

CLINICAL TRIALS EXAMINING CERVICAL BARRIERS AS POTENTIAL METHODS FOR PREVENTION OF HIV AND OTHER SEXUALLY TRANSMITTED INFECTIONS

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The scale of the AIDS pandemic demands more tools to stop the spread of new HIV infections. In urgent need are women and girls, who are most vulnerable to sexually transmitted infections (STIs), including HIV, for biological, economic, and socio-cultural reasons. For example, the female reproductive tract is more vulnerable to infection than the male reproductive system, violence against women and girls is widespread, and the imbalance of power in relationships means that women and girls are often unable to negotiate safer sex practices.

Current cervical barrier methods, as well as new designs under development, are being looked at with renewed interest to determine whether they may offer a female-controlled method for preventing STIs and HIV. Depending on research results, microbicides and cervical barriers may be combined to increase the effectiveness of both methods for STI/HIV prevention. This paper provides background information on cervical barriers, evidence for the value of conducting clinical research, an up-to-date summary of current clinical trials, and ideas for future research.

Cervical Barriers of Yesterday and Today

Cervical barriers for contraception have existed for thousands of years in a variety of forms. Barrier methods that may seem crude today—the insertion of lemon halves, crocodile dung, and beeswax plugs, for example—were widely used by women in ancient times as family planning devices.

The designation “modern” cervical barrier typically refers to diaphragms and cervical caps. The diaphragm is a latex or silicone cup with a firm, flexible rim and shallow dome that can be coated with gel and inserted into the vagina. The cervical cap is smaller than the diaphragm and is designed to adhere to the cervix by suction and hold spermicidal gel close to the cervix. When used with a spermicide, the diaphragm is up to 94% effective in preventing pregnancy, while the cap can be up to 91% effective when used correctly and consistently.¹

Other cervical barrier devices used for contraception include the sponge, marketed in the United States under the Today® brand, and Lea's Shield®. The sponge is a one-size, over-the-counter, foam barrier impregnated with spermicide that fits against the cervix. Lea's Shield® is a reusable silicone barrier with a valve that allows the passage of cervical secretions and air, and

a loop that assists in removal; it does not require clinician fitting, but in the United States is available by prescription only.

Two new cervical barriers under development are the SILCS diaphragm and the BufferGel Duet®. The SILCS diaphragm is a one-size-fits-most silicone device that has a pre-shaped rim to cling high in the vaginal vault and a finger cup on one edge for easy removal. The BufferGel Duet® is a disposable, pre-coated, one-size-fits-all diaphragm-like device made of polyurethane that delivers and distributes BufferGel™, a candidate microbicide and contraceptive, to the opening and interior of the vagina and cervix. These new devices attempt to address concerns about the diaphragm such as insertion, removal, and cleaning, by improving upon design elements (*see Figures 1 and 2*).

Evidence for the Value of Conducting Clinical Trials

Why is there new emphasis on cervical barrier methods? Researchers have revived their interest in cervical barriers partly due to observational research that demonstrates an association between diaphragm use and reduced risk of STIs (*see Table 1*), including cervical neoplasia, chlamydia, gonorrhea, pelvic inflammatory disease, and trichomoniasis.

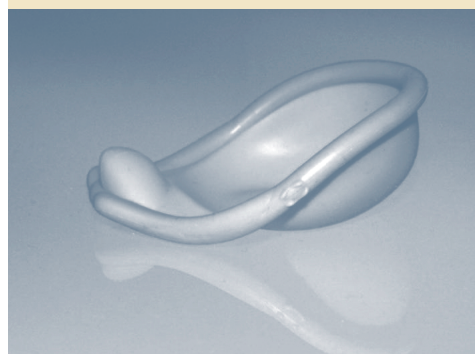
¹ Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, et al., *Contraceptive Technology: Eighteenth Revised Edition*. New York: Ardent Media, 2004.

FIGURE 1. CERVICAL BARRIERS*



Clockwise from upper left: Ortho® All-Flex diaphragm, Millex Wide Seal® diaphragm, Ortho® Coil Spring diaphragm, Lea's Shield®, Prentif cap, FemCap™.

FIGURE 2. SILCS DIAPHRAGM



There is also accumulating evidence that certain characteristics of the cervix, which is protected by these various barrier technologies, may make it more vulnerable to STIs, perhaps particularly HIV infection, than is the case for other areas of the female reproductive tract.² For example, the cervix:

- has a high concentration of HIV-susceptible cells, resulting in a heightened vulnerability to HIV infection;
- is more fragile than the thicker cell lining of the vagina because it is covered by a single layer of cells, making it more vulnerable to trauma and consequent infection than other areas of the reproductive system;
- is the preferential site for many STIs, including chlamydia, gonorrhea, and the human papilloma virus (HPV); and
- is the entryway to the upper genital

tract (fallopian tubes, ovaries, and uterus), which may also be an important site for HIV infection.

It is nevertheless important to bear in mind that the results listed in Table 1 below must be seen as suggestive rather than definitive, since the studies from which they were derived were not designed to test whether the diaphragm could prevent STIs. Future research will be needed to clearly determine whether cervical barriers could significantly reduce a woman's risk of STI/HIV infection.

Cervical Barrier Research for STI/HIV Prevention and Acceptability

There is a growing body of research whose objective is to evaluate the acceptability, feasibility, performance, safety, and effec-

tiveness of cervical barriers for STI/HIV prevention. Five studies are using the diaphragm in combination with the candidate microbicides ACIDFORM™/Amphora™, BufferGel™, and/or cellulose sulfate/CS (Ushercell). Study sites are located in Madagascar, South Africa, the United States, and Zimbabwe. Also under way are a randomized controlled trial of the diaphragm in combination with a lubricant gel in South Africa and Zimbabwe, and a trial in the United States and the Dominican Republic of the BufferGel Duet®.

