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A prospective study of couples who use the female condom: Occurrence and determinants of condom failure during use.

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A PROSPECTIVE STUDY OF COUPLES WHO USE THE FEMALE CONDOM: OCCURRENCE AND DETERMINANTS OF CONDOM FAILURE DURING USE

by

MONA LOUISE LAWSON

A DISSERTATION

Submitted to the graduate faculty of the University of Alabama at Birmingham, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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ABSTRACT OF DISSERTATION
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Title A Prospective Study of Couples Who Use the Female Condom: Occurrence and Determinants of Condom Failure During Use

In this follow-up study of female condom users, information was collected prospectively through a form filled out at the time of intercourse and returned with each used condom and coital logs completed daily by the participants. Objective assessment of condom failure was based on the inspection and water testing of the used condom and on a biomarker (prostate specific antigen) of the presence of semen in the vagina following condom use. Participants were trained to use the female condom, to compile a detailed coital log, to collect pre- and postcoital vaginal swabs, and to package and return swabs and used condoms to the project staff.

During the study, 2232 female condoms were used. Breakage was rare (<1%), while slippage occurred in 13% of uses. Breakage and slippage were associated with discontinuing use of the condom and with semen exposure. The upper boundary of semen exposure during use of the condom was 7% and the lower boundary was 21%. Semen exposure was related to intensity of the intercourse, diaphragm size, penis size, and the interaction of the two, as well as to certain attitudes about the condom at the beginning of the study and to the lifetime number of partners.

While the female condom may provide an option to women who cannot or will not use the male condom, problems with the device during use are common and are related both to discontinuing use of the product and to exposure to semen. In addition, anatomical characteristics of the couple and high-intensity intercourse may interfere with the efficacy of this barrier method. Couples who use or are considering adopting the female condom should be advised of these potential drawbacks. This study demonstrates that rigorous evaluation methods can be employed in phase II studies of condom efficacy. Similar studies need to be carried out to fully evaluate the male latex condom and other condoms made of new materials.

ACKNOWLEDGEMENTS

This study was funded by the Centers for Disease Control and Prevention Cooperative Agreement (U48/CCU409679-02) "Special Interest Project No. 10: Women of Reproductive Age - Female Controlled Methods of Contraception" and by the Association of Schools of Public Health/CDC/ATSDR Cooperative Agreement Year 16 (S490-16/16) "A Study of Mechanical Failure of the Female Condom."

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INTRODUCTION

Barrier methods of contraception, especially condoms, are effective in reducing the transmission of microorganisms during sexual intercourse. Regular use of condoms, in particular, is associated with reduced incidence of human immunodeficiency virus infections (HIV), gonorrhea, mycoplasma, chlamydia, trichomoniasis, hepatitis, cytomegalovirus, and herpes.[1-6] The development and promotion of effective barrier contraceptive methods directly under a woman's control is a public health concern of the highest priority. A potentially effective female controlled barrier method, the Reality female condom, has recently been developed and marketed.

The Female Condom

The female condom is an intravaginal barrier device. It consists of a soft, loose-fitting polyurethane sheath with two flexible rings. When the device is properly inserted, the inner ring rests between the posterior fornix and the posterior aspect of the symphysis pubis, while the external ring and approximately one inch of the sheath remains outside the vagina, partially covering the labia and base of the penis during intercourse. The limited information available suggests that the female condom may provide a viable alternative to the male condom for preventing unintended pregnancy and sexually transmitted diseases (STD).

A 6-month follow-up study of 377 women attending family planning clinics in the United States (US), Mexico, and the Dominican Republic evaluated the contraceptive efficacy of the female condom. The gross 6-month failure rate was 15%. Failure was lower among US women (12%) and among women who reported perfect (ie, correct and consistent) use of the device (4%). Although the study group consisted of women who were engaged in mutually monogamous relationships and who had agreed to use the female condom as their primary contraceptive device, only 36% reported perfect use.[7]

Comparison of the contraceptive efficacy of the male condom with that of the female condom is difficult because no large scale trial data are available on the male condom,[8] and the only large scale follow-up study of the male condom is based on a cohort of adult, married women who were selected for having successfully used contraception.[9] Thus, it is possible that differences in ability to use contraception successfully, fecundity, and frequency of intercourse account for the apparently higher failure rates observed among users of the female condom. The failure rates of US women who used the female condom perfectly are close to the lowest expected failure rates reported for the male condom.

An *in vitro* study with mechanical simulation of coitus showed no leakage of cytomegalovirus or of HIV through the polyurethane membrane of the female condom.[10] Preliminary studies of the acceptability and reliability of the female condom suggested that fluid leakage after intercourse is considerably lower than for the male condom.[11] A prospective study of 126 women treated for trichomoniasis showed that, among the 104 women who completed a 45-day follow-up period, no reinfection occurred among 20 women who used the female condom all the time, 7 reinfections occurred among 50

women who did not use the device, and 5 reinfections occurred among 34 women who used it inconsistently.[12] A report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) suggests that Thai prostitutes given both the male and female condom developed 1/3 fewer STDs than women given only the male condom.[13] Whether the increased protection was due to use of the female condom or increased use of the male condom was not clear. In an ongoing study of the female condom in STD clinic patients in Alabama, mixed use of the male and female condom is common.[14]

If these preliminary findings about the characteristics of the female condom are confirmed, and if consistent and correct use of the device can be achieved by a large number of women, this device could prove as effective as the male condom in preventing STD. Alternatively, the female condom may prove a useful complement to the male condom by facilitating better overall rates of protected intercourse.

Breakage and Slippage of Condoms

A valid and precise assessment of breakage and slippage rates of the female condom must be an integral part of a comprehensive research effort to evaluate the acceptability and efficacy of the device. Mechanical failure of a condom can lead to exposure of the vaginal mucosa to semen ("spillage"). Spillage may be due to specific forms of mechanical failure such as a breach in the condom sheath ("breakage") or displacement of the sheath ("slippage"). Trussel et al have suggested that breakage should be further divided into clinical and nonclinical breakage, the latter being breakage that occurs before use and results in the use of a replacement condom.[15]

Methods for Assessing Condom Failure

Standard methodology exists to evaluate the physical strength and permeability of latex condoms *in vitro*. Typical tests of condom quality include the water leakage test, air burst tests, and tests of tensile properties, which are usually done by the manufacturer for quality assurance.[16] In the water leakage test, a condom is filled with 300 ml of water and examined for obvious water leakage. Recent studies updated this method by testing for leakage of viruses or virus-sized particles from condoms during simulated coitus.[1,2,4,5,17] One study found leakage of virus-sized particles in some condoms but found no pores large enough for the condoms to have failed the water leakage test.[17]

While the newer *in vitro* studies provide useful information, evaluation of spillage during actual human use is necessary to assess the efficacy of condoms as barriers to STD. Only recently has research begun to focus on methods to evaluate condom breakage and slippage during use. No standard methodology is yet in place, and the design of early studies in this field has been fraught with limitations. Some studies have attempted to estimate condom slippage and breakage rates from coital logs or interviews.[18-24] While this method can be effective in assessing slippage rates in a prospective follow-up design, the possibility of unnoticed breakage resulting in exposure to both semen and microorganisms may lead to an underestimation of breakage and the overall failure rate. One study which evaluated both the male and female condom examined used condoms for breakage using the 300 ml water leakage test.[11] Although this is an improvement on studies relying entirely on self-report, the water leakage test may not detect small increases in permeability which are sufficient for the transmission of microorganisms. A recent article proposes a series of recommendations for the design and conduct of a slip-

page/breakage study.[15] Unfortunately, the recommendations are insufficient to specify the design of a rigorous study, in particular because they do not identify the need for an objective and accurate measure of semen leakage.

One purpose of the research described in this dissertation was to develop and test a valid study design for the assessment of condom leakage and breakage *in vivo*, specifically addressing mechanical failure of the female condom. In this prospective follow-up study, used condoms, vaginal samples, and a form describing problems with the condom were returned after each condom use. This data was augmented by prospectively completed coital logs that were turned in at follow-up visits. Objective assessment of condom failure was based on inspection and water testing of the used condom and on laboratory assays to evaluate semen spillage during condom use.

Biomarkers of semen spillage. Objective measurement of mechanical failure must be based on laboratory assays that evaluate semen spillage during condom use. A variety of assays are used in forensic medicine to test for semen exposure. These include, among others, the microscopic examination of vaginal fluid specimens to detect spermatozoa, biochemical assays to measure the enzymatic activity of acid phosphatase (AP),[25,26] and immunologic assays to detect prostate specific antigen (PSA, also known as P-30),[25,27] and the human seminal plasma antigen MHS-5.[28,29] Although the presence of sperm confirms semen exposure, the test has several limitations, and the false negative rate is high. Furthermore, spermatozoa are much larger than the organisms which cause STD, and sperm detection may underestimate the rate of condom failure with respect to STD risk.[30] In addition, spermatozoa are not stable in samples, are an insensitive predictor of small

amounts of exposure, and give false negative results in infertile men. Other assays for detecting semen exposure have been proposed, including zinc measurement and tests for semen-specific prostaglandins. Zinc is a controversial marker and is not specific enough for our purposes.[31,32] Tests for semen-specific prostaglandins appear promising, but the actual assays are new and need further development.[33,34]

An alternative semen marker, MHS-5, has recently been employed for detection of semen in cases of suspected rape.[28,29] A study in which semen specimens were serially diluted in centrifuged cervicovaginal lavage (CVL) specimens reported that this assay detected semen in dilutions of 1 to 2 million.[29] Due to the high sensitivity of the assay in CVL specimens and the low cost of the assay, the SEMA assay for MHS-5 (Humagen Fertility Diagnostics, Charlottesville, VA, USA) was evaluated as a semen marker for use in this study.

AP occurs in many tissues, with the highest concentrations occurring in the prostate. Because of the wide tissue distribution of AP, the biochemical assessment of its enzymatic activity may be a relatively nonspecific test of semen exposure, although some assays are selective for the activity of the prostatic isosyme. [35] Nevertheless, AP activity is a commonly used biochemical marker for semen exposure in forensic analysis.[27,36] Levels of AP in the vagina have been shown to be high in the vagina for periods of up to 4 days after intercourse.[36] However, AP is present in low levels in vaginal secretions, and the distribution of levels varies widely among women and within individuals.[36] Consequently, this marker may be unsuitable for detecting small semen leaks from condoms. In spite of this, the ACA assay for AP activity (The Dupont Company, Wilmington, DE, USA) was evaluated as a potential semen marker in this study.

Another common forensic marker of semen exposure is PSA. PSA is specific to human semen and concentrations of 0.3-0.4 mg/ml are present in semen regardless of fertility.[26,27,37] PSA can be detected in dilutions up to 1 ng/ml.[38,39] Previous studies indicate that PSA can be detected in dried semen after several years.[39,40] Because PSA has been widely used as a prognostic marker for prostate cancer patients, commercial assays are commonly available in hospital laboratories. The IMx immunoassay for PSA (Abbott Laboratories, Abbott Park, IL, USA), which has been proven to be an accurate clinical assay for serum levels of PSA, was evaluated for use in this study.[41]

Sampling protocol. In addition to the identification of the optimal biological marker for semen, a good vaginal self-sampling protocol is indispensable to accurately identify condom failure. A vaginal self-sampling device is desirable for obtaining pre- and postcoital vaginal samples without a clinical exam. Such a device should be safe, easy for women to use, protected from contamination, appropriate for multiple assays, and inexpensive. Also, it is important that the sample be protected from any contamination by semen on the woman's hands or external genitalia which could result in false positives. Because semen markers could be present in the vagina for some time after unprotected intercourse, it is also necessary that precoital samples be taken for comparison. This means that the self-sampling device will be inserted into a relatively dry vagina to obtain precoital samples.

Tampons were considered inappropriate for precoital vaginal self-sampling because inserting a tampon into a dry vagina is uncomfortable and potentially damaging to the vaginal mucosa. In addition, all of the proposed semen detection assays required that

the samples should be dried shortly after collection. Tampons are not suitable for a fast drying process. Furthermore, the risk of contaminating a tampon with semen from hands or external genitalia during removal from the vagina is higher than the risk of contaminating a swab. The variety of materials in commercially available tampons also increases the risk of cross-reactivity with a semen detection assay, making the tampon a poor choice as a standard sampling device. Finally, the large amount of fluid required to elute samples from a tampon could lead to excessive dilution of the sample and could decrease the sensitivity of many assays.

A gynecological swab protected by a cardboard tampon tube was developed as a vaginal self-sampling device for this study. Gynecologic swabs are smaller than tampons and are inserted into a dry vagina without difficulty. Self-administered swabs have been used for semen detection in the past[27] and are appropriate for assays requiring both wet and dry preparations. Preliminary studies with the self-administered vaginal swabs indicate that they are easy for women to use and cause little or no discomfort upon insertion.

Preliminary Results

Two female condoms were tested for permeability to small molecules. One was filled with a solution of glucose (diameter of 7.2 Å) and the other was filled with a solution of urea (diameter of 3.2 Å). Both were placed in .9% saline solution and left overnight. Samples were taken from the saline solution outside the condom and assayed for urea and glucose. The condoms showed no measurable leakage of water and virtually no permeability to urea and glucose. The amount of exchange across the membrane was below the limit of detection for both chemicals (1 part in 10,000 for glucose and 1 part in

1000 for urea). In addition, each female condom is tested by the manufacturer for helium leakage prior to shipment. Based on this information, the intact female condom was considered to be impermeable to small molecules, and any detection of semen marker molecules (eg. PSA, AP, or seminal antibodies) after correct use of a female condom was considered to be due to either mechanical failure of the condom or previous semen exposure.

The stability of PSA in dried swabs was tested by placing measured amounts of semen on swabs and leaving them for up to 2 weeks. After 2 weeks, PSA was detectable even when the semen amount placed on the swab was as low as 25 nl. Thus, PSA appears to be stable in dry swabs.

Study Objectives

The main objective of this study was to assess the usefulness and safety of the female condom as a barrier to sperm and sexually transmitted microorganisms.

The specific aims of the study were (1) to develop a method for *in vivo* assessment of exposure of the vaginal mucosa to semen ("spillage") due to mechanical failure of the female condom; (2) to measure the frequency of semen spillage with use of the female condom and assess the extent to which any exposure to semen is due to specific forms of mechanical failure, such as a breach in the condom sheath (breakage) or displacement of the sheath (slippage); and (3) to evaluate possible determinants of condom failure.

Three papers are presented in this dissertation to address the specific aims: "Objective Markers of Condom Failure" (Specific Aim 1), "A Prospective Study of Couples Who Use the Female Condom. Occurrence of Self-Reported Problems and Semen Expo-

sure During Use" (Specific Aim 2), and "Determinants of Semen Exposure During Use of the Female Condom" (Specific Aim 3). In addition, the paper "Determinants of Use of the Reality Female Condom" provides information about how user reported problems with the condom may affect continued use.

Study Design

This was a prospective study of couples who agreed to use the female condom. The study protocol, informed consent, and data collection forms were approved yearly by the UAB Institutional Review Board (Appendix). Women attending family planning clinics at the UAB Department of Reproductive Biology and at Planned Parenthood of Alabama, Inc. and volunteers responding to local advertising were screened for participation in the study. Eligible subjects who were willing to try the female condom participated in a training session, which included a brief promotional intervention and instruction on the correct use of the female condom. They also were trained to complete a detailed coital log, collect pre- and postcoital vaginal swabs, and package and return swabs and used condoms to the project staff. During the training phase, each participant was asked to use five condoms, after which she returned to review her coital log and sample data forms with project staff. Once through the training phase, each participant entered the proficiency phase of the study, during which she was asked to test 15 condoms using the pre- and postcoital swabs and coital log techniques.

Based on the results of the laboratory studies ("Objective Markers of Condom Failure"), PSA was used as an objective marker of semen spillage. The comparison of PSA levels in pre- and postcoital vaginal swabs was the indicator of semen spillage. Lab

personnel inspected all returned used condoms to assess usage and tested breakage/leakage using a water leakage test. The standard water leakage test was modified for this purpose to include addition of methylene blue dye to the water to assist in visualizing leaks. This relatively inexpensive set of laboratory methods provided an objective counterpart to self-reported experience of displacement and breakage as reported in the coital logs.

Potential determinants of condom breakage, slippage, and semen exposure include duration and intensity of intercourse, positions during intercourse, number of position changes during intercourse, the size of the partner's penis, and distance between the pubic bone and the cervical os. Potential confounders of the PSA assay include recent unprotected intercourse, contamination of the swab tip and menstruation. Information on these factors was collected prospectively, using physical exams and forms completed by the participant.

OBJECTIVE MARKERS OF CONDOM FAILURE

by

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SUMMARY

Context

Studies of condom efficacy rely on self-reported behavior. Objective markers of exposure to semen may provide a more valid assessment of condom failure and failure to use condoms.

Objective

To compare three semen biomarkers: acid phosphatase (AP) activity, prostate specific antigen (PSA), and the human seminal plasma antigen (MHS-5).

Design

Quasi-experimental with each participant providing her own control.

