

The Use of PSA to Measure Condom Effectiveness

John Gerofi - 2004

Introduction

Prostate Specific Antigen (PSA) was first called P30. It is a glycoprotein secreted by the prostate gland, and is present in semen, and in mens' blood. It is not present in secretions from women. In 1978, Sensabaugh et al¹ reported its isolation and potential as a marker for semen. The test is very sensitive and very specific. PSA is detectable in the vagina for about 24 hours after it was deposited, and not detectable after about 27 hours.

Subsequently, elevated PSA levels in the blood became an indicator of likely prostatic cancer, and routine pathology tests for it have been available for about 10 years.

The assessment of condom performance has attracted increased attention since the emergence of HIV. On the basis of all available evidence, most scientists believe that male condoms, when properly used, provide a barrier against the transmission of both HIV and many other STIs. There is a lobby group, primarily in the USA, that does not accept the effectiveness of condoms to prevent diseases, and, as a result, there has been increasing pressure to "prove" that condoms are an effective barrier against disease organisms.

Although there are many published articles which indicate that condoms provide some level of protection against diseases, several have been challenged on the grounds of the robustness of the evidence available. Conducting more clinical trials where disease transmission is the outcome to satisfy the sceptics would be extremely expensive, and would be riddled with ethical problems.

Most experts are prepared to measure male condom effectiveness in terms of the results of slippage and breakage studies, and on laboratory tests for freedom from holes. In other words, a condom which has no holes, does not slip off and does not break in use is assumed to provide a very effective barrier to sperm and HIV. Its effectiveness against other diseases depends on the mode of transmission of the disease.

With female condoms, there are other use failure modes that may not be obvious to the users.

The use of PSA in any condom trial could give an "objective" marker of whether sperm had reached the vagina. This would supplement, and possibly partly displace, observations and records made by the condom users. PSA has the added advantage that its molecular size is just a little smaller than that of Hepatitis B, and thus considerably smaller than HIV.

PSA and Male Condoms

The first published trials using PSA were for male condoms, and were conducted by Walsh et al, of the California Family Health Council. Their first publication in 1999², described a small comparative trial of five male condoms - two latex, two polyurethane and one from lamb ceacum. There were only 50 intact condoms used, and of these, 47 appeared to have functioned correctly, although users reported some difficulty (eg stretching or bunching with 10 of these). PSA was detected in one vaginal swab, which was a result of one of the

condoms where the user had reported a usage difficulty.

In the 3 cases where the condom was reported as failing, it had slipped off during withdrawal, and PSA was detected in two of these cases.

The study also measured vaginal PSA levels after intercourse using 40 condoms each with a 1 mm diameter hole in it. Among these, the users did not notice any problems or noticed some difficulty as above with 34, but in 13 of the 34 uses, PSA was detected in the post-coital vaginal swabs. The remaining 6 holed condoms either broke (4) or slipped off (2).

The median level of vaginal PSA found after use of the condoms with holes was less than one tenth of the level after unprotected intercourse. The level of vaginal PSA detected after use of intact condoms that failed was less than one third of the level after unprotected intercourse.

Walsh et al published a second paper on PSA in 2003³. Two types of condom were compared, a latex condom and an experimental SEBS condom. There were about 18,000 uses for each condom type in this extensive study. It had the very encouraging outcome of 0.2% breakage and 0.5% slippage for the latex condom over the whole study. Condom failure rates were higher on the first 5 uses. The non-latex condom had failure rates over double the latex one. Most breaks were SEBS condoms.

PSA swabs were only taken when the users perceived slippage or breakage. The results showed that even where the condoms broke or slipped off, the PSA level was lower than would be found with no condom present, even if the condom failure was only noticed after ejaculation. If a break was noticed after ejaculation, the PSA level was about 60% of the unprotected value, while with a slip-off, the level was about 25% of the unprotected value.

Walsh et al went on to construct a model to predict pregnancy rates for consistent condom use, based on the PSA readings. They concluded that for latex condoms, the total 6 month pregnancy rate should be 0.82, compared with an actual value from their study of 1.11 (95% CI 0.0 - 2.8).

