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The Use of Biomarkers of Semen Exposure in Sexual and Reproductive Health Studies

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Abstract

Biomarkers of semen exposure have been used in studies investigating the safety and efficacy of barrier methods of contraception. They have been used as objective indicators of semen exposure when studying sexual behaviors and in human immunodeficiency virus/sexually transmitted infection research interventions where participants are advised to avoid unprotected sex. Semen biomarkers have also been used to assess or validate self-reported sexual behaviors or condom use in reproductive health settings. Prostate-specific antigen (PSA) and Y chromosome DNA (Yc-DNA) have each been evaluated in the past as semen biomarkers and are the most widely used in the field. While both are considered reliable for evaluating exposure to semen, each has unique characteristics. In this report, we summarize the literature and provide some considerations for reproductive health researchers who are interested in using PSA or Yc-DNA as semen biomarkers. We also synthesize our previous published work on the optimal conditions of collecting and storing specimens and assay performance in the presence of other vaginal products that may influence various assays. Semen biomarkers are innovative and promising tools to further study and better understand women's reproductive and sexual health and behavior. More research is needed to better understand the strengths, limitations, and optimal performance conditions of specific assays *in vivo*.

Introduction

Biomarkers of semen exposure have been used in forensic settings for more than four decades. [1-3] More recently, they have also been applied in reproductive health study settings as objective markers of semen exposure.[4-28] In the 1990s, public health researchers began to use semen biomarkers in studies investigating the safety and efficacy of barrier methods of contraception.[4-9] Women participants were asked to take vaginal swabs before sex and then again after sex with a condom (or a new barrier device under investigation). The swabs

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would then be evaluated for the presence or absence of a semen biomarker, and if a semen biomarker was found in vaginal secretions, semen exposure was presumed to occur. Two of the most widely used semen biomarkers are Y chromosome DNA (Yc-DNA) and prostate-specific antigen (PSA).[29] Yc-DNA is a genomic marker found only in males on sperm cells,[29-32] whereas PSA is a protein present in seminal plasma independently of spermatozoa.[1-4,27] Although PSA is also present in other tissues and body fluids in both men and women (such as in blood, urine, and even breast milk), its presence in semen is higher by many orders of magnitude. Thus, PSA found in vaginal secretions above a certain threshold is indicative of semen exposure.[27]

In addition to studies investigating the safety and efficacy of barrier methods of contraception, semen biomarkers have been used in other reproductive health settings such as in human immunodeficiency virus (HIV) and sexually transmitted infections (STI) research. In this case, their detection can help evaluate the efficacy of a physical barrier (such as condom), chemical barrier method, or a microbicide or assess study participants' compliance with study procedures. For example, PSA or Yc-DNA may be used as indicators of semen exposure from unprotected sex or incorrect condom use in study participants who were advised to avoid unprotected sex.[8-23] Yc-DNA has also been used in studies evaluating self-reported condom use of adolescents.[10] PSA has been used to validate self-reports of recent sexual activity,[10-20] including among female participants receiving treatment for STIs advised to avoid sex (or unprotected sex),[14-15] and as an indicator of condom nonuse or failure.[4-11,14,15,21]

General Considerations for Determining the Need for Semen Biomarkers in Reproductive Health Studies

Objective indicators of sexual activity (in particular, semen exposure) could be important tools for reproductive, sexual, and women's health studies, especially for investigating new methods of barrier contraception that have biological outcomes (such as pregnancy or STI) and have traditionally relied on self-report of condom use.[24-27] Objective indicators of sexual activity have been identified as critically needed by the Microbicide Trial Network (www.mtnstophiv.org), and others.[24-27] Semen biomarkers can also be used as a measure of compliance with study procedures when the study calls for condom use or avoidance of sex; if researchers know that women did not comply with study procedures, they could adjust for semen exposure in relevant analyses.[24-27]