Setting

A study of breakage and slippage in the female condom conducted at the University of Alabama at Birmingham (UAB).

Participants

Twenty mutually monogamous couples who were either using an effective method of birth control or trying to conceive were recruited, primarily from UAB staff and students.

Intervention

Twenty women were intravaginally inoculated with 6 measured, increasingly larger amounts of their partners' semen. Vaginal fluid was collected on swabs and tested.

Main Outcome Measures

Pre- and postinnoculation levels of the potential semen markers.

Results

Background levels of PSA were low (0.00-1.25 ng/ml), background levels of AP were variable (0-350 U/l), and all preinnoculation samples were negative for MHS-5. All postinoculation samples were positive for PSA, 64 of 117 (55%) were positive for AP, and 14 of 120 (12%) were positive for MHS-5.

Conclusions

The PSA immunoassay was the best semen biomarker.

INTRODUCTION

Condoms have been shown to be effective barriers to HIV and other sexually transmitted disease (STD) organisms in laboratory experiments.[1,2] In addition, epidemiologic studies with HIV sero-discordant heterosexual couples have consistently shown condoms to be effective barriers to HIV transmission.[3] Studies of the efficacy of condoms in preventing pregnancy and other STD, however, have provided less conclusive

evidence.[4,5] This apparent inconsistency is of uncertain interpretation, mainly because information on condom use historically relied on self-report. Thus, it is unclear whether certain pregnancy and STD outcomes should be attributed to failure to use condoms correctly and consistently or failure of the condom itself as a physical barrier against exposure to semen and other secretions. In the context of a study quantifying the slippage and breakage rates of the female condom, a simple method for self-sampling of vaginal fluid before and after condom use was developed to assess semen exposure during condom use.

Several assays are currently used in forensic medicine to test for the presence of semen in vaginal fluid: microscopic examination of vaginal fluid specimens to detect spermatozoa (which is known to be an insensitive method); biochemical assessment of the enzymatic activity of AP, and immunologic detection of antigens associated with seminal fluid, such as PSA (P-30) and the human seminal plasma antigen MHS-5.[6-10] Few comparisons of assay sensitivity are available however, especially with respect to detecting the small amounts of semen likely to be present following condom failure.

The present study was initiated to identify the most sensitive and specific biomarker assay for detecting semen exposure. We compared AP activity, PSA, and MHS-5 assays using the same set of vaginal fluid samples collected before and after inoculation of measured amounts of semen.

METHODS

Design

Twenty couples at low risk of STD who were using an effective birth control method or planning a pregnancy participated in this study. The female partner was intravaginally inoculated with measured, increasingly larger amounts of her partner's semen. She used a self-sampling device to collect pre- and postinoculation samples of vaginal fluid, each of which was tested for the three semen markers. The study protocol was reviewed and approved by the UAB's Institutional Review Board.

Study Group

The median age of the female participants was 29 years (21–54); the median age of the male participants was 31 years (24–55). The median time the couples had been mutually monogamous was 5 years (2–20), and none of the women reported an STD in the previous 2 years. The 20 women reported a median of 7 days since last vaginal intercourse (4–30 days).

Intravaginal Inoculation and Sampling Procedures

A swab enclosed by a cardboard tube similar to a tampon applicator was designed to assist with self-sampling of vaginal secretions before and after intercourse. Each woman was trained to use the swab and obtained a vaginal sample before inoculation to assess background levels of AP, PSA, and MHS-5. All 20 women were observed to collect vaginal specimens properly; none reported difficulty using the sampling device.

The male partner was asked to bring a semen sample obtained in the half hour preceding the clinic appointment or to obtain a sample at the clinic. Semen samples were left to liquefy at room temperature for at least 20 minutes between collection and intra-vaginal inoculation.

A nurse practitioner used an artificial insemination catheter and a tuberculin test syringe to measure and inoculate the semen. Each woman was inoculated six times with progressively increasing amounts of her partner's semen (5 µl, 10 µl, 15 µl, 20 µl, 25 µl, and 1 ml) and was observed while she obtained a vaginal swab after each inoculation. The interval between successive inoculations was less than 2 minutes.

Laboratory Procedures

Laboratory personnel were blinded to the subject ID number and volume of the semen inoculum. Swabs were placed in a jar containing desiccant and dried overnight at room temperature. Samples were extracted in 3 ml of saline for 15 minutes. Fluid was expressed from the swab by pressing it against the side of the extraction tube, resulting in approximately 2 ml of eluent, which was frozen and stored in a -80° C freezer. Eluents were later thawed and tested with the ACA assay for AP activity (The Dupont Company, Wilmington, DE, USA), the SEMA assay for MHS-5 (Humagen Fertility Diagnostics, Charlottesville, VA, USA), and the IMx immunoassay for PSA (Abbott Laboratories, Abbott Park, IL, USA).

Data Analysis

The distribution of AP and PSA in the preinoculum samples was used to assess background variability of these markers and to determine whether a quantitative threshold could be specified for determining a "positive" result. The Cochran-Mantel-Haenszel chi-square test for linear trend was used to evaluate the statistical significance of the overall association between the volume of the semen inoculum and assay results. AP results were grouped into 4 approximately equal categories. Because 59 (42%) of the 140 PSA results were at or above the maximum measurable level of 100 ng/ml, the 81 results below 100 ng/ml were grouped in 3 categories of approximately equal size.

Finally, to evaluate the sensitivity of the PSA and AP assays, positive results were defined by comparing postinoculation and preinoculation results. In this analysis, an AP or PSA result was considered positive in a postinoculation sample when the level was higher than the level in the corresponding preinoculation sample. SEMA results were considered positive if the sample produced any visible color change in the test well (no color change was obtained in any of the preinoculation samples). Exact distribution methods were used to make inferences regarding sensitivity, and McNemar's chi-square test was used to determine the significance of the difference in sensitivity between two assays.

RESULTS

Background levels (ie, before semen exposure) of PSA were consistently very low, with a median of 0.11 ng/ml and a range of 0.00 to 1.25 ng/ml (Figure 1). Background levels of AP were highly variable, with a median of 13.4 U/l and a range of 0.0 to

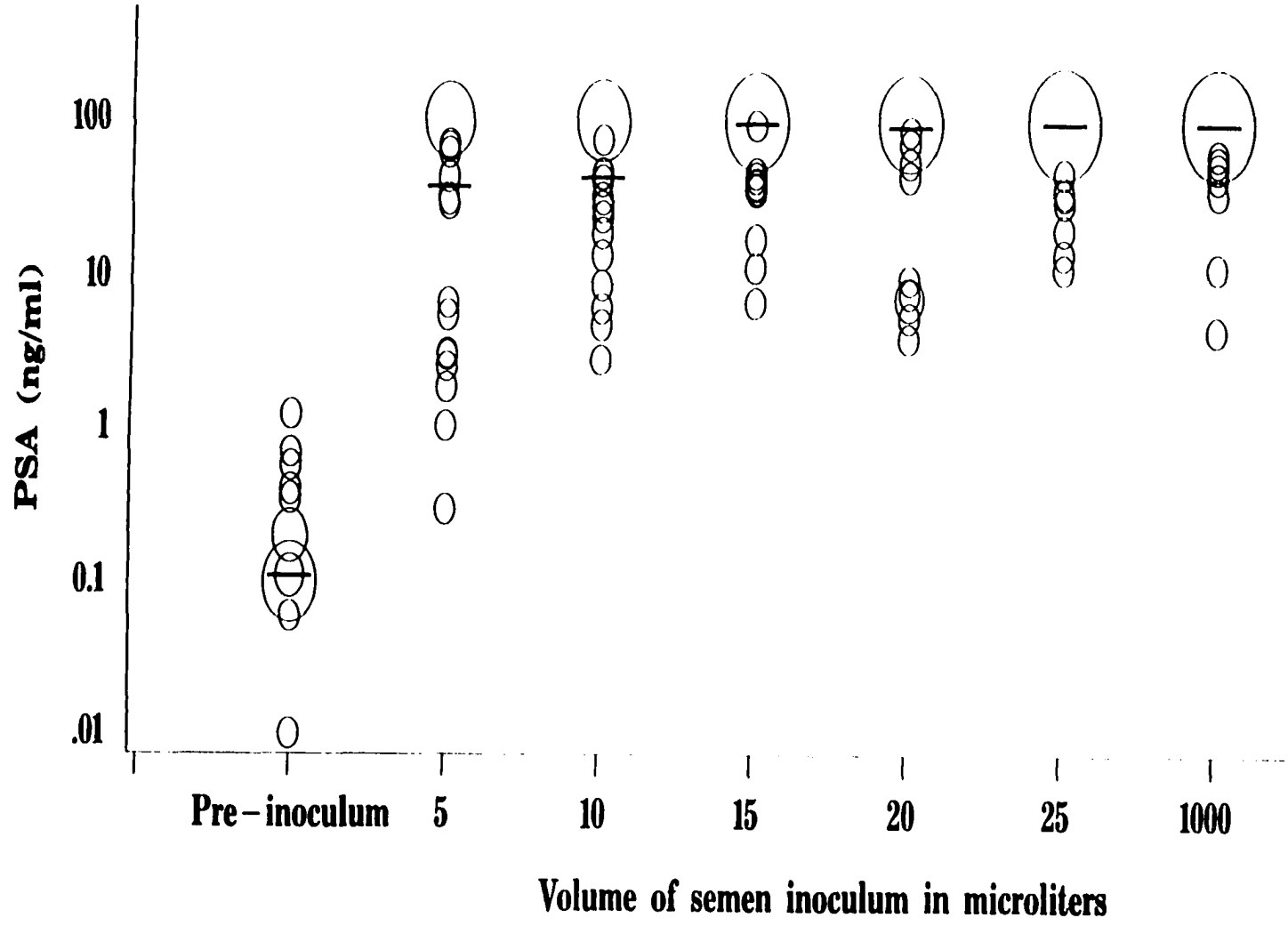

Figure 1. Distribution of PSA values by volume of semen inoculum. Bubble size is proportional to the number of samples with the same value. Horizontal bars indicate median values.

350 U/l (Figure 2). The median PSA concentration increased consistently with increasing volumes of semen, whereas the median AP activity levels showed an inconsistent pattern, and increased AP activity was apparent only after exposure to 1 ml of semen.

The proportion of results for the PSA assay at or above 100 ng/ml increased from about 30% for 5 µl and 10 µl of semen inoculum to 65% for 25 µl and 1 ml of semen inoculum. Even though in our analysis we considered all of these values to be 100 ng/ml, the linear trend test was highly significant (χ^2 = 8.9, P = .003). By contrast, there was no real trend of increasing AP activity with volume of semen inoculum, and the overall association was of borderline statistical significance (χ^2 = 3.65, P = .06). The association between the MHS-5 results and the volume of semen inoculum was inconsistent: the proportion of positive results was < 5% for semen inoculum volumes below 1 ml and reached only 55% at 1 ml (Table 1).

Table 1.—Sensitivity of Prostate Specific Antigen (PSA), Acid Phosphatase (AP), and SEMA Assay for MHS-5 Seminal Vesicle Antigen, by Volume of Semen Inoculum

Amount of Semen (µl)	**% PSA Positive (n)**	**% AP Positive (n)**	**% SEMA Positive (n)**
5	100 (20)	55 (20)	0 (20)
10	100 (20)	45 (20)	5 (20)
15	100 (20)	60 (20)	0 (20)
20	100 (20)	47 (19)	5 (20)
25	100 (20)	50 (18)	5 (20)
1000	100 (20)	70 (20)	55 (20)
TOTAL	100 (120)	55 (117)	12 (120)

The association was statistically significant (linear trend χ^2 = 15.0 , P = .001), due in large measure to the sharp increase in sensitivity associated with the largest vol-

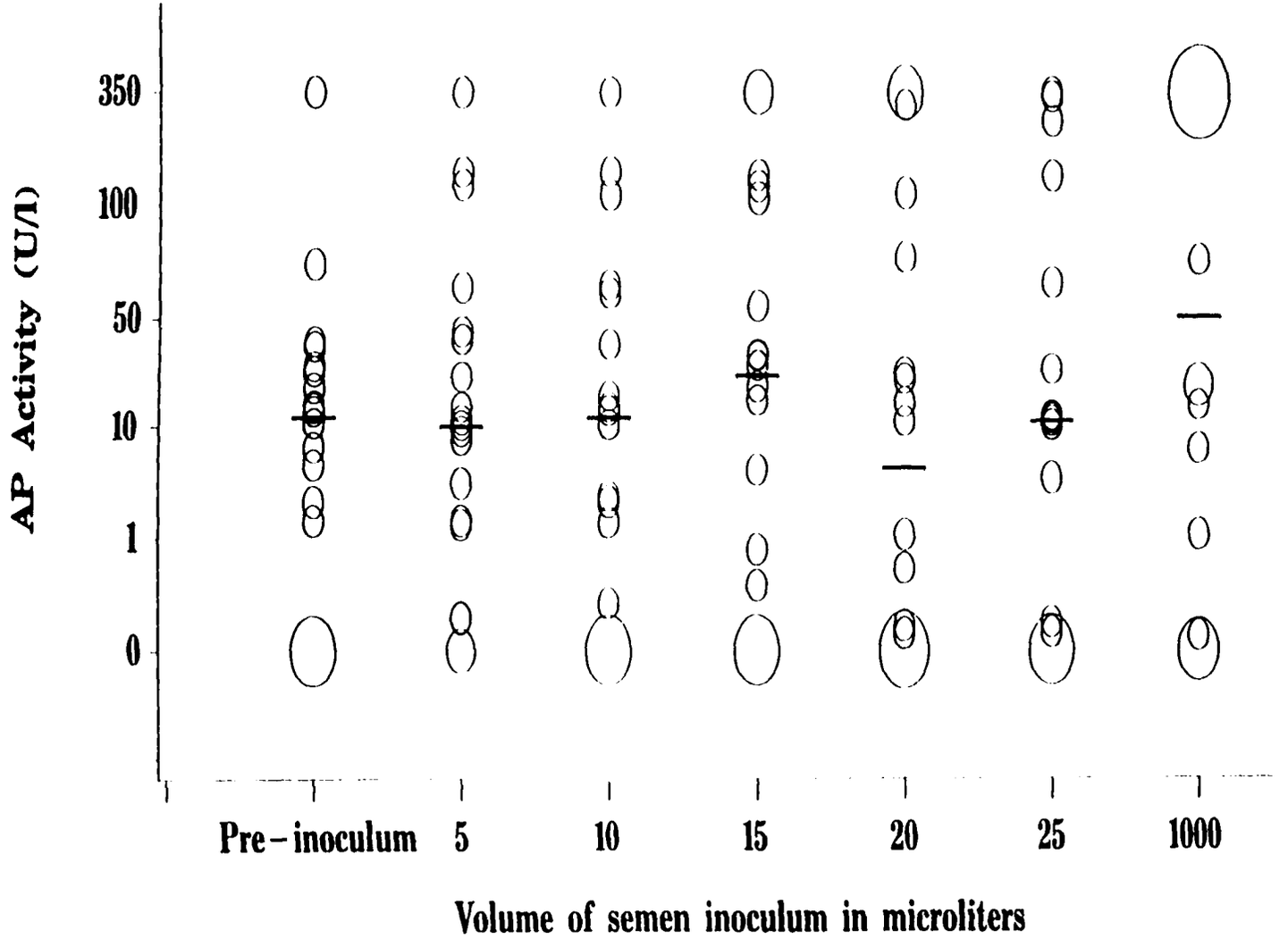

Figure 2. Distribution of AP values by volume of semen inoculum. Bubble size is proportional to the number of samples with the same value. Horizontal bars indicate median values.

ume of semen inoculum. Generalized estimating equation (GEE) regression analyses[11] and analysis of variance (ANOVA) models taking into account the within-subject correlation among test results yielded similar results for all three markers.

All of the 120 swabs obtained after intravaginal inoculation of semen were positive for PSA, 64 of 117 were positive for AP, and 14 of 120 were positive for MHS-5 (Table 1). Thus, the estimated overall sensitivity was 100% for PSA, 55% for AP, and 12% for MHS-5. Pairwise comparisons of the sensitivity of the three methods clearly showed that the PSA assay was consistently more sensitive than the other assays, as the differences between PSA and AP activity and between PSA and MHS-5 were statistically significant for each of the semen volumes inoculated (Table 2). The AP activity assay was significantly more sensitive than the SEMA assay for all but the largest volume of semen inoculum.

Table 2.—Significance of the Difference in Sensitivity Between Semen Detection Assays, by Volume of Semen Inoculum

Amount of Semen (μl)	PSA vs. AP		PSA vs. SEMA		AP vs. SEMA	
	N_{10}/N_{01}*	P†	N_{10}/N_{01}*	P†	N_{10}/N_{01}*	P†
5	9/0	.003	20/0	.00001	10/0	.002
10	11/0	.001	15/0	.0001	7/1	.03
15	8/0	.005	20/0	.00001	10/0	.002
20	10/0	.002	15/0	.0001	8/0	.005
25	9/0	.003	15/0	.0001	9/1	.01
1000	6/0	.014	9/0	.003	4/1	.18

*N_{10}/N_{01}: Number of results in which the first assay listed was positive and second was negative/number of results in which the first assay listed was negative and the second was positive.
†P value of McNemar's chi-square test.

