented to using study condoms for months.

Although we lacked statistical power due to the small sample size of the efficacy substudy, our results suggest that while participants in a functionality study are much less likely to self-report condom failure than participants in an efficacy study, the rates of objectively measured semen exposure are very similar for both study populations. Our results support the premise that functionality studies that measure semen exposure using PSA as a biomarker can provide a reasonable alternative to contraceptive efficacy studies in evaluating the contraceptive effectiveness of female condoms. In addition, since it is not feasible to directly evaluate the prevention of the transmission of STIs in clinical trials, semen exposure estimates in functionality studies may provide a better inference of STI protection.

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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.2019.07.143>.

References

- [1] United Nations Population Fund UNFPA prequalified female condom products (in alphabetical order) <http://www.unfpaprocedure.org/documents/10157/37547/UNFPA+Female+Condom+Prequalification+List/05feba45-4893-474a-81d4-7b61e4f68ae7>; 2019 [accessed 5 May 2019].
- [2] Forbes A. Promoting global access to female condoms. Our bodies ourselves, <https://www.ourbodiesourselves.org/book-excerpts/health-article/promoting-global-access-to-female-condoms/>; 2014 [accessed 5 May 2019].
- [3] US Food and Drug Administration Obstetrical and Gynecological Devices. Reclassification of single-use female condom, to be renamed single-use internal condom. Final Order Federal Register 2018; 83(188):48711–48713 (2018-09-27).
- [4] Kosova E. The power of protection: Why the FDA's policy on female condoms matters. National Women's health network, <https://nwhn.org/power-protection-fdas-policy-female-condoms-matters/>; 2018 [accessed 5 May 2019].
- [5] Beksinska M, Joanis C, Manning J, Smit J, Callahan M, Deperthes B, et al. Standardized definitions of failure modes for female condoms. *Contraception* 2007;75:251–5.
- [6] Lawson ML, Macaluso M, Bloom A, Hortin G, Hammond KR, Blackwell R. Objective markers of condom failure. *Sex Transm Dis* 1998;25:427–32.
- [7] Macaluso M, Lawson L, Akers R, Valappil T, Hammond K, Blackwell R, et al. Prostate-specific antigen in vaginal fluid as a biologic marker of condom failure. *Contraception* 1999;59:195–201.
- [8] Mauck CK, Doncel GF. Biomarkers of semen exposure clinical working group. Biomarkers of semen in the vagina: applications in clinical trials of contraception and prevention of sexually transmitted pathogens including HIV. *Contraception* 2007;75:407–19.
- [9] Mauck CK, Weaver MA, Schwartz JL, Walsh T, Joanis C. Critical next steps for female condom research-report from a workshop. *Contraception* 2009;79:339–44.
- [10] Snead MC, Black CM, Kourtis AP. The use of biomarkers of semen exposure in sexual and reproductive health studies. *J Womens Health (Larchmt)* 2014;23(10):787–91.
- [11] Walsh TL, Freziers RG, Nelson AL, Wrxall BG, Clark VA. Evaluation of prostate-specific antigen as a quantifiable indicator of condom failure in clinical trials. *Contraception* 1999;60:289–98.
- [12] Lawson ML, Macaluso M, Duerr A, Hortin G, Hammond KR, Blackwell R, et al. Partner characteristics, intensity of the intercourse, and semen exposure during use of the female condom. *Am J Epidemiol* 2003;157:282–8.
- [13] Macaluso M, Lawson ML, Hortin G, Duerr A, Hammond KR, Blackwell R, et al. Efficacy of the female condom as a barrier to semen during intercourse. *Am J Epidemiol* 2003;157:289–97.