Rocket electrophoresis was the method used to detect PSA presence.

PSA and Female Condoms

Also in 2003, the American Journal of Epidemiology published a group of 4 articles on PSA and female condoms, based on work conducted from 1996 to 1998. The first⁴ analysed semen exposure as measured by PSA presence as a function of partner characteristics and intensity of exposure. The second⁵ analysed the overall efficacy of the device as a barrier to semen, the third was a commentary on the articles by another group, and the fourth was a reply to the commentary by the authors of the first two articles. The work was done by staff at the University of Alabama at Birmingham, in association with CDC, Atlanta.

The first two articles are significant for a number of reasons:

1. They provide further failure rate data for female condoms. To this author's knowledge, there have been only two other published contraceptive efficacy trials and one small STI trial on the female condom, despite dozens of acceptability studies.

2. They augment the slippage, breakage and pregnancy data so far available with a marker that indicates the presence of semen in the vagina. This makes the assessment of efficacy more robust, and provides a more credible surrogate for studies where the outcome is either pregnancy or disease
3. They document difficulties people have faced in using the female condom
4. They attempt to relate the failure of the condom to the anatomy of the couple and the intensity of the intercourse.

210 couples were recruited. None had any previous experience with female condoms. They were required to keep a coital log and to take vaginal swabs before and after intercourse.

They were measured for diaphragm fit, and asked to estimate their partner's erect penis size from a series of drawings. They were also given a penis measuring kit, to use on their partner. Each participant was asked to use 20 condoms.

Penis size was determined by measuring its circumference at the mid-shaft and behind the glans, as well as the total length. A resultant total volume was estimated, and used in the analysis, by comparing it with the partner's diaphragm size.

Only 1149 of the total of 2232 uses were adequately documented to be included in the study on partner characteristics and intensity of intercourse. One analysis is by demographic and lifestyle characteristics. Chosen characteristics were turned into dichotomous variables, and evaluated against semen exposure (as measured by PSA) using logistic regression. Only income, lifetime number of partners and relationship length were judged significant factors, with odds ratios of 0.36 to 0.5 and p values between 0.04 and 0.07. All other p values were higher. Interestingly, number of previous children was not included as a variable.

The second analysis was by physical and intercourse characteristics. Once again, the criteria were dichotomised, The question of size was dealt with by dividing the women into two groups, those with diaphragm size 65 to 70 mm, and those with size 75 to 80 mm. The men's penises were also divided into two sizes, below median and above median. Women requiring the larger diaphragms with men whose penises were below the median size were very likely to have a condom failure (odds ratio 3.7, p value 0.01). The other very significant variable was the activity level, which could be reported as high medium or low. High activity was associated with high failure (odds ratio 3.2, p value 0.004). Use of what was called mixed positions appeared to have a protective effect (odds ratio 0.61, p value 0.07).

On the basis of the first two analyses, a final regression model was constructed, in which the following variables were included:

Age (<24 years)
Race (white)
Relationship length (<2 years)
Per capita income (> \$900/month)
Number of sexual partners (>3)
Condom use order (experience with device)
Diaphragm size and penis size
Activity level of intercourse.

Of these, only the length of the relationship, the income, the relative sizes as described above, and the activity level were significant without the confidence interval overlapping 1.0. The age, per capita income and number of sexual partners had odds ratios suggesting an effect, but the confidence intervals included 1.0.

The relative size of the penis and diaphragm was the most significant predictor of condom failure. The article gives no rationale or physical model for the criteria adopted to measure the sizes. The relationship between failure and sizes is presented without any hypothesis of mechanism by which it occurs.

The penis size is characterised by a notional volume, and the vagina size is characterised by the diameter of a diaphragm ring. A slightly more sophisticated model for the penis would involve a length and a diameter. It seems likely that any causative model of condom failure would involve the penis coming back out of the condom and then being thrust in beside it rather than into it. This more likely to be associated with the length of the penis than the circumference. Presence and mobility of a foreskin could also play a role.