DISCUSSION

In this study we evaluated three of the assays commonly used in forensic medicine for detecting semen exposure. AP activity could theoretically be a good semen marker, as high AP activity has been found in the vagina for periods of up to 4 days after intercourse.[12] AP activity, however, may be a relatively nonspecific indicator of semen exposure because the assay cannot perfectly discriminate between prostatic and nonprostatic AP isoenzymes that may also be present in the vagina. In this study, which used a method that is selective for the prostatic isozyme, widely variable levels of AP activity were found in vaginal secretions, even though participants reported no recent semen exposure. The baseline (preinoculation) variability of AP activity was so large that it was impossible to assign a level of AP activity that would meaningfully indicate recent semen exposure. Furthermore, even when a positive result was defined by comparison with the pre- inoculation activity level, the assay displayed relatively low sensitivity (50-60%) after inoculation of small volumes of semen and only 70% sensitivity after inoculation of 1ml.

Immunoassays for semen antigens should be more specific than AP activity in detecting recent exposure to semen. The SEMA assay employs a monoclonal antibody to MHS-5 and has been marketed specifically for detection of semen in cases of suspected rape.[8,9] The present study is the first evaluation of the SEMA assay *in vivo* using vaginal swabs, and our findings suggest that, although the SEMA assay is very specific, it is not sensitive. The sensitivity of the SEMA assay was very low (0-5%) for semen inoculum volumes of 25 µl or smaller and was only 55% for 1 ml volume. These findings contra-

dict the results of a recent study in which the SEMA assay was sufficiently sensitive to detect semen in dilutions of 1:2,000,000.[9] In that study, however, semen was diluted *in vitro* in the supernatant of centrifuged cervicovaginal lavage specimens, whereas in our study semen was diluted *in vivo* in unprocessed vaginal fluid. Earlier, Herr et al tested the monoclonal antibody used in the SEMA assay by adding semen to undiluted cervicovaginal mucus *in vitro*; their results indicated that the sensitivity of the test is substantially reduced at low semen concentrations.[8] It is possible that the SEMA test is insensitive in the presence of excess cervicovaginal secretions or adversely affected by the use of a swab for sample collection.

Using PSA as a biomarker of semen exposure has several advantages. PSA is present in concentrations of more than 1 mg/ml in semen, whereas concentrations in female tissues, blood, and vaginal secretions are very low, usually below 0.1 ng/ml.[7,13] PSA is a relatively stable protein that can be detected in the eluent of dry semen samples after long-term storage.[14,15] In addition, serum PSA has been widely employed as a prognostic marker for prostate cancer, and commercial assays for measuring PSA at concentrations of less than 1 ng/ml are commonly available in hospital laboratories.[13] Finally, the specificity of the assay appears to be very high, and an objective threshold can be specified to determine recent exposure to semen. In this study, if a result above 1 ng/ml is considered to be positive for recent semen exposure, the specificity of the assay (based on the preinoculation data) was 95%, and the overall sensitivity was 99%. For inoculation levels above 5 μl, the sensitivity of the PSA assay was 100%. If a more conservative threshold of 2 ng/ml was chosen, the specificity of the PSA assay would increase to

100%, and the overall sensitivity would decrease to 97.5%. Sensitivity of the assay would still be 100% for semen inoculation volumes larger than 5 μl. The performance of PSA as a marker of recent semen exposure can be further improved when a positive result is defined by comparing postinoculum values and preinoculum values. This method is employed in an ongoing study of condom efficacy, in which PSA levels are compared before and after condom use. An after-use increase in vaginal PSA exceeding a specified threshold is considered positive for semen exposure during condom use.[16]

In interpreting this report, two potential limitations of the study design should be considered. First, serial correlation of results was possible within subjects. As each woman was inoculated with increasing amounts of her partner's semen in rapid succession, traces of semen remaining in the vagina after one inoculation/sampling cycle may have influenced the result of the following cycle through signal carryover, thereby creating potential for bias in estimating the association between inoculum volume and test results. Analyses using appropriate statistical models to control for within-subject correlation yielded results very similar to the findings described in detail in this report. Although signal carryover may bias the assessment of the increase in assay response with a unit increase in semen exposure, it would not affect the relative sensitivity of the assays. For the first semen inoculum, which was free from both signal carryover and within-subject correlation of results, the superior sensitivity of the PSA assay was as evident as it was for the entire study.

A second possible limitation is that the sampling, specimen handling, and specimen processing techniques used may not be comparable to those used in other settings.

Thus, our findings may not be directly comparable to results obtained under other experimental conditions. The techniques designed for this study, however, are well suited for application in large-scale studies and rape investigations. The observation that the PSA assay is accurate in these circumstances has important implications for forensic medicine and contraceptive research and development.

The limitations discussed above are of modest consequence in interpreting the results of this study and are offset by the study strengths. The semen marker assays were evaluated in aliquots of the same vaginal samples that were collected under carefully controlled experimental conditions. Therefore, the between-assay comparisons have high internal validity. In addition, this study evaluated the *in vivo* performance of three assays at a wide range of semen exposure levels and thus provides information more relevant to clinical practice and epidemiologic research than previous *in vitro* experiments.

In conclusion, this study demonstrates that self-sampling of vaginal secretions with a swab followed by PSA immunoassay evaluation is a simple and accurate method for obtaining information about recent exposure to semen. Women can easily be taught to use the inexpensive sampling device designed for this study, and the dried sample is easy to store and transport. PSA is a very sensitive and specific semen biomarker in vaginal fluid under these conditions, even when the vaginal secretions have been exposed to semen volumes as small as 5 μl. Because the PSA immunoassay is available in most hospital laboratories, the methodology developed for this study is suitable for widespread application.

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DETERMINANTS OF USE OF THE REALITY FEMALE CONDOM

by

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SUMMARY

Context

The female condom has been marketed as an alternative to the male condom for the prevention of pregnancy and sexually transmitted disease (STD).

Objective

To assess how attitudes about the condom, socio-demographic characteristics and problems with use of the female condom relate to discontinuation of use.

Design

A prospective follow-up study.

Setting

A study of breakage and slippage in the female condom conducted at the University of Alabama at Birmingham (UAB).

Participants

A total of 210 low-risk women were recruited primarily from UAB staff and students, with some additional participants from the Birmingham community.

Intervention

Participants were trained to use the female condom and follow study procedures during a 2 hour group training session.

Main Outcome Measures

Completion of use of 5 condoms and survival to study completion by using 20 condoms.

Results

Of the 210 women trained, 35 (17%) never returned a female condom, 128 (61%) used at least 5 condoms, and 81 (39%) women completed the study protocol of using 20 female condoms. White women were 17% less likely to drop out of the study before using 5 condoms than non-White participants. Breakage, slippage, or semen leakage experienced prior to an individual use increased the risk of discontinuing use of the condom by 29%. None of the attitudes expressed about the condom prior to use were predictive of use discontinuation.

Conclusions

Problems with use of the female condom are the only important determinants of discontinuing use of the condom. Therefore, adequate training and provision of backup methods are essential for couples selecting this method of barrier contraception.

INTRODUCTION

For much of the world's population, condoms are the sole STD prevention method available. Cohort studies offer strong evidence that male condoms are effective in preventing transmission of Human Immunodeficiency Virus (HIV) in sero-discordant couples, and *in vitro* experiments indicate that male condoms may provide some protec-

tion against gonorrhea, mycoplasma, chlamydia, trichomoniasis, hepatitis, cytomegalovirus, and genital herpes.[1-6] Although male condom use can be negotiated by a woman, active participation by the male partner is required. The limited availability of barrier contraceptive methods that are directly under a woman's control is a public health concern of the highest priority. The Reality female condom has been marketed as a female controlled method and appears to be partially effective in preventing pregnancy if used consistently (5% 12-month pregnancy rate US women reporting perfect use).[7]

Currently, the female condom is the only barrier contraceptive other than the male condom that is recommended for prevention of HIV and other STD. Evidence for the efficacy of the female condom in preventing STD is from one small study of trichomonas re-infection[8] and a report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) evaluating STD rates among Thai female prostitutes who were given both male and female condoms.[9] Theoretically, the female condom should provide an effective barrier to both sperm and STD, as it is made of a strong polyurethane sheath that is impermeable to small molecules (eg, gaseous helium).[10]

Acceptability of the device among couples is crucial to assessing its viability as a method of contraception and STD prevention. We conducted a study to measure breakage and slippage rates of the female condom among couples at low risk of STD. This paper describes factors associated with use discontinuation among couples who participated in the breakage and slippage study.

METHODS

A prospective follow-up study of low risk couples was conducted to test breakage and slippage rates in the female condom. The study protocol, which was reviewed and approved by the UAB Institutional Review Board, included both a training and proficiency phase. During the training phase, the participant used 5 condoms. The participant then entered the proficiency phase of the study, during which up to 15 condoms were used. At the end of each phase, each participant was interviewed about her experience with the condom. Women attending family planning clinics of the UAB Division of Reproductive Biology and Planned Parenthood of Alabama, Inc. and volunteers responding to advertisements in UAB publications were screened for eligibility during a telephone interview. Inclusion criteria were current use of an effective method of birth control, involvement in a mutually monogamous relationship, a minimum coital frequency of 6/month, experience with tampon use, no STD in the previous 6 months, an intact uterus, and age between 21 and 49 years.

Eligible women who gave informed consent participated in a group training session that included a brief promotional intervention and instruction on the correct use of the female condom. After practicing insertion with an anatomical model, each participant inserted the female condom; proper vaginal placement was verified by a nurse practitioner. The participant was trained to take pre- and postcoital vaginal swabs, package swabs and used condoms, and return them to the project staff on the next business day. She was trained to complete a form describing her experience using the condom and instructed to include the form with each returned condom. The form included questions about the time and duration of intercourse, problems experienced, partner ejaculation, and time elapsed since previous intercourse. Specific potential problems listed on the form included swab

associated problems, condom breakage, condom slippage, penile misrouting, semen leakage, noise, and discomfort. Each participant was also trained to keep a coital log, which included information about positions used and intensity of intercourse. The coital log was collected at follow-up visits.

At the initial visit the participant also completed a questionnaire designed to measure attitudes and beliefs about the male and female condom. This brief questionnaire was adapted from a longer instrument created for a study of the psychosocial determinants of female condom use among high-risk women.[11] Participants were asked to respond to a series of 30 statements about female condoms using a 4-level Likert scale. Participants were instructed to answer "don't know" if they had no opinion on a particular item. Subsets of the questions (attitude factors) were created from these statements using principal component analysis.

Data Analysis

The analysis plan included (1) assessment of the characteristics that discriminate participants who completed the training phase from those who did not, (2) assessment of predictors of discontinuation of use among participants who used at least one condom, and (3) assessment of predictors of discontinuation during the proficiency phase.

Predictors of Training Phase Noncompletion

Sociodemographic characteristics and attitudes/beliefs as assessed at the end of the training session but before any condom use were considered potential predictors of training phase noncompletion. A parsimonious model building strategy was adopted in

the analysis. The potential risk factors were grouped into two broad domains: (1) sociodemographic and lifestyle characteristics and (2) attitudes about the female condom. Rounded mean scores for each attitude factor were used to create a binary outcome variable indicating whether or not the participant agreed with the factor, which was used as the predictor variable. Logistic regression was used to estimate odds ratios (OR) for each risk factor with and without adjustment for all other factors in the same domain. The risk factors that displayed an adjusted OR of greater than 2 (or less than .5) or were statistically significant (at alpha < .2) were included in a logistic regression model with predictors from both domains. Because the OR estimated in logistic regression models only approximates the risk ratio (RR), we used a log linear model to obtain direct estimates of the RR. Thus, the predictors selected through logistic regression were included in a generalized linear model with a log link and a binomial error distribution to obtain the adjusted RR and 95% confidence interval (CI). Age and race were also included as they were considered potential confounders *a priori*. Goodness of fit was evaluated by examining the model deviance and plotting the Pearson and deviance residuals against the predictor variables.

Predictors of Use Discontinuation Analysis

For the determinants of use discontinuation, potential predictors were included in Cox proportional hazards models, with number of condoms used as the dependent variable and each condom use modeled as a discrete interval. As in the analysis described above, potential predictors were first analyzed by domain. Variables from the sociodemographic and attitude domains with a significance level of less than .2 or an RR of

greater than 2 (or less than .5) were included in the complete proportional hazards model. In addition to the sociodemographic and attitude domains, a third domain related to problems reported by the participants during condom use was included in this analysis. Because the problems were considered *a priori* as predictors of discontinuation of use, all problem variables were retained in the final model. Past experience of problems that were predictive of discontinuation was collapsed into a single variable. Problems that were not strong predictors of discontinuing use (RR between 0.9 and 1.1) were collapsed into two variables, one describing the past experience and one describing current experience. The proportional hazards assumption was tested by including interaction terms for time and the predictor variables. Model fit was assessed by plotting the Martingale residuals for estimated linear predictor values and the local influence statistic dfbeta[12] for individual participants.

RESULTS

Participation in the study is summarized in Table 1. Two hundred and ten women participated in the training session. Of these, 35 (17%) never returned a female condom, 128 (61%) returned for the first follow-up visit, and 81 (39%) women completed the study protocol of using 20 female condoms each. Thirty women (14%) returned for a final visit having used fewer than 20 condoms each. Overall, 745 condoms were used in the training phase of the study, and 1487 condoms were used in the proficiency phase. At least one problem with the condom was reported in 35% of training phase uses and 20% of proficiency phase uses. Demographic information was missing for 3 of the participants, and attitude questionnaires were not available for 5 participants.

Table 1.—Participation in the Female Condom Slippage/Breakage Study

Participation Status	Number of Women
Screened for eligibility	387
Eligible	279
Agreed to participate	269
Participated in training session	210
Did not use any condoms	35
Used up to 5 condoms, did not return for follow-up visit	47
Used 5 condoms and returned for follow-up visit	128
Used fewer than 20 condoms, did not return for final visit	17
Used fewer than 20 condoms, returned for final visit	30
Used 20 condoms and returned for final visit	81

The women who participated in the training session had a median age of 27 years, and a median household per capita income of about $600 a month. They had been in their current relationship for a median of 4 years and reported a median of 12 sexual contacts per month. Over 70% were White, over half were married, and over half had completed college. Only 9 (4%) of the participants were users of barrier contraception.

Table 2 lists the attitude questions included in each attitude factor and reports indices of internal consistency for each factor. Table 3 shows the distribution of the responses to individual attitude questions and the subjects' mean score for each attitude factor. Participants usually agreed with positive statements but tended to respond that that they did not know if a positive statement implied experience with using the device. For example, 66% of the participants responded that they did not know if female condoms make sex better for women. Therefore, questions that implied experience with the device were excluded from the analysis. Participants generally disagreed with negative

statements, such as "Female condoms aren't worth the trouble." One hundred sixty-one (79%) agreed with at least one of these factors (indicating some negative attitudes about the female condom), but no participant agreed with all of the factors. The majority (60%) of the participants who agreed with at least one factor agreed with only one factor. Thus, most participants have positive, or at least nonnegative, attitudes about the female condom immediately following the intervention.

Table 2.—Composition of Attitude Factors From Initial Questionnaire (n = 205)

Averse to inserting (R_c = .82)
Agreed that she didn't like having to touch herself to put the condom in
Agreed that she didn't like having to use her finger to push the condom in
Agreed that she didn't like putting the female condom inside herself
Difficult to use (R_c = .66)
Disagreed that female condoms are easy to use
Agreed that the female condom takes too long to put in
Agreed that female condoms are inconvenient
Agreed that female condoms are messy
Does not give female control (R_S = .73)
Disagreed that women who carry female condoms are taking charge
Disagreed that female condoms put the woman in charge
Do not like appearance (R_C = .61)
Agreed that having part of the female condom hang out is gross
Agreed that female condoms are weird
Agreed that she was embarrassed for her partner to see what the female condom looks like
Does not work (R_S = .58)
Disagreed that female condoms help keep her from getting pregnant
Disagreed that female condom help stop STD
Is not needed in long-term relationships (R_S = .64)
Agreed that a female condom isn't necessary when you know enough about the person to trust him
Agreed that a female condom isn't necessary when you are with the person for a long time

R_c = Cronbach's Coefficient Alpha.
R_S = Spearman's Rank Correlation Coefficient.

One hundred thirty-one women (62%) completed the training phase by using at least 5 condoms. White women were 17% less likely to drop out of the study before completing the training phase than non-White (primarily Black) participants. No other

demographic or attitude variable represented a significant risk factor for dropping out of the study prior to completion of the training phase.