- [14] Walsh TL, Freziers RG, Peacock K, Nelson AL, Clark VA, Bernstein L, et al. Use of prostate-specific antigen (PSA) to measure semen exposure resulting from male condom failures: implications for contraceptive efficacy and the prevention of sexually transmitted disease. *Contraception* 2003;67:139–50.
- [15] Galvao LW, Oliveira LC, Jua D, Dj Kim, Marchi N, van Dam J, et al. Effectiveness of female and male condoms in preventing exposure to semen during vaginal intercourse: a randomized trial. *Contraception* 2005;71:130–6.
- [16] Walsh T, Warner L, Macaluso M, Freziers R, Snead M, Wrxall B. Prostate-specific antigen as a biomarker of condom failure: comparison of three laboratory assays and self-reported condom use problems in a randomized trial of female condom performance. *Contraception* 2012;86(1):55–61.
- [17] Gallo MF, Behets FM, Steiner MJ, Hobbs MM, Hoke TH, Van Damme K, et al. Prostate-specific antigen to ascertain reliability of self-reported coital exposure to semen. *Sex Transm Dis* 2006;33:476–9.
- [18] Chen MP, Macaluso M, Blackwell R, Galvao L, Kulczycki A, Diaz J, et al. Self-reported mechanical problems during condom use and semen exposure. Comparison of two randomized trials in the United States of America and Brazil. *Sex Transm Dis* 2007;34:557–62.
- [19] Jamshidi R, Penman-Aguilar A, Wiener J, Gallo MF, Zenilman JM, Melendez JH, et al. Detection of two biological markers of intercourse: prostate-specific antigen and Y-chromosomal DNA. *Contraception* 2013;88(6):749–57.
- [20] Kulczycki A, Brill I, Snead MC, Macaluso M. Prostate-specific antigen concentration in vaginal fluid after exposure to semen. *Contraception* 2017;96(5):336–43.
- [21] Carey RN, Frye RM, Cook JD, Koch TR, Harris EK. Between-lot/between-instrument variations of the Abbott imx method for prostate-specific antigen. *Clin Chem* 1992;38:2341–3.
- [22] Kort SA, Martens F, Vanpoucke H, van Duijnhoven HL, Blankenstein MA, Kort SAR, et al. Comparison of 6 automated assays for total and free prostate-specific antigen with special reference to their reactivity toward the WHO 96/670 reference preparation. *Clin Chem* 2006 Aug;52(8):1568–74.
- [23] Bahamondes L, Diaz J, Marchi NM, Castro S, Villarroel M, Macaluso M, et al. Prostate-specific antigen in vaginal fluid after exposure to known amounts of semen and after condom use: comparison of self-collected and nurse-collected samples. *Hum Reprod* 2008;23:2444–51.
- [24] United States Food & Drug Administration. CFR – Code of Federal Regulations Title 21, Part 50.25, 2018. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=50.25> (accessed 10 June 2019).
- [25] Snead MC, Melendez JH, Kourtis AP, Chaney DM, Brown TM, Black CM, et al. Effect of lubricants and a vaginal spermicide gel on the detection of prostate specific antigen, a biomarker of semen exposure, using a quantitative (Abbott ARCHITECT) assay. *Contraception* 2014;89(2):134–8.39.
- [26] Becton Dickinson and Company. BD Falcon SWUBE – Single Swab Sterile (cited 2009 FNovember 9); Available from <http://www.bd.com/ds/productcenter/220210.asp>
- [27] Abbott Diagnostics. ARCHITECT i2000SR (cited 2009 November 9); Available from: <http://www.abbottdiagnostics.com/products/instruments/byplatform/default.cfm?system=architect&suffix=i2000sr®-us>
- [28] Slev PR, La'ulu SL, Roberts WL. Intermethod differences in results for total PSA, free PSA, and percentage of free PSA. *Am J Clin Pathol* 2008 Jun;129(6):952–8.
- [29] Macaluso M, Blackwell R, Jamieson DJ, Kulczycki A, Chen MP, Akers R, et al. Efficacy of the male latex condom and of the female polyurethane condom as barriers to semen during intercourse: a randomized clinical trial. *Am J Epidemiol* 2007;166:88–96.