Whether or not an objective indicator of semen exposure will add value to a particular study depends on the focus and scope of the study. In many reproductive health studies, the use of semen biomarkers is often in addition to self-reported sexual behavior. Laboratory-confirmed presence of semen biomarkers in vaginal secretions is considered objective[22,24-27] as opposed to self-report, which is subject to several types of bias. When the research involves sensitive behaviors such as sex and condom use, reporting bias is known or suspected to occur. Previous studies have detailed a variety of types of reporting bias such as underreporting, overreporting, recall bias, or social desirability bias.[27] In addition to reporting bias, sometimes participants are unaware of their exposure.[15,22] Participants in clinical trials evaluating barrier methods of contraception, for example, may

not be aware of some exposures such as a condom slippage or breakage that results in small exposures to semen.[22,27] By contrast, some participants may report that they had an exposure or experienced issues with the condom, when the use of biomarkers yields negative results for semen exposure.[22] Since perceptions are real in consequences,[28] both types of information (self-report and the biomarker) could be of value to the research.[22] For example, if a participant experienced and reported problems with a condom, then they may change their behavior accordingly, such as not using the condom and believing that it doesn't work, based on their subjective experiences. Each measure (objective and subjective) offers different types of information that are important, especially when evaluating the safety and efficacy of new barrier methods of contraception.

Specific Considerations for the Semen Biomarker Assays

In addition to deciding whether a semen biomarker is useful for a study, a researcher must also decide which biomarker to use, as well as which assay to employ. There are many types of semen biomarkers that have been used, including, for example, semenogelin (Sg), sperm analysis, acid phosphatase, PSA, Yc-DNA, and testis-specific protein, Y-encoded, each with strengths and limitations for use as a biomarker. We focus here on the two that are most widely used in the field, and the ones that our group has had the most experience with, PSA and Yc-DNA. While both are indicators of semen exposure, these two markers have unique characteristics that researchers need to take into consideration when choosing the appropriate marker for their study. PSA reliably indicates very recent semen exposure (immediately post exposure and up to 24 hours, and then clearing by 48 hours),[27] while Yc-DNA can reliably detect semen starting at about 12 hours post exposure and then clearing by 1 to 2 weeks post exposure.[29-33] Real-time polymerase chain reaction is used for detection of Y chromosome DNA.[30-34] While the assay offers a qualitative indication of the presence of Y chromosome DNA, it also yields quantitative results that have been shown to decrease with time since exposure.[29-33] This assay is sensitive to five copies of Y chromosome for up to 14 days post exposure.

PSA is often considered the "gold standard" biomarker for recent semen exposure.[19,22] There are several assays to detect PSA. The two that we have the most experience with are the Abbott Architect's Total PSA quantitative assay and the Abacus ABAcard assay. The total PSA assay used on the Abbott Architect system is a chemiluminescent immunoassay that yields quantitative results, with a readable range of 0 to 100 ng/mL.[35] This assay was developed for prostate cancer detection in serum and the Architect platform is commercially available from Abbott.[27,35] The Abacus One Step ABAcard is a rapid qualitative or semiquantitative assay with a lower limit of detection of 4 ng/mL.[36-38] This assay was developed for semen exposure detection for use in forensic settings.[36] Our CDC group has developed a training module for laboratory professionals on using the ABAcards for reproductive health research; this can be found on the CDC TRAIN website (http://cdc.train.org; course ID: 1030498).

Besides the decay/residence time of the semen biomarker in the vagina, other considerations include interaction with other vaginal products that may be concurrently used, either as part of a study protocol or individually, by a woman. Such products may include lubricants,

vaginal moisturizers, spermicides, or microbicides. Over the past few years, our laboratory has explored the *in vitro* effect of several different substances that may be used intravaginally and may affect some of the semen biomarker assays. Our experiments have demonstrated that some vaginal products (including microbicides) can affect the performance of some of the PSA[38-41] or Yc-DNA[40-41] assays. A summary of our results, which have been previously published,[38-41] is outlined in Table 1. It should be noted that considerations are specific to the assay and the vaginal product. For example, the microbicide product tenofovir did not interfere with the performance of the quantitative PSA assay (total PSA for the Abbott Architect system), but did interfere with the performance of the qualitative assay (ABAcard).[40-41]

Other considerations such as cost and access to biomarker testing may also be important in choosing an assay.[27] The quantitative PSA and the Yc-DNA assays require more laboratory skill and resources (such as specialized equipment) and are more costly compared with some of the qualitative PSA assays.[27]