Table 3.—Responses to Individual Attitude Questions and Factors (n = 205)

Attitude	Agree n (%)	Don't Know n (%)	Disagree n (%)
Aversion to product insertion	15 (7)	30 (15)	160 (78)
Difficulty of use	6 (3)	143 (70)	56 (27)
Lack of female control	24 (12)	23 (11)	158 (77)
Negative product appearance	7 (3)	71 (35)	127 (62)
Lack of product efficacy	5 (2)	39 (19)	161 (79)
No need for protection in long term relationships	19 (9)	35 (17)	151 (74)
Female condoms aren't worth the trouble*	7 (3)	49 (24)	149 (73)
Like female condom because the woman uses it*	162 (79)	27 (13)	16 (8)
Can make female condom sexy with the right attitude*	187 (91)	15 (7)	3 (2)
Like being able to put female condom in ahead of time*	162 (79)	31 (15)	12 (6)

* Individual question that did not load in a factor.

Table 4 shows the unadjusted and adjusted RRs for the predictors included in the proportional hazards model of use discontinuation among all participants who tried the condom at least once. The outcome of interest was whether the participant stopped using the female condom after a given use. Problems experienced prior to an individual use (regardless of experience of problems at that use) appear to have a significant influence on discontinuation of use. Each time a couple experienced breakage, slippage (as defined by the condom coming out of the vagina or the outer ring being pushed inside), or semen leakage, their risk of discontinuing use of the condom increased by 29%. The cumulative

Table 4.—Determinants of Female Condom Use Discontinuation (n = 2148 uses, 175 users)

Cumulative Experience Prior to Current Intercourse	Median (Mean) Value	Unadjusted RR	Adjusted RR (95% CI)*
Breakage, slippage and semen leakage	0 (.99)	1.22	1.29 (1.10 – 1.50)
Any other problems	1 (1.89)	1.04	.98 (.89 – 1.10)
Problems at Current Intercourse	**% of All Intercourses With Problem**	**Unadjusted RR**	**Adjusted RR (95% CI)***
Breakage	0.7	4.51	2.43 (.47 – 12.67)
Condom came out of vagina	6.0	.43	.24 (.06 – 1.02)
Penis entered outside of condom	1.7	1.55	1.64 (.36 – 7.43)
Outer ring pushed into vagina	3.4	.89	.64 (.18 – 2.24)
Semen leaked onto woman's body	2.4	2.10	1.58 (.58 – 4.35)
Man felt pain or discomfort	3.7	1.91	1.59 (.69 – 3.67)
Any other problem	13.1	1.26	1.34 (.74 – 2.42)
Demographic Variables and Attitudes	**% of All Participants With Characteristic**	**Unadjusted RR**	**Adjusted RR (95% CI)***
Currently attending school	47.7	1.41	1.30 (.81 – 2.10)
Disagrees that she likes the female condom because it's something the woman uses	7.6	1.69	1.89 (.88 – 4.03)
Age	N/A	.97	.97 (.93 – 1.02)
White	74	.72	.72 (.44 – 1.16)

*Adjusted in a Cox proportional hazard regression model by all other variables shown. Demographic and attitude variables were modeled as nontime varying.

experience of other problems was not significantly associated with discontinuation of use. Surprisingly, women who reported that the condom came out of the vagina were more likely to use another female condom.

The use discontinuation analysis was repeated for uses occurring after the first 5 condoms (Table 5). For the women who continued use after the training phase, the couple's risk of discontinuing use was increased 25% each time they reported breakage, slippage, semen leakage, or the woman's experience of pain or discomfort. No other problems or couple characteristics were significantly associated with discontinued use in the proficiency phase.

DISCUSSION

A few conclusions can be drawn from this analysis. First, in this study group, most women had positive attitudes toward the female condom after an intervention promoting the device and providing training. While it is possible that the women responded to the attitude/belief questions in the way they felt was socially desirable, the variation in the distribution of responses indicates that the responses were probably an honest reflection of attitudes and beliefs immediately following the intervention. Thus, these data show that women who are not regular users of barrier contraception have positive attitudes about the female condom when it is initially presented to them.

The majority of women (83%) went on to use the condom at least once with their regular partner and returned the used condom. However, 38% of women did not complete the training phase by using at least 5 condoms each. In addition, even though the majority of women used at least five female condoms, only 39% completed the study

Table 5.—Determinants of Female Condom Use Discontinuation During the Proficiency Phase (n = 1403 uses, 120 users)

Cumulative Experience Prior to Current Intercourse	Median (Mean) Value	Unadjusted RR	Adjusted RR (95% CI)*
Breakage, slippage, semen leakage, and woman's pain/discomfort	1 (2.03)	1.94	1.25 (1.08 – 1.45)
Any other problems	1 (1.84)	1.02	.96 (.81 – 1.13)
Problems at Current Intercourse	**% of All Intercourses With Problem**	**Unadjusted RR**	**Adjusted RR (95% CI)***
Breakage	0.7	4.16	1.81 (.19 – 17.31)
Semen leaked onto woman's body	2.0	2.54	2.93 (.35 – 34.35)
Condom rode on penis during sex	4.7	.47	.36 (.04 – 3.49)
Woman felt pain or discomfort	4.8	2.38	2.63 (.82 – 8.49)
Any other problem	14.0	.95	.40 (.09 – 1.85)
Demographic Variables and Attitudes	**% of All Participants With Characteristic**	**Unadjusted RR**	**Adjusted RR (95% CI)***
Currently employed	75.8	.62	.59 (.27 – 1.28)
Disagrees that she likes being able to put the female condom in ahead of time	5.2	.47	.69 (.09 – 5.27)
Age	N/A	1.01	1.01 (.95 – 1.08)
White	77.5	.96	.99 (.44 – 2.21)

*Adjusted in a Cox proportional hazard regression model by all other variables shown. Demographic and attitude variables were modeled as nontime varying.

protocol by using 20 condoms each. The only real predictor of discontinuing use of the female condom was the cumulative experience of breakage, slippage, and semen leakage. In the proficiency phase, pain or discomfort experienced by the woman was an additional problem predictive of discontinuation. These specific problems appear to have a long-term effect, in that each time any of these problems is experienced the risk of discontinuing use increases by almost 30%. Overall, 12% of uses resulted in at least one of these problems that cause long-term effects. While the problems were most common with the first few condom uses, 5% of participants reported one of these problems at the 20th use. Therefore, dissatisfaction with the product due to breakage, slippage, or semen exposure appears to be a serious threat to achieving consistent use of the female condom.

In this study, women who experienced the condom coming out of the vagina were 4 times more likely to use another condom than women who did not experience this problem. We conducted additional analyses to further understand this seemingly contradictory result. Although there was no statistically significant time trend in the hazard, the hazard ratio did change over time for this variable. At the first few uses, experiencing the condom coming out of the vagina had a protective effect, but this disappeared after the seventh use. During the intervention, women were told to expect slippage of the condom and given suggestions for solving the problem. It is possible that women who experienced the problem early in the study were, in fact, more likely to try an additional condom than women who did not experience slippage but were dissatisfied with the condom. In other words, women who were dissatisfied with the condom but experienced slippage may have tried an additional condom with the assumption that their dissatisfaction was due to slippage, which they had been advised to expect and was easy to correct. More

importantly, interaction was observed between the condom coming out of the vagina and race. While this effect was not statistically significant when included in the model, inclusion of this interaction term accounted for almost all of the protective effect of this form of slippage. The mechanism of the interaction is unclear.

Other problems (eg, noise, pain, or discomfort) appeared to have had no immediate or cumulative effect. In addition, none of the demographic characteristics, attitude factors, or individual attitude questions examined were predictive of use discontinuation. Although attitudes and race influenced a woman's trying the condom more than a few times, these factors were not important predictors of long-term use. Because the vast majority of women in this study had positive (or nonnegative) attitudes about the condom, we had little ability to detect small effects of negative attitudes. Future studies that do not include an intervention to help modify attitudes may be able to demonstrate such effects.

Several aspects of the study design limit generalization of its findings. First, the study consisted of low risk women who were well educated and usually had been in their current relationship for several years. The group was not representative of the population that is typically targeted for use of the female condom. Thus, it is possible that the participants, overall, were not sufficiently in need of the device and were not motivated to use it. On the other hand, the participants were well trained and motivated to participate in the study, and there is no reason to believe that the reported problems in this particular population would be significantly different from other populations. Furthermore, the majority of the participants expressed positive attitudes toward the device, and positive perceptions were associated with returning at least one condom.

Another potential limitation of the study is that, as part of the study protocol, the women were asked to take pre- and postcoital swabs, return the swabs and used condom to the clinic, and maintain records of their sexual activity and experience with the condom. The demanding nature of the study probably increased the likelihood that a woman would decide not to continue in the study. We collected information on the frequency of problems encountered with collecting the specimens, and such problems occurred in only 7% of uses. In addition, there was no relationship between problems with collecting the specimens and discontinuing use of the condom. Finally, the participants were compensated for each condom that they tested and returned, which probably added motivation to use the device.

The study has considerable strengths, however. The participants were asked to complete the sample data form at the time of intercourse and return the form and the used condom on the next business day after use. Thus, the data on problems with use was collected prospectively, so that the report of a specific problem is likely to be accurate. In addition, the request that the women use 20 condoms each allowed us to separately evaluate information about early use and about long-term experience with the condom. Collection of the used condom provides objective confirmation that the condom was actually used. Also, since the Reality condom is being promoted to women who cannot or will not use the male latex condom with their partners, this population of nonbarrier users may actually represent the eventual target users of the condom more accurately than women who use the male latex condom.

In conclusion, women who are not regular users of barrier contraception express positive attitudes about the Reality female condom and can be trained to use it. Attitudes

expressed by women prior to use are not predictive of success with the condom, however. The only variable we can identify that is associated with willingness to use the condom at least 5 times and can be measured prior to use of the condom is race. Among women who try the condom, only problems with use of the product has a significant effect on whether or not the woman continues to use the condom in the long term. Although some women have problems with the condom even after they become experienced users, 25% use the condom without any problems. This 25% is presumably the most likely group to use the female condom consistently. Given the high frequency of problems experienced by trained users, the merit of promoting the female condom as an alternative to the male latex condom is debatable. Furthermore, adequate training should be made available to women who choose the device as their main method of contraception or STD prevention to prevent unnecessary frustration and use failure. Counseling should also be made available to assist with the transition to other methods should dissatisfaction with the product lead to early discontinuation.

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A PROSPECTIVE STUDY OF COUPLES WHO USE THE FEMALE CONDOM. OCCURRENCE OF SELF-REPORTED PROBLEMS AND SEMEN EXPOSURE DURING USE

by

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SUMMARY

Context

The female condom has been marketed as an alternative to the male condom for the prevention of pregnancy and sexually transmitted disease (STD).

Objective

To assess the frequency of semen exposure and the relation between semen exposure and user reported problems during use of the female condom.

Design

A prospective follow-up study.

Setting

A study of breakage and slippage in the female condom conducted at the University of Alabama at Birmingham (UAB).

Participants

A total of 210 low-risk women were recruited primarily from UAB staff and students, with some additional participants from the Birmingham community.

Intervention

Participants were trained to use the female condom and follow study procedures during a 2 hour group training session.

Main Outcome Measures

Self-reported problems during use and semen exposure as defined by comparing pre- and postcoital prostate specific antigen (PSA) levels in vaginal fluid (upper and lower boundaries of semen exposure rates were calculated).

Results

Of 2322 uses of the female condom, 25% resulted in at least one reported problem. The overall rate of semen exposure was between 7 and 21%. Semen exposure was more likely to occur if the participant reported the penis entering outside of the condom, the outer ring moving into the vagina, or semen leaking from the condom. No problem was reported during use of 1677 condoms. The rate of semen exposure in the group reporting no problem was between 5 and 19%.

Conclusions

Semen exposure occurs often in the absence of user-reported problems. To the extent that semen exposure is an indicator of pregnancy and STD risk, these findings indicate that self-report underestimates the frequency of female condom failure.

INTRODUCTION

The Reality female condom is an intra-vaginal barrier contraception device developed as an alternative to the male latex condom for the prevention of pregnancy and STD. The female condom is a reasonably effective contraceptive when used for every act of intercourse,[1] with a 6-month pregnancy rate of about 4% among perfect (ie, correct and

consistent) users. Evidence from one small study of trichomonas re-infection[2] and from a Joint United Nations Programme on HIV/AIDS (UNAIDS) study[3] suggests that the female condom may be effective in preventing STD as well.

Assessment of the frequency of mechanical failure of the female condom is a necessary part of a comprehensive effort to evaluate the acceptability and efficacy of the device. For mechanical failure to have biologic significance, it must lead to exposure to semen (which is necessary for conception) or to male urogenital secretions (a necessary cause of STD). Semen exposure may be due to mechanical failure, such as breakage or slippage, but is not commonly evaluated as an endpoint in breakage and slippage studies. Thus, it is not known whether semen exposure correlates well with user-reported condom failure or whether semen exposure can occur in the absence of detectable failure. Problems that do not result in semen exposure, such as discomfort, are still potentially important indicators of the acceptability of the device.

We conducted a study to assess mechanical failure, semen exposure, and other problems associated with female condom use. Assessment of semen exposure was based on an immunoassay to detect PSA in vaginal fluid after intercourse. Information on problems experienced by users was collected prospectively, and specific problems were evaluated as potential determinants of semen exposure.

METHODS

Study Design

This was a prospective follow-up study of low risk couples who volunteered to test the female condom. The study procedures have been described in detail elsewhere.[4]

Briefly, women who were in mutually monogamous relationships and without recent STD were recruited to participate in the study. Each woman who agreed to participate in the study took part in a training session including a brief motivational intervention and instruction on the correct use of the female condom. She also was trained to collect pre- and postcoital vaginal swabs and to package and return the swabs and used condom with a form describing problems on the next business day after use. During the training phase, the participant used 5 condoms, after which each participant returned to review her coital log and data forms with project staff and review any use problems with a nurse. Once through the training phase, the participant entered the proficiency phase of the study, during which she tested 15 additional condoms. The used condoms were evaluated using a modified water leakage test, and the postcoital swabs were tested for PSA, a sensitive and specific semen marker.[5,6] The study protocol was reviewed and approved by the UAB Institutional Review Board.

Sampling Protocol

A gynecologic swab protected by a cardboard tampon tube was developed as a vaginal self-sampling device for this study. The swab had a 3/8" diameter rayon tip and was 8" long (Hardwood Products Company, Guilford, ME, USA). The cardboard sheath was similar to a tampon tube, with a 1/2" diameter and a 3" length (Custom Paper Tubes, Cleveland, OH, USA). One end of the tube was closed to keep the swab protected inside the tube. With each condom packet, the participant received 2 plastic zipper bags each containing one swab and two packets of desiccant (Desiccite 25, Tigerpak Inc, Clifton, NJ, USA). One bag was labeled "Before" and one bag was labeled "After." A nurse

practitioner observed each participant in the clinic to ensure that the participant was able to remove the swab from the bag, take a vaginal sample, anchor the swab in the tube, and return the swab to the bag, all without touching the swab tip. The participant was also instructed to take a vaginal sample just before inserting the female condom and immediately after removing the female condom.

Processing of Swabs and PSA Testing

The dried swab samples were stored at room temperature and then extracted in 3 ml of 0.9% saline for 15 minutes. Fluid was expressed from the swab by rotating and pressing it against the side of the extraction tube, resulting in approximately 2 ml of eluent, which was frozen and stored in a -80°C freezer. Eluents were later thawed and tested with the PSA IMx immunoassay (Abbott Laboratories, Abbott Park, IL, USA). All postcoital proficiency phase swabs were tested for PSA. If the postcoital swab had a PSA level over 1 ng/ml, then the precoital swab was tested. In the sampling and assay conditions described here, a PSA level of 1ng/ml is a highly sensitive and specific indicator of recent semen exposure.[5,7] All training phase postcoital swabs from individuals who completed the study were tested, as was a sample of training phase postcoital swabs from individuals who did not complete the study.

Water Leakage Testing of Used Condoms

The standard 300 ml water leakage test was modified by adding methylene blue in the test water to assist with visualizing leaks. Used condoms were rinsed in a bucket par-

tially filled with tap water and then suspended from a 2" x 1/2" pipe reducer coupling. Water containing methylene blue was poured into the condom (300 ml), and the outside of the condom was carefully dried using a paper towel. The condom was left for 5 minutes, and then the outside of the condom was wiped using a folded white tissue (Kimwipe, Kimberly-Clark Corporation, Atlanta, GA, USA). Any blue marks on the Kimwipe were considered as possible leaks, and the condom was dried again with a paper towel and allowed to stand for another 5 minutes. A second Kimwipe test was done, and blue marks on the second wipe indicated a positive test for condom leakage. Condoms with large tears were not tested for water leakage. All condoms that were broken or failed the water leakage test were soaked in bleach for 30 minutes, dried, and stored.

Data Analysis

Problem rates per 100 condom uses were calculated among participants who used the female condom at least once in the study. The first five condom uses were considered the "training phase" and the remaining condom uses were considered the "proficiency phase." Participants successfully completed the study if they returned all 20 condoms. Crude problem rates, problem rates stratified by phase, and problem rates stratified by use order were computed by dividing the number of reported problems by the total number of condoms used in each stratum, and multiplying the result by 100.