Similarly, the slippage of the condom may have more to do with the introitus than with the fundus. Alternatively, a large fundus may require a larger condom retention ring if the position of the device is being challenged. (The retention ring is under 60 mm OD, - smaller than the smallest diaphragm ring.) Further, there is a documented tenting effect in the vagina during sexual arousal, and the size under those conditions may be more relevant than the measurement presented. Gaining physical understanding to support these and other statistical associations should be the next step.

The second article deals with a different analysis of the same data. Users' coital logs were analysed for reported problems, which were divided into mechanical and acceptability problems. Overall, one or more problem was reported in 25% of the uses. There were mechanical problems in 17% of uses and acceptability problems in 12%. Most problems were more prevalent during the first 5 uses than during the subsequent 15 uses. As expected, the number of problems reported declined as the users gained experience. But breakage and the penis entering the vagina beside the condom were actually higher in the subsequent 15 uses.

The researchers used a commercial PSA test kit, intended for use with blood and serum. It is much more sensitive than the method used by Walsh et al, but may be prone to false positives due to other proteins and other interfering agents. Collection of samples from mucous membrane is a known source of problems with this method. The test always gives a positive result, and it was a threshold was established for a legitimate positive reading. To do this, women had to take both pre-coital and post-coital swabs and send them for testing each time. Two alternative criteria for semen exposure were developed, based on the difference between post-coital and pre-coital readings and on the threshold. The two alternative results were used to give upper and lower bounds for the proportion exposed to semen.

PSA exposure (positive in 45 to 75% of cases) was associated with breakage, the penis penetrating beside the condom, the condom slipping in, or leakage onto the woman on withdrawal. These four problems had a high odds ratio of association with semen exposure. Other mechanical problems with use were associated with 0 to 35% positive PSA exposure readings. Acceptability issues were associated with under 20% exposure, except in the case

of the man feeling pain, which had a range of 11 to 32% positive readings.

In an invited comment on the two female condom articles, Steiner et al⁶ concentrated on the on-going debate about whether or not condoms protect against STIs. They discussed the inevitable difficulties and uncertainties inherent in any study of condom use, and ask whether PSA can help. They point out that even with the PSA measurement, the information is still vulnerable to misreporting by the user, and mishandling of the swabs. Although Steiner et al do discuss possible uses of PSA testing to facilitate product approval testing, and they agree that PSA measurements may be used as a surrogate for disease outcomes, their major focus is on the difficulties of dealing with the persistent and unreasonable claims that condoms are ineffective.

Steiner et al also draw attention to the relatively high rate of PSA exposure in the trials (7 to 21% of uses, depending on the criterion). They note the arbitrary definition of thresholds, and the inevitable reliance on user-reported data. The study authors replied to Steiner et al's comments.⁷

Discussion

The introduction of a biochemical marker increases the level of quantification in an area of research where we have previously had to rely on self reporting of private acts during which the participants may not be in an analytical frame of mind, and which are generally not discussed in detail. This increased quantification comes at a financial cost, in terms of the cost of doing the PSA testing, and a compliance cost, in terms of the added tasks asked of the participants.

The studies on the male condom used PSA primarily to examine the level of protection provided if the condom failed, although the smaller initial study looked at whether PSA was transmitted through an intact condom.

The first study on male condoms used only a small study population, and it suggested that use of intact condoms prevented the passage of PSA (implying that viruses and sperm would also not pass). It also suggested that even with punctured condoms, there was a significant reduction in PSA compared with not using a condom.

The second study (with a very large number of condoms used) showed:

1. The slippage and breakage rates of latex condoms were surprisingly low.
2. The rates improved during the currency of the study
3. Latex condoms broke and slipped less often than the synthetic ones being tested
4. There is a measure of protection even if the condom has slipped or broken.

PSA in this study was used only in those cases where the user perceived that the condom failed.

Overall, the conclusions agree with in-vitro studies using bacteriophage ϕ 174 which showed that surrogate viruses about the size of HIV do not penetrate intact condoms, and that even

condoms with holes in them will attenuate the transmission of virus considerably.