Previous research has also been devoted to determining the optimal conditions of specimen collection and storage for PSA testing. Studies comparing collection of vaginal swabs by study participants—as opposed to health care providers—found that self-collected swabs and those collected by nurses were equivalent when tested for PSA.[42] One concern may be that in large-scale clinical trials, study participants may forget to take swabs and turn in unused swabs. Some work has been done to develop an assay that will confirm that self-collected swabs were vaginally exposed (i.e., the swabs were inserted into the vagina).[43] This would be especially informative for barrier contraceptive trials when semen biomarker testing is negative.[25-27,43] Our CDC group also outlined optimal methods for collecting and storing vaginal specimens for PSA testing. Large capacity swabs (1 mL) were found to be superior and, once collected, stored at low temperatures (−80°C) until testing, resulted in superior PSA detection by the total PSA assay used on the Abbott Architect system.[44] Specimen processing may also affect assay results.[45] For example, saline (as opposed to the manufacturer's provided or suggested extraction medium) used to extract specimens from vaginal swabs worked well for the ABAcard for detection of PSA, but not for the Rapid Stain Identification-Semen test (Independent Forensics, Hillside, IL) for detection of Sg.[45]

An emerging research question that must be addressed is what specimen types are appropriate for particular assays. This is especially important because many clinical trials collect cervicovaginal lavage specimens (CVLs) rather than vaginal swabs. Such specimens are diluted through the lavage process; in addition, in studies that collect multiple specimens, the order in which the particular specimen was collected may also affect semen biomarker detection. The solution used to obtain the CVL may not be appropriate for, or may interfere with, the assay. More work needs to be done to determine whether CVLs are a good specimen type for detection of biomarkers of semen exposure.

Conclusions

Semen biomarkers can be very useful tools for reproductive and sexual health researchers. Yc-DNA and PSA are both reliable indicators of vaginal semen exposure. Each marker is

unique, with a variety of characteristics that the researcher should take into account. The best studied assay in this regard is the quantitative total PSA assay on the Abbott Architect system. Various assays for a particular marker have certain strengths and limitations that also need to be considered. To date, we know much more about PSA and Yc-DNA assays compared with other semen biomarker assays. For example, we know how certain PSA and Yc-DNA assays perform in the presence of other vaginal products *in vitro* and what the ideal conditions for specimen collection and storage are for the quantitative total PSA assay on the Abbott Architect system. Most of the work done has been *in vitro*, which is appropriate for obtaining some needed information on the assays. More research is needed to better understand the strengths, limitations, and optimal performance conditions of specific assays *in vivo*. Semen biomarkers are innovative and efficient tools that can be used to further study and better understand reproductive and sexual health.

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Table 1

Effect of Vaginal Products on Select Semen Exposure Biomarker Assays *In Vitro*

		Semen biomarker assays		
		PSA		Yc-DNA
Product (manufacturer) – main ingredient(s)	**Type**	**ABAcard[a]**	**Total PSA[b]**	**Real-time PCR**
K–Y Jelly (Johnson & Johnson) – hydroxyethylcellulose (HEC)	Lubricant	Not recommended	Caution	Caution
Astroglide (BioFilm, Inc) – glycerin and propylene glycol	Lubricant	Not recommended	No known problems	Not recommended
Silicorel (Formulated at Eastern Virginia Medical School [EVMS]) – polydimethylsiloxane (silicone based)	Medical grade lubricant	Not tested	No known problems	No known problems
Surgilube (Fougera) – Chlorexidine gluconate and water soluble gums	Medical grade sterile lubricant	Not recommended	Not tested	Not tested
CMC Formulated at EVMS – carboxymethylcellulose	Ingredient in lubricants	No known problems	Caution	No known problems
Replens (LDS Consumer Products) – polycarbofil	Vaginal moisturizer	No known problems	Not recommended	Not recommended
Carbopol Formulated at EVMS – polycarbofil (acrylic polymer)	Main ingredient of Replens	Not tested	Not recommended	Not recommended
Gynol 2 (Ortho) – 2% nonoxynol 9 in propylene glycol	Spermicide	Not recommended	Caution	Caution
N9 (Formulated at EVMS) – 2% nonoxynol 9 in saline	Spermicide	No known problems	No known problems	No known problems
HEC (ReProtect) – 2.5% hydroxyethylcellulose	Placebo[c]	Not recommended	No known problems	Caution
TFV (Gilead Sciences) – 1% tenofovir with 2.5% hydroxyethylcellulos	Microbicide	Not recommended	No known problems	Caution
UC781 (Cellegy Pharmaceuticals) – 0.1% in methycellulose and carbomer 974P	Microbicide	Not recommended	Not recommended	Caution

[a]Key: Not recommended, product substantially interfered; Caution is warranted, product slightly interfered; No known problems, product did not interfere; Not tested, product was not tested.

[b] For the Abbott Architect system.

[c] Used in microbicide trials.

PCR, polymerase chain reaction; PSA, prostate-specific antigen; Yc-DNA, Y chromosome DNA.