Each condom use for which the postcoital swab had a PSA level of 1 ng/ml or lower was defined as negative for semen exposure. For each condom use resulting in a postcoital PSA level higher than 1 ng/ml, the precoital specimen was tested for PSA and the result was compared to the postcoital result. Two criteria were used to classify the re-

sults as positive for exposure to semen. The first criterion, based on threshold PSA value, was satisfied if the precoital specimen had a PSA of 1 ng/ml or lower. The second criterion, based on the difference between PSA levels, was satisfied if the postcoital PSA value was 22 ng/ml higher than the precoital swab. (In another semen exposure study, 22 ng/ml indicated the 95th percentile of the difference between any two vaginal swabs taken 24 hours after exposure to 1 ml of semen.[7]) The number of condom uses that satisfy either criteria represents an upper boundary (high sensitivity) estimate of semen exposure, while the number of condom uses that satisfy both criteria represents a lower boundary (high specificity) estimate. All analyses of predictors of semen exposure were conducted with both definitions of semen exposure. The above-mentioned semen exposure study also demonstrated that PSA levels in vaginal fluid sharply increase after semen exposure, almost invariably returning to levels below 1 ng/ml 24 hours after exposure. Thus, analyses of the relation between semen exposure and self-reported problems was further restricted to condom uses that took place at least 24 hours after the previous act of intercourse.

The crude association between user reported problems and semen exposure was evaluated first in 2 x 2 tables. The odds ratio (OR) was the measure of association, and the significance of the association between semen exposure and problems was evaluated using a Chi-square test. Adjusted ORs were estimated using logistic regression. Because each participant used up to 20 condoms, correlation of results within an individual was possible. The correlation of errors within each individual participant was modeled explicitly in generalized mixed linear models for binary outcomes (the mixed model equivalent of logistic regression, as implemented in the SAS macro GLIMMIX[8]). The

order of condom use was included in all models to evaluate and adjust for the effect of experience with female condom use.

RESULTS

Two hundred and ten women participated in the training session. Of these, 35 (17%) never returned a female condom, 128 (61%) returned for the first follow-up visit, and 81 (39%) women completed the study protocol of using 20 female condoms each. The women who participated in the training session had a median age of 27 years, and a median household per capita income of about $600 a month. They had been in their current relationships for a median of 4 years and reported a median of 12 sexual contacts per month. Over 70% were White, over half were married, and over half had completed college.

A total of 2,232 female condoms were used during the study. Of these, 745 (33%) were used during the training phase, and 1,487 (67%) were used during the proficiency phase (Table 1). A total of 15 condoms broke during use, corresponding to a rate of 0.7 per 100 uses. The condom completely came out of the vagina in 131 instances (6 per 100 uses), the outer ring was pushed inside the vagina in 73 instances (3 per 100 uses), and the condom rode on the penis in 153 instances (7 per 100 uses). Any of the three outcomes was considered as slippage, and the combined slippage rate was 13 per 100 uses. The woman felt discomfort in 6% and the man felt discomfort in 4% of the uses. Overall, at least one problem was reported in 25% of the 2232 female condom uses. The frequency of problems was higher during the training phase than during the proficiency phase for most specific problems (with the exception of breakage and bleeding) and for the aggregate category "any problem." The difference between the training and profi-

ciency phases was statistically significant at the 5% level for 8 of 12 comparisons. Despite the reduction in user problem rates during the proficiency phase, problems remained. Among women who completed the training phase, 74% reported at least one problem with any of the first 5 condoms, while 79% of the women who completed the study reported at least one problem during the proficiency phase.

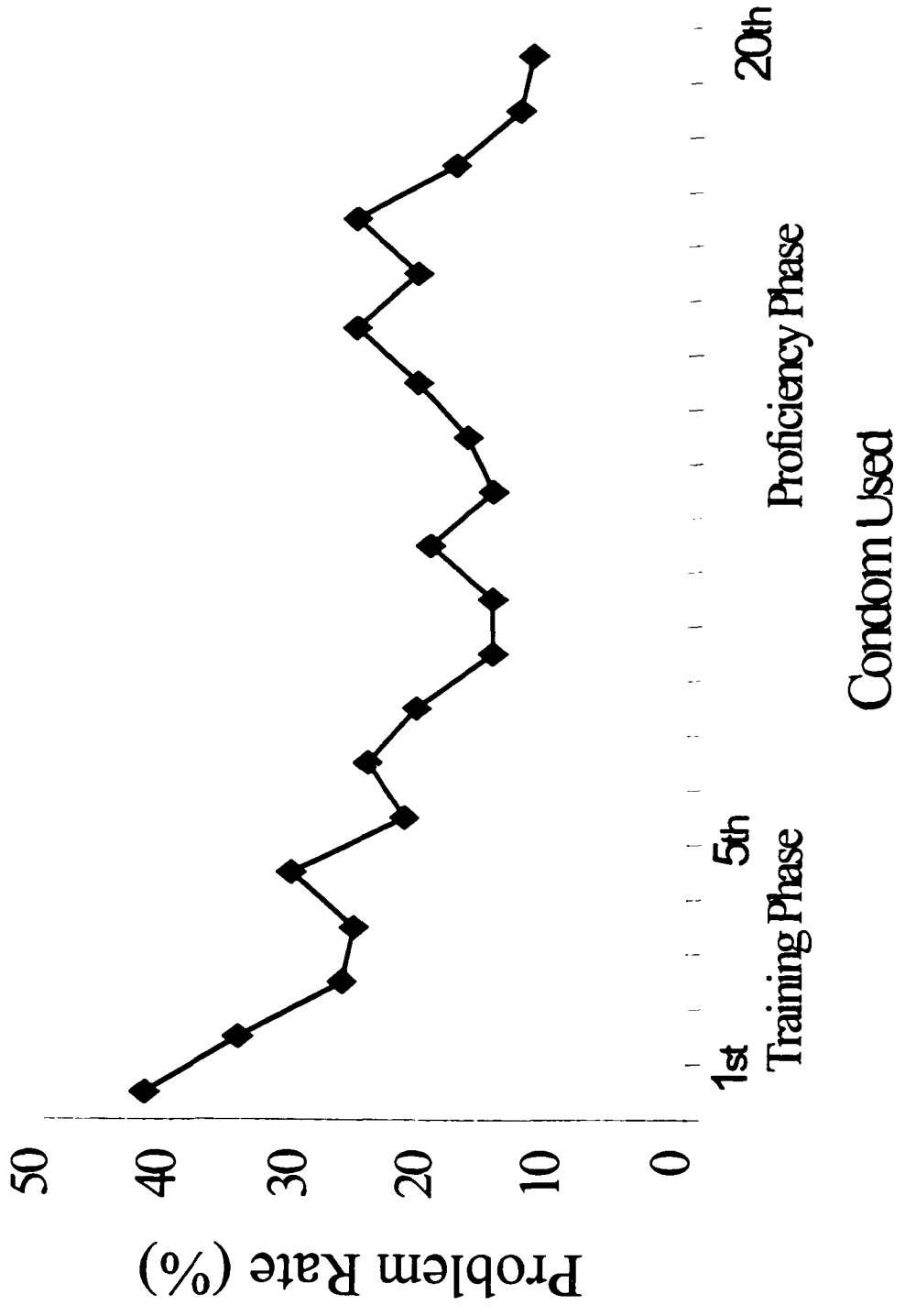
Over 40% of the women reported having one or more problems with the first female condom used (Figure 1). The rate declined with the number of condoms used but was still 10% at the 20th use. To clarify whether the decline in problem occurrence is a real effect of experience with condom use rather than an artifact due to the early withdrawal of couples who experience frequent problems, the average problem rates by use order were evaluated separately for women who withdrew from follow up after using fewer than 20 condoms each and for women who completed the study. The women who discontinued early showed higher problem rates than the women who continued in the study, but the decline in problem rates from the training phase to the proficiency phase remained evident among the women who completed the study (results not shown in detail).

Postcoital PSA results were obtained for almost all specimens collected by the 81 women who completed the study (394 results for 405 condoms used during the training phase and 1207 results for 1218 condoms used during the proficiency phase) and for most condoms used during the proficiency phase by women who attended the follow-up visit but did not complete the protocol (262 results for 269 condoms used). Results were incomplete for condoms used by women who attended the follow-up visit but did not complete the protocol (79 results for 195 condoms used) and for condoms used by women

Table 1.—Frequency of Problems Reported with Female Condom Use, by Study Phase

Reported Problem	Training Phase 745 Uses	Proficiency Phase 1487 Uses	TOTAL (2232 Uses)	
	n Reports (Rate/100 Uses)	n Reports (Rate/100 Uses)	n Reports (Rate/100 Uses)	*P* value*
Condom broke	4 (0.5)	11 (0.7)	15 (0.7)	0.6
Condom came out of vagina	59 (8)	72 (5)	131 (6)	0.004
Penis entered outside condom	7 (1)	29 (2)	36 (2)	0.07
Outer ring pushed into vagina	31 (4)	42 (3)	73 (3)	0.09
Semen leaked on woman's body	24 (3)	28 (2)	52 (2)	0.05
Condom rode on penis	85 (11)	68 (5)	153 (7)	0.001
Condom made noise	44 (6)	31 (2)	75 (3)	0.001
Woman felt pain or discomfort	62 (8)	70 (3)	132 (6)	0.001
Man felt pain or discomfort	49 (7)	30 (2)	79 (4)	0.001
Bleeding (other than menstrual)	8 (1)	13 (1)	21 (1)	0.6
Inner ring problem	19 (3)	19 (1)	38 (2)	0.03
ANY PROBLEM	259 (35)	296 (20)	555 (25)	0.001

* *P*-value for the test of the null hypothesis of no difference between training and proficiency phase.



who did not complete the training phase (54 results for 145 condoms). Overall, PSA results were available for 527 (71%) of 745 condoms used during the training phase and for 1469 (99%) of 1487 condoms used during the proficiency phase. About 62% of the postcoital PSA levels (n = 1232) were lower than 0.5 ng/ml, 9% were between 0.5 and 1 ng/ml (n = 185), and 29% were higher than 1 ng/ml (n = 579), indicating potential exposure to semen (Figure 2). The precoital specimens of the latter group were tested for PSA to assess whether semen exposure occurred during condom use or was the result of previous semen exposure. Between 7% and 22% of female condom uses resulted in semen exposure (Table 2). Using criterion 1 to define exposure (postcoital PSA >1 ng/ml, precoital PSA ≤ 1 ng/ml) led to the classification of 381 condom uses as positive for semen exposure, corresponding to an exposure rate of 21%. Criterion 1 also resulted in the exclusion of 198 condom uses for which exposure status could not be determined because the precoital PSA was >1ng/ml.

Precoital PSA levels higher than 1 ng/ml were considerably more common for condom uses that occurred within 24 hours of the previous intercourse (102/511, 20%) than for condom uses that occurred at least 24 hours after the previous intercourse (96/1485, 6%). This finding suggests that PSA levels > 1 ng/ml may be found in precoital specimens as a carryover effect of recent unprotected intercourse. According to criterion 1, a relatively small difference between the two specimens is sufficient to categorize condom use as resulting in exposure. Thus, criterion 1 is prone to false positive results (eg, random between-specimen variability resulting from previous semen exposure). It also is prone to detecting minute exposure levels that may be without biological signifi-

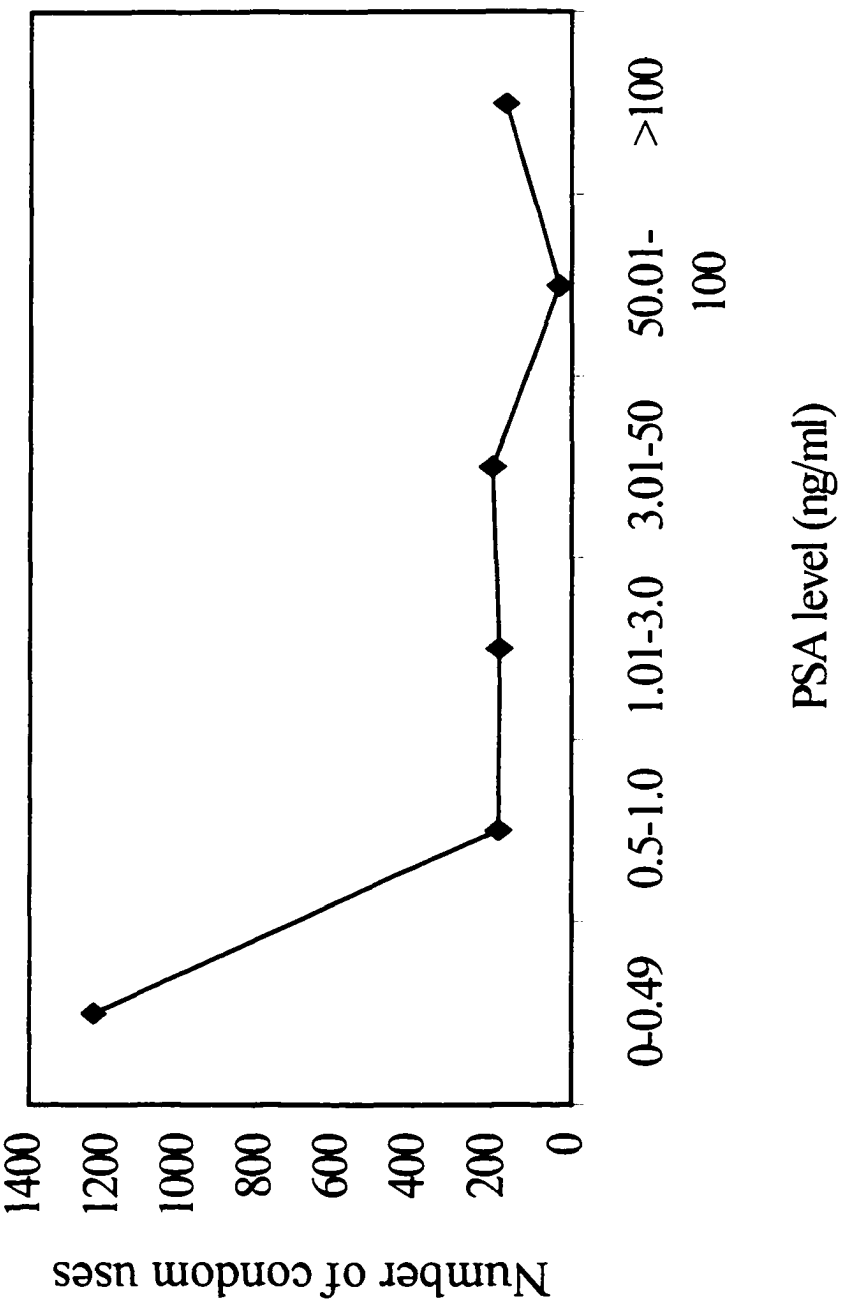


Table 2.—Acts of Intercourse Resulting in Semen Exposure and Semen Exposure Rate, According to Criterion and Time Since Previous Intercourse

Exposure Criterion	Time Since Previous Intercourse: <24 hours (511 Uses) Exposures	<24 hours (511 Uses) Rate per 100 Uses	≥24 hours (1485 Uses) Exposures	≥24 hours (1485 Uses) Rate per 100 Uses	Total (1996 Uses) Exposures	Total (1996 Uses) Rate per 100 Uses
Criterion 1*	80	19	301	22	381	21
Criterion 2†	32	6	121	8	153	8
High sensitivity‡	96	19	315	21	411	21
High specificity§	16	3	107	7	123	6

* Postcoital PSA >1 ng/ml, precoital PSA ≤ 1 ng/ml; exposure was considered as undetermined in 198 instances in which the precoital PSA was > 1 ng/ml.

† Postcoital PSA >1 ng/ml and at least 22ng/ml higher than precoital PSA .

‡ Either criterion 1 or criterion 2 is met.

§ Both criterion 1 and criterion 2 are met; exposure was considered as undetermined in 30 instances in which the precoital PSA was > 1 ng/ml and the postcoital PSA was at least 22 ng/ml higher than precoital PSA.

cance and cannot detect even large exposures that occur in the presence of background PSA levels from previous exposure intercourse (eg, a very high postcoital PSA following a precoital PSA that was very low, but higher than 1 ng/ml, would result in an undetermined exposure status).

Criterion 2 (postcoital PSA > 1 ng/ml and at least 22ng/ml higher than the precoital PSA) imposes a stricter definition of exposure which is both less prone to false positive results, and is more likely to detect larger exposures. According to this criterion, 153 condom uses resulted in semen exposure, corresponding to an exposure rate of 8%. On the other hand, criterion 2 probably has lower sensitivity than criterion 1 and results in an unspecified number of false negative results.

The union of the two criteria (either criterion 1 or criterion 2 is met) yields a high sensitivity criterion, which we regarded as the upper boundary for the exposure rate. According to the high sensitivity criterion, 411 condom uses resulted in semen exposure, for

an exposure rate of 21%, virtually identical to the result of criterion 1. The intersection of the two criteria (both criterion 1 and criterion 2 are met) yields a high specificity criterion, which we regarded as the lower boundary for the exposure rate. According to the high specificity criterion, 123 condom uses resulted in semen exposure, for an exposure rate of 6%, slightly lower than the result of criterion 2. The results of this analysis suggest that the frequency of exposure to semen during female condom use is likely to be in the range of 6% to 21%.