The female condom study used PSA far more extensively. As there are a number of mechanisms for failure apart from breakage and slippage, this appears necessary in any assessment of its efficacy. The most robust principal outcomes were:

1. Women on low incomes were more likely to have failures
2. Women in relationships less than 2 years old were more likely to have breakages
3. Women with a larger vaginal fundus whose partners' penises were below median "volume" were more likely to have failures
4. If the activity level during intercourse was unusually high, failure was more likely
5. Having white skin, being under 24 years old and having 3 or fewer sexual partners may be associated with lower failure rate.
6. An acceptability problem (pain, discomfort, noise or bleeding) was reported in 12% of the uses.
7. Mechanical problems were reported in 17% of the uses.
8. PSA levels suggesting failure of the method were found in 7 to 21% of uses, depending on which criterion was used for assessment of the PSA test results.
9. A positive PSA result was not necessarily related to reported problems - between 53 and 70% of cases with exposure (depending on the criterion) were associated with no reported problem.

This study highlights the state of development of the female condom. While it has its role in a number of situations, it is not yet as reliable as the male condom. Even though the male and female condom studies cannot be directly compared, they do reinforce the previous studies (largely based on pregnancy) which showed a difference in efficacy between the two devices, .

Without PSA, the obvious measurable outcome from such a study would have been pregnancy. Such a study would have had to have been much larger, and would have had ethical issues associated with it. To try to do a similar study with disease as the outcome would have presented major practical and ethical obstacles. Observed mechanical problems, while significant, do not cover some important failure modes.

Use of PSA is a means of identifying cases of semen ending up in the woman despite use of a condom. It is clearly more important with female condoms than with male ones, although it is unlikely that male condom users would notice small holes in the condom (which would allow small amounts of semen or virus to pass through). But the measurement still involves reliance on the user to report activity and take swabs correctly.

With male condoms, a study analogous to the female condom study discussed would give results one step closer to showing whether the condom had worked or not in any particular

use. While this is of some scientific interest, it will come at considerable cost, and logical inference can predict the outcome in terms of pregnancy and disease based on the bacteriophage studies, condom quality tests and slippage and breakage studies. In any case, there are still condom sceptics who seem determined to discredit the method, claiming lack of adequate evidence that it works. They may continue to find fault, and not accept anything but in-vivo studies on real viruses, which are effectively impossible to perform with the power they demand.

¹ Sensabaugh GF. Isolation and characterization of a semen-specific protein from human seminal plasma: a potential new marker for semen identification. *J. Forensic Sci.* 23(1), 1978, 106-15.

² Walsh T. L., Frezieres R. G., Nelson A. L. Wraxall B. G. and Clark V. A. Evaluation of Prostate-specific antigen as a quantifiable indicator of condom failure in clinical trials, *Contraception* 60, 1999 269-298

³ Walsh T. L., Frezieres R. G., Peacock K., Nelson A. L., Clark V. A., Bernstein L. and Wraxall B. G. Use of Prostate-specific antigen (PSA) to measure semen exposure resulting from male condom failures: implications for contraceptive efficacy and the prevention of sexually transmitted disease, *Contraception* 67, 2003, 139-150.

⁴ Lawson L. M. Macaluso M., Duerr A., Hortin G., Hammond K. R., Blackwell R., Artz L., and Bloom A. Partner characteristics, intensity of the intercourse and semen exposure during use of the female condom, *Am J. Epidemiology* 157, 4, 2003, 282-288

⁵ Macaluso M., Lawson L. M., Hortin G. Duerr A., Hammond K. R., Blackwell R, and Bloom A. Efficacy of the female condom as a barrier to semen during intercourse, *Am J. Epidemiology* 157, 4, 2003, 289-297

⁶ Steiner J., Feldblum P. J., and Padian N, Invited commentary: Condom effectiveness – Will prostate specific antigen shed new light on this perplexing problem? *Am J. Epidemiology* 157, 4, 2003, 298-300

⁷ Macaluso M., Lawson L. M., Duerr A. and Hortin G., Macaluso et al. respond to “Condom effectiveness and prostate specific antigen” *Am J. Epidemiology* 157, 4, 2003, 289-297