The following analyses focused on the correlation of self-reported problems with female condom use and exposure to semen. Specifically, the objectives of this analysis were to determine the exposure rates associated with specific self-reported problems, including breakage and slippage, and to determine whether semen exposure could occur in the absence of self-reported problems. Both the high sensitivity and the high specificity criteria were used to classify exposure status in this analysis. To minimize the problem of carryover exposure from recent unprotected intercourse, the analysis was restricted to the 1485 condom uses that occurred at least 24 hours after the previous intercourse.

Table 3 shows the distribution of semen exposure by categories of self-reported problems. At least one problem was reported with 324 (22%) of the 1485 uses. The overall exposure rate when any problem was reported was 17% according to the high specificity criterion and 30% according to the high sensitivity criterion. By contrast, the range of exposure rates when no problem was reported was between 5% and 19%. The average postcoital PSA in the presence of any problem was 19.3 ng/ml (median: 0.33 ng/ml) while the mean postcoital PSA in the absence of any reported problem was 7.8 ng/ml (median: 0.24 ng/ml). The difference was statistically highly significant (P =

0.002), indicating that there is an association between user-reported problems and semen exposure. This association was much stronger with specific user-reported problems: it was strongest with condom breakage and was considerably stronger than average for problems associated with severe displacement of the sheath, such as misrouting of the penis and pushing of the outer ring into the vaginal cavity. It was also strong when semen spilled on the woman's body during or after intercourse. Other user-reported problems were associated with exposure rates and postcoital levels similar to those observed in the absence of any reported problems.

Although the frequency of exposure in the absence of reported problems was lower than when problems were reported, it was not negligible. According to the high specificity criterion, 107 of 1485 condom uses led to substantial exposure to semen, but only 50 (47%) of the exposures were associated with a user-reported problem. If exposure is classified according to the high sensitivity criterion, user-reported problems account for only 94 of 315 exposures. Thus, between 50% and 70% of semen exposures occur in the absence of any user-reported problems.

As observed with the frequency of user-reported problems, semen exposure rates declined with condom use (Table 4). The trend was statistically significant only when exposure was classified according to the high sensitivity criterion but was also present in maximum-specificity estimates.

The user-reported problems that appeared to be associated with semen exposure were evaluated in a regression model that included condom use order (ie, 1st, 2nd, etc.) and explicitly modelled the correlation between repeated condom uses of the same couple. The results of this analysis are presented in Table 5. Even accounting for the corre-

Table 3.—Rates of Semen Exposure by Categories of User-Reported Problems

Reported Problem	n of Uses	Semen Exposure Rate (per 100 uses)		Postcoital PSA Mean (Median)
		High Sensitivity	High Specificity	
Any	324	30	17	19.3 (0.33)
Condom broke	11	73	67	72.8 (100)
Came out of vagina	79	22	12	16.6 (0.21)
Penis entered outside condom	23	57	52	44.8 (31.5)
Outer ring pushed into vagina	42	74	55	56.9 (100)
Semen leaked onto woman's body	35	57	44	40.7 (3.7)
Condom rode on penis	96	18	7	9.4 (0.20)
Condom made noise	51	18	8	8.9 (0.22)
Woman felt pain or discomfort	82	17	7	9.2 (0.18)
Man felt pain or discomfort	45	33	11	11.5 (0.46)
Bleeding (other than menstrual)	17	18	18	10.9 (0.25)
Inner ring problem	21	14	0	0.5 (0.13)
No problem	1,161	19	5	7.8 (0.24)
All uses	1485	21	7	

Restricted to 1485 acts where no sex was reported in the previous 24 hours.

Table 4.—Semen Exposure Rate by Condom Used

Exposure Criterion	Condom Used: 1st-5th Exposures/Uses (Rate)	6th-10th Exposures/Uses (Rate)	11th-15th Exposures/Uses (Rate)	16th-20th Exposures/Uses (Rate)	Trend *P*
High sensitivity	103/414 (25%)	99/435 (23%)	72/351 (21%)	41/285 (14%)	0.001
High specificity	33/388 (8.5%)	36/404 (8.9%)	24/328 (7.3%)	14/263 (5.3%)	0.11

Restricted to 1485 acts where no sex was reported in the previous 24 hours.

lation of repeated measurements and for the order in which the condom was used, condom breakage, misrouting of the penis during intercourse, pushing the outer ring into the vaginal cavity, and spillage of semen on the woman's body were strong predictors of semen exposure. These associations are moderate to very strong and were statistically significant in models using either the high specificity or the high sensitivity criterion. For each type of problem, the association with semen exposure was stronger when exposure was classified according to the high specificity criterion. This finding is compatible with reduced misclassification of exposure in the high specificity model but is also compatible with the tendency of the four user-reported problems to produce high levels of semen exposure. Table 5 also reports the number of semen exposures that can be attributed to each problem. According to the high sensitivity analysis, a total of 59 (19%) of the 315 exposures are due to the four user-reported problems. The attributable proportion would range from 13%, if the number of attributable exposures were computed using only the lower 95% confidence boundary of the problem-specific OR, to 21%, if the upper confidence boundary were chosen. According to the high specificity analysis, 44 (42%) of the 107 exposures are due to the four user-reported problems. The attributable proportion range

was 34% - 45%. Thus, it appears that well-identified problems, such as breakage and slippage, can only account for a fraction of the total burden of semen exposure.

Table 5.—Multiple Regression Analysis of User-Reported Problems and Semen Exposure*

Predictor	Semen Exposure Odds Ratio* (95% Confidence Interval)		Semen Exposures Attributable to Specific Problems	
	High Sensitivity	High Specificity	High Sensitivity	High Specificity
Use number	.96 (.94 – .99)	.96 (.91 – 1.0)	Not applicable	Not applicable
Condom broke	13.3 (3.1 – 56)	38 (7.9 – 180)	7.4 (5.5–7.9)	5.8 (5.2–6.0)
Penis entered outside condom	2.9 (1.2 – 7.2)	6.6 (2.4 – 18)	8.5 (1.7–11.2)	9.3 (6.5–10.4)
Outer ring pushed into vagina	9.3 (4.6 – 19)	13.6 (6.4 – 29)	27.7 (24.3–29.3)	18.5 (16.9–19.3)
Semen leaked onto woman	4.3 (2.1 – 8.8)	6.3 (2.8 – 14)	15.4 (10.6–17.7)	10.9 (8.3–12.1)

* Restricted to 1485 acts where no sex was reported in the previous 24 hours.
* Adjusted by all other variables shown in a generalized linear model with repeated effects.

DISCUSSION

This is the first study to evaluate the frequency of user-reported problems and semen exposure among female condom users. Despite the select nature of the study group (low risk, relatively high income couples) and state-of-the-art training, user problems during female condom use were reported in over 25% of uses and 75% of users. We have documented[4] that the cumulative number of reported problems is a strong predictor of use discontinuation, suggesting that acceptability of the device for long-term use is limited even among well-trained and motivated users.

A unique characteristic of this study is the collection of an objective indicator of condom failure. For the mechanical failure of the condom to have biological significance,

it must lead to release of semen into the vaginal cavity. A simple procedure was developed to assess semen exposure as an intermediate marker of condom failure, which is based on the detection of PSA in self-collected vaginal fluid samples. We have shown that the procedures employed in this study comprise a highly sensitive and specific method for detecting recent exposure to semen, especially when vaginal fluid is sampled shortly after exposure.[7] Vaginal fluid specimens were collected by the participant women before and after each condom use, thus allowing the measurement of pre- and postcoital PSA levels to ascertain the frequency of semen exposure during use. This was the first time that such measurements were available in a large scale study of condoms, and the findings provide considerable new insight into the efficacy of condoms, in general, and into the biological significance of commonly reported reasons for condom failure, such as breakage and slippage.

This study documented that user-reported problems are correlated with semen exposure. In particular, condom breakage and certain categories of displacement were associated with high rates of semen exposure and high average postcoital PSA levels. A large number of user-reported problems did not result in semen exposure in this study, and it is clear that user-reported problems can explain only a fraction of the instances of semen exposure. To the extent that semen exposure is a biological marker of condom failure, users detect only a fraction of condom failures. Also, given that over 50% of the instances of semen exposure were not associated with a specific problem, it also seems possible that condom failure can occur through mechanisms that are still unknown.

The frequency of reported problems declined with experience but was relatively high even after many uses of the condom. The frequency of semen exposure also de-

clined, albeit more weakly, with experience. The decline in frequency of problems and semen exposure is compatible with the effect of experience on modifiable determinants of condom failure, but the relatively high residual frequency of problems and semen exposure suggests that non-modifiable determinants of failure play a significant role.

Several limitations must be acknowledged in interpreting the present investigation. First, the study was carried out in a highly select group of couples. Thus, some caution should be exercised in generalizing these findings. On the other hand, low risk couples are the usual target of phase II studies of new condoms, and it was important that the present investigation follow the guidelines for the conduct of such studies. It is likely that the same categories of problems would have been experienced by other groups of users, although it is prudent to assume that couples of lower socioeconomic and educational levels may have experienced higher problem rates and more semen exposure. This consideration is particularly disturbing given the high rates observed in this study.

Second, loss to follow up was high, with fewer than half of the women who initially enrolled in the study completing the study protocol. The impact of withdrawals on the interpretation of our findings is uncertain. Women who contributed data to this analysis were not substantially different from those who did not. There were no differences in sociodemographic characteristics or semen exposure rates between the two groups of women. The women who did not complete follow up were more likely to dislike the appearance of the female condom and to express an aversion to inserting it. Also, because user problems are associated with increased risk of withdrawal and are associated with semen exposure, it is likely that selective withdrawal of couples who experienced high rates of problems and semen exposure led to an underestimation of the frequency of

semen exposure in the study. On the other hand, the cohort dynamics likely reflect what would occur in the population at large, with some couples experimenting with the new product and discontinuing its use early (possibly because of high problem rates), and some couples continuing on at lower frequency of problems and exposure. Thus, the experience of this study group may relevant to the general population.

Third, assessment of semen exposure presented several challenges. The most important challenge was to identify a threshold PSA level that would indicate recent exposure to semen. We had previously documented that levels above 1 ng/ml are indicative of semen exposure.[5] On the other hand, low PSA levels may persist for 24-48 hours after unprotected intercourse.[7] Thus, a higher threshold may be more appropriate to avoid false positive results. Furthermore, the biological significance of low semen exposure is uncertain. It is unlikely that small semen exposures leading to low PSA levels bear a high risk of conception. On the other hand, even a small amount of semen or other male secretions can carry a number of pathogenic microorganisms that may be sufficient to transmit infection. A high sensitivity level is also desirable for forensic applications (eg, rape investigations). Given these uncertainties, we specified two alternative exposure assessment criteria and combined them to provide a lower (high specificity) and an upper (high sensitivity) boundary for the frequency of exposure to semen resulting from female condom failure. The true rate of semen exposure during female condom use most likely lies between 7 and 21%, although, in our opinion, the more conservative 7% figure is probably closer to the rate of exposure that is biologically relevant.

The limitations described above are more than compensated by several strengths of the study. This is the first time an objective marker of condom failure has been used to

assist with the interpretation of problems reported by the users. The successful implementation of the study protocol shows that it is possible to conceive of a new generation of phase II studies in which semen exposure is used as an intermediate marker of pregnancy or STD risk. Although only 81 of 210 women completed the study, compliance with the sampling and record-keeping requirements of the protocol was exceptionally high while the participants were in the study. The request that each participant return a form describing experience with each condom used secured the most critical information even if the participant withdrew from the study. Overall, 175 women returned 4464 vaginal samples during the study, demonstrating that implementation of the sampling procedures is possible on a large scale. Finally, the availability of data on self-reported problems concurrent with water leakage tests and semen exposure data allowed for the first time validation of user reports with objective measurements. Water leakage testing of the used condom provided evidence that user-reported breakage is not always accurate, and semen exposure data were correlated well with those user-reported problems that most likely indicate condom failure.

In conclusion, this study developed objective methods for assessing condom failure and demonstrated the application of these methods among couples at low risk of pregnancy and STD who used the female condom. The rate of female condom failure as measured by semen exposure was relatively high in this study. Furthermore, semen exposure occurred often in the absence of user-reported problems. To the extent that semen exposure is an indicator of pregnancy and STD risk, these findings indicate that self-report is not an accurate source of information on the frequency of condom failure. It is

not known whether this problem is specific to the female condom. The male latex condom and condoms made of new materials should be evaluated using similar procedures.

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DETERMINANTS OF SEMEN EXPOSURE DURING USE OF THE FEMALE CONDOM

by

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SUMMARY

Context

The female condom has been marketed as an alternative to the male condom for the prevention of pregnancy and sexually transmitted disease (STD).

Objective

To assess the determinants of semen exposure during use of the female condom.

Design

A prospective follow-up study.

Setting

A study of breakage and slippage in the female condom conducted at the University of Alabama at Birmingham (UAB).

Participants

A total of 210 low-risk women were recruited primarily from UAB staff and students, with some additional participants from the Birmingham community.

Intervention

Participants were trained to use the female condom and follow study procedures during a 2 hour group training session.

Main Outcome Measures

Semen exposure as defined by pre- and postcoital prostate specific antigen (PSA) levels in vaginal fluid.

Results

Couples with a large disparity in diaphragm diameter and penis size were at significantly increased risk of semen exposure (odds ratio [OR] 3.8, 95% confidence interval [CI] 1.33-8.09). Engaging in extremely active intercourse also increased the risk of semen exposure (OR 1.99 95% CI 1.23-3.23). Women who were not sure that they could easily use the condom were also at increased risk of semen exposure (OR 2.22 95% CI 1.25-3.96). Women with high incomes were protected against semen exposure, indicating that more sophisticated users are potentially more successful in correctly using the condom.

Conclusions

The female condom may not be the best choice for some couples, and users should be cautioned to avoid extremely active intercourse. Training should be provided to insure correct use.

INTRODUCTION

The Reality brand female condom is an intravaginal barrier device marketed as an alternative to the male condom for the prevention of pregnancy and STD. A key factor in determining the appropriateness of promoting the female condom to at risk women is

whether or not the condom is an effective barrier to STD and human immunodeficiency virus (HIV). The theoretical efficacy of the Reality condom in preventing STD is high. An *in vitro* study with mechanical simulation of coitus showed no leakage of cytomegalovirus or HIV through the polyurethane membrane of the female condom.[1] Unfortunately information available about the efficacy of the female condom in preventing STD *in vivo* is limited. The only evidence of a protective effect is from one small study of trichomonas re-infection[2] and a report from a Joint United Nations Programme on HIV/AIDS (UNAIDS) study of Thai female prostitutes who were given both the male and female condom.[3]

Current guidelines for testing new condoms require phase I studies evaluating hypersensitivity in animals and acceptability/adverse effects in humans, followed by phase II ("slippage and breakage") studies that evaluate self-reported mechanical failure of the condom among couples at low risk of pregnancy and STD. Phase III/IV efficacy trials complete the efficacy evaluation. These phases generally measure pregnancy and STD rates among large groups of couples who use the condom. We have developed a protocol for phase II/III studies based on the measurement of biological markers of semen exposure to augment the traditional assessment of self-reported user problems and replace pregnancy and STD as outcomes.

We recently used this protocol to determine the frequency of breakage, slippage, and semen exposure among female condom users and found that breakage of the condom was extremely rare (less than 1% of uses) and slippage was relatively common (13% of 2300 condom uses). More importantly, we found a relatively high rate of semen exposure after use of the condom (range 7-21%, depending on the criteria chosen to define

semen exposure) and documented that semen exposure occurs in the absence of any user-reported problems.[4] Thus, the efficacy of the condom in preventing semen exposure is not high.

To assist with developing effective strategies to promote the female condom and interventions to counsel and train prospective users, it is important to know not only how often the condom fails in general but also under what specific circumstances the condom fails. For example, because the female condom is manufactured in only one size, the possibility exists that the physical characteristics of the users influence the likelihood of semen exposure. It is also reasonable to assume that the probability of condom failure is a function of characteristics of each sexual act. The purpose of the analysis reported here was to describe the relation between characteristics of the user, characteristics of the intercourse, and semen exposure during use of the female condom.

METHODS

The study design has been described in detail elsewhere.[5] Briefly, this was a prospective study of couples using the female condom. Potential participants were screened for eligibility during a telephone interview. Eligibility criteria included current use of an effective nonbarrier method of birth control, being in a mutually monogamous relationship, maintaining a minimum coital frequency of 6/month, experience with tampon use, being at low risk of STD, having an intact uterus, and being between 21 and 49 years of age. The female partner of an eligible couple participated in a training session, including a brief promotional intervention and instruction on the correct use of the female condom. She was also trained to (1) take pre- and postcoital vaginal swabs and package and return

used condoms and swabs to the project staff; (2) complete a form describing her experience using the condom and include the form with each returned condom; and (3) keep a coital log, which included information about number of times the couple changed positions during intercourse, positions used, activity level and length of intercourse. At the end of the training visit, the participant practiced inserting the female condom and taking vaginal swabs under the supervision of a nurse practitioner. The nurse practitioner took a diaphragm measurement of each participant using an Ortho fitting diaphragm set with 5 ring sizes (65, 70, 75, 80 and 85 mm diameter Ortho Pharmaceutical Corporation, Raritan, NJ, USA). Finally, the participant was shown 5 different sized drawings of an erect penis and asked to indicate which was closest to her partner's penis size.

Each participant left the clinic with 5 female condoms to test with her partner. After testing the 5 condoms, she returned for a follow-up visit. At follow up, the participant returned her coital log and was interviewed about her use of the female condom and any problems associated with it. The participant was issued 15 more condoms to test and was asked to return for the final visit after all of the condoms had been used. She was also given a penis measuring kit (Los Angeles Regional Family Planning Council, Inc., Los Angeles, CA, USA) and instructed on how to use the kit at home with her partner. The final visit was usually scheduled within 3 months of the training session and was similar to the follow-up visit.

Assessment of Semen Exposure

The laboratory procedures have been described elsewhere[4] and were based on the detection of PSA in vaginal specimens.[6,7] Briefly, vaginal swabs were returned dry to the

study office. Swabs were eluted in saline and frozen at -80° C. Thawed eluent samples from all postcoital swabs were tested for PSA with the Abbott IMx immunoassay (Abbott Laboratories, Abbott Park, IL, USA). If the postcoital sample had a PSA level of above 1 ng/ml, the matching precoital sample was also tested for PSA.

Each condom use for which the postcoital swab had a PSA level of 1 ng/ml or less was defined as negative for semen exposure. A condom use resulting in a postcoital PSA level of greater than 1 ng/ml was considered positive for semen exposure if the value of the precoital swab was less than 1 ng/ml and the difference between pre- and postcoital swabs was greater than 22 ng/ml. If the precoital sample was less than 1 ng/ml but the difference between the two samples was less than 22 ng/ml, the condom use was considered negative for semen exposure. If the difference was greater than 22 but the precoital swab was over 1 ng/ml, then semen exposure was classified as undetermined for that condom use. We consider these criteria to maximize the specificity of the test for recent semen exposure.[4]

Estimates of Penis Volume

Participants measured the circumference of the penis at mid-shaft and at the base of the glans, and the length of the penis from the base to the tip. The kit used for penis measurements included long strips of colored paper without any markings. Measurements were taken by wrapping the paper at the appropriate level for the circumference or laying it against the penis for the length and tearing off excess paper from each strip. Participants were trained to take the measurements in the clinic during the follow-up visit and were also given written instructions. Penis volume was estimated by assuming that

the glans was a cone with height equal to the diameter of the base. The length of the shaft was calculated by subtracting the estimated height of the glans from the reported total penis length, and the volume of the shaft was calculated from the estimated length and the reported shaft circumference. The estimated volumes of glans and shaft were added to obtain total penis volume.

Data Analysis

The objective of this analysis was to assess the association between semen exposure and physical attributes, demographic and lifestyle characteristics, and attitudes. Age, race, diaphragm size, penis volume measurements, and their interaction term were forced into the final model because they were considered potential confounders *a priori*. A parsimonious model building strategy was adopted in the analysis. The potential risk factors were grouped into three broad domains: (1) sociodemographic and lifestyle characteristics, (2) attitudes about the female condom, and (3) physical characteristics of the couple and the sexual act.

Sociodemographic and lifestyle variables included age, race, education, employment status, relationship length, reported number of sex acts per month, marital status, student status, current tampon use, per capita income (ie, household income divided by number of people in the household), and lifetime number of partners. The characteristics of the sexual act were determined from the coital log and included length of intercourse, number of position changes, types of positions used, and activity level. Because the coital log was returned at follow-up visits, coital log information is available only for those

participants who were not lost to follow up, and this analysis is restricted to those acts of intercourse for which coital log information is available.

At the initial visit the participant completed a questionnaire designed to measure her attitudes about the female condom.[8] Participants responded to a series of 30 statements about female condoms using a 5-level Likert scale. Participants were instructed to answer "don't know" if they had no opinion on a particular item. In a previous analysis of determinants of female condom use,[5] subsets of questions (attitude factors) were created from these statements using principal component analysis. Rounded mean scores for the attitude factors were calculated for each participant. These scores describe attitudes toward the female condom (ie, she is averse to inserting it, she finds it difficult to use, she thinks it does not give the woman control, she dislikes its appearance, she believes it does not work, she believes it is not needed in long-term relationships) and were included as linear predictors of semen exposure in logistic regression models.

Logistic regression was used to estimate the OR of semen exposure for each risk factor while adjusting for all other factors in the same domain. The risk factors that displayed an adjusted OR of over 2 (or less than .5) or were statistically significant (at alpha $< .2$) were included in the final logistic regression model. Previous studies[7,9] indicated that a "false positive" PSA signal could be detected up to 24 hours after unprotected intercourse, so the analyses reported in this paper were restricted to condom uses that took place at least 24 hours after the previous act of intercourse. Because each participant used up to 20 condoms, correlation of results within an individual was possible. All logistic models were fitted using generalized estimating equations (PROC GENMOD repeated option[10]) to take into account the correlation between repeated measurements in

estimating predictors and standard errors.[11] A second model in which the within subject correlation was modeled explicitly as auto-regressive order 1 yielded virtually identical results. The order of condom use was included in all models to estimate the effect of experience on the risk of semen exposure. Goodness of fit was evaluated by examining the model deviance and plotting the deviance residuals against the predictor variables.

RESULTS

Two hundred and ten women participated in the training session. Of these, 35 (17%) never returned a female condom, 128 (61%) returned for the first follow-up visit and 81 (39%) women completed the study protocol of using 20 female condoms each. The women who participated in the training session had a median age of 27 years and a median household per capita income of about $600 a month. They had been in their current relationships for a median of 4 years and reported a median of 12 sexual contacts per month. Over 70% were White, over half were married, and over half had completed college. The 100 women who contributed information to this analysis had the same pattern of sociodemographic characteristics.

During the study 2232 female condoms were used, semen exposure data was available for 1996 uses, and coital log information was available for 1652 uses. The analysis was further restricted to include only acts of intercourse that took place over 24 hours after a previous intercourse and for which semen exposure was defined, resulting in 1149 condom uses that were included in this analysis. Attitude questionnaires were not available for 3 participants (33 condoms).

Table 1 shows the distribution of condom uses and resultant semen exposure according to selected sociodemographic characteristics. The three variables retained for the final model from this domain were relationship length, per capita income, and number of lifetime partners. Participants who had been in their current relationship for less than 2 years were twice as likely to be exposed to semen with each use of the condom, as were women who had more than 3 sexual partners in their lifetimes. Women with a relatively high per capita income of over $900/month were significantly less likely to be exposed to semen.

Table 2 shows the distribution of uses and semen exposure by responses to attitude factors. In general, women had positive attitudes about the condom after the training session,[1] so the number of uses among women who expressed negative attitudes about the condom is small. Significant associations were noted for 3 attitudes: believing that the condom is difficult to use; believing that the condom does not give the female control; and not liking the appearance of the condom. The highest levels of semen exposure were observed among women who indicated that they did not like the appearance of the condom (41% of uses positive for semen exposure) and women who believed the condom did not give the woman control (17% of uses positive for semen exposure). Women who had no opinion about whether the condom was difficult to use were more likely to be exposed to semen than other women (10% vs. 3% exposed uses).

Of the 100 couples included in this analysis, penis measurements were available for 73. Data from 65 individuals were included in an analysis of variance (ANOVA) model to determine whether the partner's penis measurements could be predicted using the woman's estimate of the partner's penis size obtained during the training visit (this

Table 1.—Semen Exposure and Selected Baseline Characteristics

Characteristic	n of Women	Exposures*/ Uses	% Positive	Odds Ratio†	*P* Value‡
Age					
< 24 years	23	15/262	6	.74	.49
≥ 24 years	77	71/887	8	1	n/a
Race					
White	77	52/897	6	.70	.30
Non-White	23	34/252	14	1	n/a
College graduate					
Yes	58	38/668	6	.97	.93
No	42	48/481	10	1	n/a
Current employment					
Yes	79	64/912	7	.73	.37
No	21	22/237	9	1	n/a
Married					
Yes	66	48/772	6	.88	.71
No	34	38/377	10	1	n/a
Current student					
Yes	46	33/500	7	.66	.23
No	54	53/649	8	1	n/a
Percapita income					
> $900/month	33	14/365	4	.36	.04
≤ $900/month	67	72/784	9	1	n/a
N lifetime partners			10	2.15	.07
> 3	59	63/635			
≤ 3	40	231/496	5	1	n/a
Relationship length					
< 2 years	16	25/219	11	2.00	.07
≥ 2 years	84	61/930	7	1	n/a
N sex/month					
< 9	28	22/381	6	.68	.30
≥ 9	72	64/768	8	1	n/a
Tampon use					
Current	74	55/847	6	.80	.58
Past only	26	31/302	10	1	n/a
TOTAL	100	86/1149	7	n/a	n/a

* Exposure to semen after use of a condom.

†Adjusted in a repeated measures logistic regression model for all other variables shown.

‡ *P*-value for the null hypothesis of no association between semen exposure and levels of the characteristic.

Table 2.—Attitudes Toward the Female Condom at the Initial Visit and Exposure to Semen During Follow Up

	Strongly Disagree	Disagree	No Opinion	Agree	
Attitude About the Female Condom	**Exposures*/ Uses**	**Exposures/ Uses**	**Exposures/ Uses**	**Exposures/ Uses**	***P* Value†**
Averse to inserting	16/202	52/705	14/179	2/30	.48
Difficult to use	0/0	12/376	71/712	1/28	.03
Does not give the female control	9/171	45/744	8/73	22/128	.05
Don't like appearance	9/184	41/607	25/303	9/22	.09
Doesn't work	5/94	50/774	20/211	9/37	.63
Isn't needed in long-term relationships	13/222	50/605	13/191	8/98	.73
Aren't worth the trouble‡	10/161	50/676	21/259	3/20	.65
Like that the woman uses‡	0/16	6/47	3/114	75/939	.25
Can make sexy with the right attitude‡	0/0	1/28	12/71	71/1017	.59
Like being able to put in before sex‡	1/9	5/49	10/200	68/858	.78

* See text for definition of exposure to semen

† *P*-value for the linear trend, adjusted by all other variables in this table and time in a repeated measures logistic regression model.

‡ Individual question that did not load in a factor.

item was available for 90 couples). While all direct penis measurements (tip, length, and shaft) were significantly predicted by the woman's estimate, the estimated penis volume had the strongest association and the clearest relationship with the woman's initial estimate ($P < .001$). The estimated mean penis volume from the ANOVA model increased in a clear dose response relationship with the woman's estimate of penis size. Based on this analysis, penis volume of each of the 27 partners with missing measurements was estimated using the mean of the nonmissing penis volume measurements reported by women who chose the same size penis during the initial visit. Penis size measurements were available for 14 additional participants who were not included in this analysis. The hypothesis that the participant's estimate was a good proxy for actual penis size was tested with all available data (n = 81) in a logistic regression model specifying a penis volume above the median as the outcome and the woman's estimate as the predictor variable. Women who chose the 2 largest penis sizes were 4 times more likely to have the partner's measured penis size fall above the median than women who chose the smallest size ($P = .04$).

Semen exposure rates for the physical characteristics of the couples and the intercourse-specific variables are presented in Table 3. Diaphragm size *above* 70 mm was strongly associated with semen exposure, but there was a strong negative interaction between penis and diaphragm size (OR = 0.19, $P = .01$). Thus, there was an almost fourfold increase in the odds of semen exposure in couples in which the woman had a diaphragm size *above* 70 mm and the man had a penis size *below* the median, as compared to couples in which the woman's diaphragm size was 70 mm or less and the partner's penis volume was *below* the median. If the diaphragm size was *above* 70 mm and the penis

size was above the median, however, the risk of semen exposure was substantially lower (OR = 1.2). Activity level was the only other variable from this domain that was associated with semen exposure and included in the final model. Women who reported that the intercourse was of a higher intensity than usual for the couple were over 3 times more likely to be exposed to semen.

Table 3.—Physical Characteristics of the Couple, Characteristics of the Intercourse, and Semen Exposure

Characteristic	Exposures*/ Uses	% Positive	Odds Ratio†	*P* Value‡
Diaphragm size 75-80				
Penis size above median	17/261	7	1.2	.63
Penis size below median	28/160	18	3.7	.01
Diaphragm size 65-70				
Penis size above median	22/322	7	1.6	.27
Penis size below median	19/406	5	1	n/a
Activity level				
High	28/223	13	3.2	.004
Usual	49/706	7	1.6	.17
Low	9/216	4	1	n/a
Intercourse duration				
Above median	50/605	8	1.3	.30
Below median	36/544	7	1	n/a
Positions used				
Woman on top only	22/215	10	1.2	.65
Other position only	2/48	4	.53	.45
Mixed postions	22/422	5	.61	.07
Man on top only	55/807	7	1	n/a
Number of position changes§				
At least one	29/475	6	.88	.57
None	72/1013	7	1	n/a

* Exposure to semen after use of a condom

†Adjusted in a repeated measures logistic regression model for time and all other variables shown.

‡ *P*-value for the null hypothesis of no association between semen exposure and levels of the characteristic.

§Included in a separate model from positions used.

Estimates from the final regression model are presented in Table 4. The risk of semen exposure for women with a large diaphragm size is lower in the final model, indicating some of the effect observed in the domain-specific analysis may be due to confounding by other variables. The negative interaction between diaphragm size and penis volume retains its strength and significance in this model. Activity level is modeled here as a linear predictor, and the effect measure of 2.02 indicates that a unit increase in activity category results in a doubling of the risk of semen exposure. In addition, women who stated that they did not know whether the condom would be difficult to insert were over 2 times more likely to be exposed to semen during use of the condom. The protective effect of high income remained strong in the final model, with high income women being over 3 times less likely to be exposed to semen than lower income women. Experience with the condom (condom use order) is not related to semen exposure in the final model of this analysis.

DISCUSSION

In this group of women, semen exposure occurred during at least 7% of the uses of the female condom. While there were several significant predictors of semen exposure, the strongest association was observed with the physical characteristics of the couple, which are not modifiable risk factors. The negative interaction of diaphragm and penis size suggests that couples who have a difference in size are at substantially increased risk of semen exposure. The reason for the increased frequency of semen exposure is unclear. It is possible that the combination of a large diaphragm and a small penis facilitate movement of the device due to a looser fit at both the cervix and within the condom.

There was no relationship between user-reported slippage and diaphragm/penis size, however (data not shown). The manufacture of female condoms of different sizes may reduce the extent of this problem.

Table 4.—Final Model: Odds of Semen Exposure After Using Female Condom

Predictor	Odds Ratio*	95% Confidence Interval
Age less than 24 years	0.98	0.45-2.14
White race	0.77	0.43-1.36
Relationship length of less than 2 years	1.75	0.90-3.38
Per capita income above $900/month	0.38	0.19-.80
Over 3 lifetime sexual partners	1.96	0.91-4.22
Has no opinion about difficulty of use	2.22	1.25-3.96
Believes condom does not give the female control	1.10	0.81-1.48
Does not like appearance of condom	1.14	0.76-1.70
Condom use order	1.00	0.96-1.04
Diaphragm size 75-80		
Penis size above median	1.20	0.45-3.21
Penis size below median	3.28	1.33-8.09
Diaphragm size 65-70		
Penis size above median	1.72	0.74-4.02
Penis size below median	1	n/a
Activity level of intercourse	1.99	1.23-3.23

*Adjusted in a repeated measures logistic regression model by all other variables shown.

The strong association between activity level and semen exposure is remarkable because no objective scale of measurement is available for intensity of intercourse. In

this study, the activity level rating is a subjective, within-couple assessment of departure from the average behavior of the couple. The woman was instructed to rate activity level as compared with her usual experience with her current partner. Across-couples comparison may be problematic, as one woman may rate as average what another woman would rate as high intensity. Despite these difficulties, the results strongly suggest that unusually intense activity could reduce the protective effect of the female condom.

The only attitude factor that was significantly associated with semen exposure after adjustment for sociodemographic and physical characteristics was having no opinion about whether the condom was difficult to use. It is conceivable that not having enough confidence about ease of use is associated with behaviors that decrease efficacy. For example, a doubtful user may be less inclined to try corrective measures (eg, adding lubricant) that could reduce the likelihood of condom failure.

A high income level is strongly associated with protection from semen exposure in this study. It is possible that the reason for this effect is that the study population was drawn from a university research environment where many of the higher paid employees are clinical or research professionals. Because many of these individuals had experience in clinical research both as participants and as research staff, higher income may be an indicator of advanced skills in following complex instructions and in maintaining adherence to a protocol. In any case, this finding suggests that maximum efficacy with using the female condom may be achieved by rather sophisticated users.

Several weaknesses should be considered when interpreting the results of this study. First, loss to follow up was high, with less than half of the women who initially enrolled in the study completing the study protocol by using 20 condoms each. The im-

pact of this loss on the interpretation of our findings is probably minimal because the women who contributed data to this analysis were not substantially different from those who did not. There were no differences in sociodemographic characteristics or semen exposure rates between the two groups of women. The women who did not complete follow up were more likely to dislike the appearance of the female condom and to express an aversion to inserting it. Thus, the women who were included in this analysis are probably similar to women who would use the product, and this potential weakness may actually be a strength.

In addition, 887 acts of intercourse were excluded from the analysis due to restrictions in the selection criteria for the analysis (eg, no matching coital log entry, no sex in the previous 24 hours). Semen exposure results were available for 141 women who used the condom, 60 of whom dropped out of the study without completing the protocol. The impact of this loss was mitigated by successfully retrieving coital logs from 36 (65%) of the dropouts. We have previously demonstrated that slippage of the condom during intercourse is associated with use discontinuation, so it is not surprising that the 464 uses which were excluded from this analysis because of loss to follow up were more likely to have reported slippage. The 423 uses that were excluded because of recent intercourse were also more likely to have reported slippage. Again, because slippage is associated with discontinuation of use, this apparent weakness actually works to make the data analyzed more reflective of those who will actually use the condom. The restriction criteria also selected for acts of intercourse between couples in which the male partner had a smaller penis (based on the woman's estimate) and the woman had a larger diaphragm size. Because of this, the proportion of acts in which the penis size and dia-

phragm measurement was disparate between couples was increased in the analysis group. This would result in an increase in power but would not bias the effect measure (odds of semen exposure).

It is possible that within couple clustering of effects could bias the results and weaken the study. A relatively large number of samples per couple was necessary to observe the effect of experience on failure, thus limiting the total number of couples that could be enrolled. On the other hand, repeated sampling allowed us to assess the effect of the couple on outcome, and effect of the couple on semen exposure was not important.[4] In this analysis, we used two different types of regression models to adjust for repeated measurements, and the results were virtually identical to the results of analyses that did not adjust for repeated measurements, indicating that there was no important clustering of effects.

Direct penis measurements were not obtained for all male partners. This inadequacy of data collection was anticipated. Each woman was asked to estimate her partner's penis size at the training visit, even though it was recognized that the method could be inaccurate, in hopes that we could obtain an acceptable correlation between the woman's estimate and the subset of couples for whom both measures were available. Compliance with the request for penis size measurement was actually higher than expected, and two thirds of the participants provided the needed data. Furthermore, there was a strong relationship between the actual size of the partner's penis and the estimate made at the training visit, lending credibility to the analysis. On the other hand, although there was a strong association between a woman's estimate and the partner's penis size, the predictive value of the ANOVA model was limited (R^2 = .23), indicating that only

23% of the variability in penis volume was explained by a difference in the category of the woman's estimate. The ability of the logistic regression model to correctly predict a penis size above the median (sensitivity of the model) was only 49%, while the ability to correctly predict a penis size below the median (specificity of the model) was 82%. The latter finding lends credibility to the association observed between semen exposure and below-median penis size. Restriction of the analysis to couples for which we had an actual measurement of the partner's penis size, however, led to the same conclusions as the results presented in this paper (although the sample size was reduced by 20% with a consequent reduction in the precision of the estimates).

Finally, this study was designed as a phase II efficacy trial. Thus, the population was at low risk of STD and highly educated. This selection of study participants somewhat limits generalizability of the study findings. It is not clear whether the same associations would be found among high risk users and whether the associations observed would have the same relative ranking. It seems likely, though, that the risk of semen exposure would be higher among women with less training and a lower education level.

These weaknesses may be inherent to the difficult nature of this type of research and, we believe, are outweighed by the study strengths. First, the outcome variable in this analysis was an objective marker of condom failure. This is the first time an objective marker of failure was used concurrently with conventional user-reported failure in a large scale study. For example, in a recently published study of male condom failure, the outcome was retrospective self-report of failure after use of 5 condoms.[12] This method is subject to recall bias and is very likely to underestimate the frequency of condom failure. User reports of female condom failure do not correlate well with the rate of semen expo-

sure.[4] Thus, this study is likely to provide a considerably more realistic appraisal of condom efficacy than slippage and breakage studies conducted according to current convention.[13] Second, data on intercourse-specific activity was collected prospectively in coital logs. Thus, recall bias is less likely and the intercourse-specific data is more likely to be accurate. Third, this analysis is based on a large number of condom uses and a sufficiently large number of couples, so that relatively subtle effects could be measured and the effects of relatively rare predictors could be assessed. Finally, to our knowledge, this is the first condom efficacy study to assess the effect of the physical characteristics of the couple and of intercourse specific characteristics on condom failure.

This study shows that the efficacy of the female condom in preventing semen exposure is limited by both modifiable and nonmodifiable characteristics. Reproductive health practitioners and educators should provide proper training to insure that women have the knowledge and self-confidence necessary to correctly use the condom. For couples in whom there is a large disparity between diaphragm and penis size, the female condom as currently marketed may not be the best option, and manufacturers may want to consider alternative designs. Couples who choose to use the female condom may want to consider extra caution or another barrier method when engaging in extremely active intercourse. Unfortunately, it is not clear that other barrier methods would perform better for such couples, because little information is available to evaluate the performance of other methods according to the characteristics of the couple or the intercourse. The design employed in this investigation can easily be applied to studies of the male latex condom and condoms made of new materials. The results presented in this paper indicate

that such studies are needed to clarify our understanding of the impact of barrier contraception on reproductive health.

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CONCLUSIONS

This investigation contributed new methods in the area of contraceptive research and results that are specifically useful for the evaluation of an important new product.

The design of this study is innovative, and the procedures developed to answer its research questions may help redefine the state-of-the-art in condom efficacy studies. Just prior to initiation of this project, Steiner et al proposed new guidelines for conducting studies of condom breakage and slippage. [15] These guidelines do not recommend using objective markers of condom failure and fail to encourage prospective collection of information.

The success of the present study shows that a rigorous design that employs a semen marker as an objective marker of condom failure is not only possible but highly desirable, in that it provides substantially richer information than conventional studies based on user reports. In addition, while the laboratory pilot study (see first manuscript in this series) demonstrated that self-sampling of vaginal secretions with a swab was feasible, the fact that 175 women returned 4464 vaginal samples during the study demonstrates that implementation of the protocol is possible on a large scale. This study also showed that PSA is a sensitive and specific marker of semen exposure and is considerably superior to other methods commonly used in forensic medicine and other research areas. The PSA assay can be used on dried samples and is widely available. Thus, virtually any

study of condom failure should be able to employ this objective marker and increase the reliability of results with a relatively modest increase in cost.

The forms developed for this study were designed to obtain detailed information with relatively little effort from the participants. Compliance with the record-keeping requirements of the protocol was exceptionally high. In addition, the request that each participant return a form describing her experience with each used condom allowed us to gather the most critical information even if the participant withdrew from the study. Water leakage testing of the used condom was relatively inexpensive and provided objective evidence that user-reported breakage is not always accurate. Finally, we were able to demonstrate that a large number of the male partners were willing to provide penis measurements, whose interaction with diaphragm size proved to be an important predictor of semen exposure.

The procedures of this study can be further refined. For example, the present study explored a few key anatomical measurements. Future studies could collect general anthropometric variables, such as height, weight, and waist-to-hip ratio. Information on douching practices would have helped to clarify issues of previous exposure to semen and residual semen. Finally, because we expected relatively low levels of semen exposure during the study, we did not require participants to observe any particular abstinence interval prior to testing a condom. In light of the results, it may be advisable to introduce an abstinence interval before testing to maximize the number of condom uses for which semen exposure can be ascertained without interference from prior sexual activity.

This project applied innovative methods to measure the rates of breakage, slippage, and semen exposure during use of the Reality female condom. Problems with the

female condom were common during this study, with 25% of uses resulting in at least one reported problem. Semen exposure was also relatively common. The lower boundary of the rate of semen exposure was 7% and the upper boundary was 21%. Semen exposure was more likely to occur if the participant reported the penis entering outside of the condom, the outer ring moving into the vagina, or semen leaking from the condom. No problem was reported during use of 1161 condoms. The rate of semen exposure in this group was 19% (lower boundary of the rate: 5%). Thus, semen exposure occurs often in the absence of user-reported problems. To the extent that semen exposure is an indicator of pregnancy and STD risk, these findings indicate that self-reported problems do not necessarily imply condom failure; however, it is also true that a large proportion of failures are not associated with user-reported problems. Thus, it is possible that our current understanding of the mechanisms that lead to condom failure is inadequate.

The analysis of determinants of semen exposure illustrated that the efficacy of the female condom in preventing semen exposure is limited by several factors. Couples with a large disparity in diaphragm and penis size were at significantly increased risk of semen exposure. For these couples, the Reality female condom may not be the best option. Engaging in extremely active intercourse also increased the risk of semen exposure. Reproductive health practitioners and educators should provide proper training to ensure that women develop the confidence to easily and correctly use the condom, as women who were not sure that they could easily use the condom were also at increased risk of semen exposure. High income among women was a protective factor against semen exposure, possibly indicating that more sophisticated users are potentially more successful in correctly using the condom.

The results of this study in low risk, highly educated women are important in that they possibly represent a best scenario of the efficacy of the female condom in preventing exposure to semen. It is reasonable to assume that the study population was more successful in using the condom correctly than less well-trained women would be. Future research should focus on high-risk women who use the female condom as a primary method of birth control and STD prevention. Conversely, our finding that problems with female condom use often lead to discontinuation may not be generalizable to high-risk groups, who could be sufficiently in need of the device to ignore or overcome such problems.

The high rates of semen exposure following use of the female condom in this study are of concern, but these results do not necessarily imply that the female condom is a less effective barrier than the male condom. No studies of this type have been conducted with the male condom, so it is impossible to compare the results of this study with available information on the male condom.

The design employed in this investigation can easily be applied to studies of the male latex condom and of condoms made of new materials. The results presented in this paper indicate that such studies are needed to clarify our understanding of the impact of barrier contraception on reproductive health.

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APPENDIX

IRB APPROVAL

OMB No. 9999-0020
Approved for use through 7/31/94

Protection of Human Subjects
Assurance Identification/Certification/Declaration
(Common Federal Rule)

POLICY: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the common rule. See Section 101(b) the common rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the common rule.

Institutions with an assurance of compliance that covers the research to be conducted on file with the Department, Agency, or the Department of Health and Human Services (HHS) should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency. Institutions which do not have such an assurance must submit an assurance and certification of IRB review and approval within 30 days of a written request from the Department or Agency.

1. Request Type — 2. Type of Mechanism — 3. Application or Proposal Identification No. *(if known)*

☐ ORIGINAL ☐ GRANT ☐ CONTRACT ☐ FELLOWSHIP
☐ FOLLOWUP ☐ COOPERATIVE AGREEMENT
☐ EXEMPTION ☐ OTHER _____

4. Title of Application or Activity

Special Interest Project No. 10: Women of Reproductive Age-Female Controlled Contraception

5. Name of Principal Investigator, Program Director, Fellow, or Other

Maurizio Macaluso, M.D.

6. Assurance Status of this Project *(Respond to one of the following)*

☐ This Assurance, on file with the Department of Health and Human Services, covers this activity

Assurance identification no. M- 1149 IRB identification no. 01NR

☐ This Assurance, on file with *(agency/dept.)* _____ covers this activity

Assurance identification no. _____ IRB identification no. _____ *(if applicable)*

☐ No assurance has been filed for this project. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

☐ *Exemption Status.* Human subjects are involved, but this activity qualifies for exemption under Section 101 (b), paragraph _____

7. Certification of IRB Review *(Respond to one of the following IF you have an Assurance on file)*

☒ This activity has been reviewed and approved by the IRB in accordance with the common rule and any other governing regulations or subparts on

(date) 1-13-94 by ☒ Full IRB Review or ☐ Expedited Review

☐ This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the common rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed and certification will be provided

10. Name and Address of Institution

The University of Alabama at Birmingham
1170R Administration Building
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11. Phone No. *(with area code)* (205)934-3789
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13. Name of Official: Ferdinand Urthaler, M.D.
14. Title: Chairman - IRB
15. Signature: Ferdinand Urthaler, M.D.
16. Date: 1-13-94

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I certify that I have read this document and examined the student regarding its content. In my opinion, this dissertation conforms to acceptable standards of scholarly presentation and is adequate in scope and quality, and the attainments of this students are such that she may be recommended for the degree of Doctor of Philosophy.

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Sten Vermund, MD, PhD	
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Amy Bloom, MD	

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Date 7/6/98

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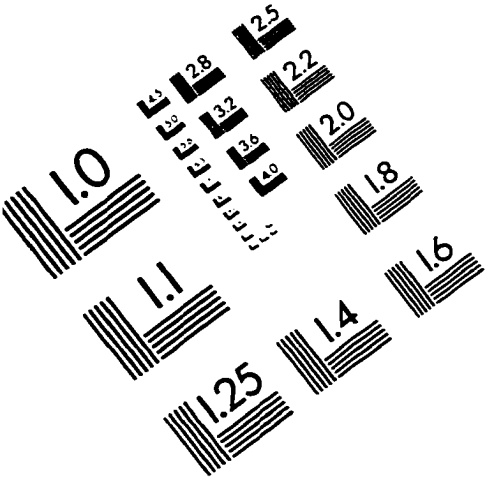

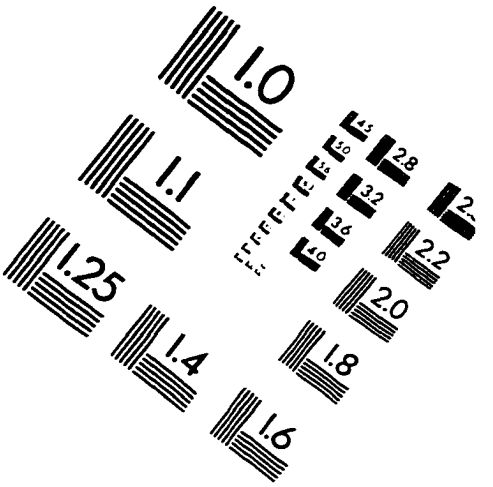

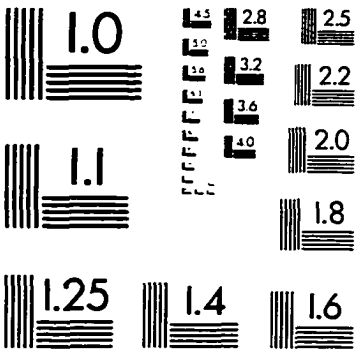

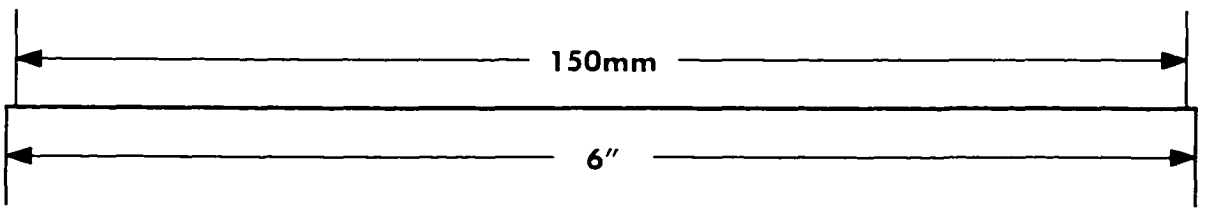

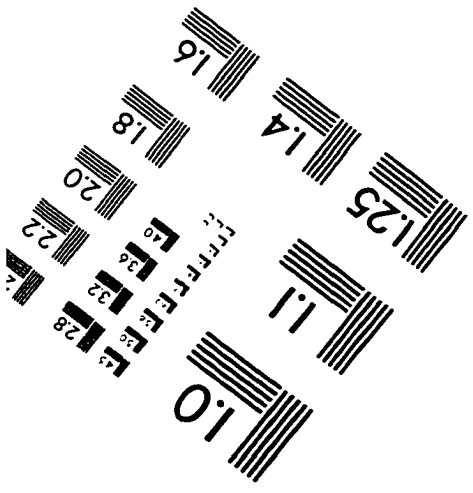

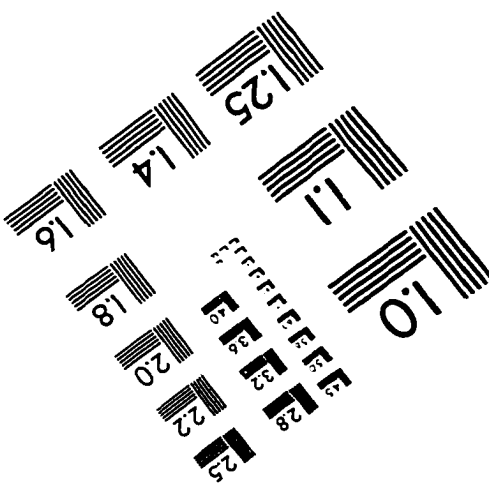

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