Two studies in Kenya are looking at user acceptability and/or safety of the diaphragm while another in Zimbabwe is assessing compliance and acceptability for contraception and HIV prevention. The diaphragm is also being compared to the SILCS diaphragm for fit, safety, and

² Moench T, Chipato T, Padian N. Preventing disease by protecting the cervix: the unexplored promise of internal vaginal barrier devices. *AIDS* 15: 1595-602, 2001.

TABLE 1. OBSERVATIONAL STUDIES REPORTING ASSOCIATION BETWEEN DIAPHRAGM USE AND STIs*

DESIGN	SAMPLE	STI	ODDS RATIO	95% CONFIDENCE INTERVAL	AUTHOR
Case-control	STI clinic	cervical neoplasia (CIN I, II)	.3 ⁺	.1-.8	Becker, et al. ³
Cross-sectional	STI clinic	gonorrhea	.8		Magder, et al. ⁴
Cross-sectional	STI clinic	gonorrhea chlamydia trichomoniasis	.32 ⁺ .25 .24 ⁺	.16-.45 .05-1.36 .12-.48	Rosenberg, et al. ⁵
Case-control	STI clinic	pelvic inflammatory disease (PID)	.3	.09-.75	Wolner-Hanssen, et al. ⁶
Case-control	hospital	pelvic inflammatory disease (PID)	.4	.2-.7	Kelaghan, et al. ⁷

* Listed alphabetically by STI.

⁺ Also significantly protective when compared specifically to condom users.

acceptability in the Dominican Republic. Another study is looking at these same endpoints for the SILCS diaphragm with K-Y Jelly® in South Africa and Thailand. In the United States, the SILCS diaphragm with K-Y Jelly® is being evaluated against the SILCS with N-9 for effectiveness, fit, safety, and user acceptability.

Cervical barriers are also being tested among diverse populations. For example, in the Dominican Republic, researchers recently tested the acceptability of the

diaphragm as a potential STI prevention method among sex workers. This research will inform a future study to introduce and measure the acceptability of the diaphragm as well as the female condom in this high-risk population. Although not a clinical trial, another study being undertaken in South Africa, the United States, and Zimbabwe seeks to gain a better understanding of providers' perceptions of the diaphragm and their willingness to recommend use to their clients (*see Table 2*).

Future Research

The range of studies described above reflects the current interest in determining whether the promise of cervical barriers as female-controlled STI/HIV prevention methods can be realized and whether women will find these methods practical and acceptable as ongoing protection from STIs and HIV.

Although these studies will provide answers to important questions, there are related

³ Becker TM, Wheeler CM, McGough NS, et al. Contraceptive and reproductive risks for cervical dysplasia in southwestern Hispanic and non-Hispanic white women. *Int J Epidemiol* 23: 913-22, 1994.

⁴ Magder LS, Harrison HR, Ehret JM, et al. Factors related to genital *Chlamydia trachomatis* and its diagnosis by culture in a sexually transmitted disease clinic. *Am J Epidemiol* 128: 298-308, 1988.

⁵ Rosenberg MJ, Davidson AJ, Chen JH, et al. Barrier contraceptives and sexually transmitted diseases in women: a comparison of female-dependent methods and condoms. *Am J Public Health* 82: 669-74, 1992.

⁶ Wolner-Hanssen P, Eschenbach DA, Paavonen J, et al. Decreased risk of symptomatic chlamydial pelvic inflammatory disease associated with oral contraceptive use. *JAMA* 263: 54-9, 1990.

⁷ Kelaghan J, Rubin GL, Ory HW, Layde PM. Barrier-method contraceptives and pelvic inflammatory disease. *JAMA* 248: 184-7, 1982.

TABLE 2. TRIALS EVALUATING CERVICAL BARRIERS FOR STI/HIV PREVENTION**

LOCATION	PRODUCT	PURPOSE/ENDPOINT	RESEARCHERS/SPONSOR
Dominican Republic	diaphragm and female condom	user acceptability for STI prevention among sex workers	<ul style="list-style-type: none"> • Bill and Melinda Gates Foundation • Population Council
Dominican Republic	SILCS diaphragm compared to diaphragm with K-Y Jelly®	fit, safety, user acceptability	<ul style="list-style-type: none"> • PATH • Profamilia
Kenya	diaphragm	safety and user acceptability	<ul style="list-style-type: none"> • International Centre for Reproductive Health
Kenya	diaphragm and K-Y Jelly®	user acceptability	<ul style="list-style-type: none"> • Centers for Disease Control and Prevention (CDC) • CONRAD • University of Nairobi • University of Washington
Madagascar	diaphragm and ACIDFORM™/Amphora™ gel or placebo gel	effectiveness	<ul style="list-style-type: none"> • CDC • CONRAD • University of North Carolina • USAID
South Africa	diaphragm and ACIDFORM™/Amphora™ gel or K-Y Jelly®	safety and feasibility	<ul style="list-style-type: none"> • CONRAD • USAID
South Africa, Thailand	SILCS diaphragm with K-Y Jelly®	fit, safety, user acceptability	<ul style="list-style-type: none"> • Khon Kaen University • PATH • Reproductive Health Research Unit
South Africa, Zimbabwe	diaphragm and Replens® gel	effectiveness	<ul style="list-style-type: none"> • Ibis Reproductive Health • Medical Research Council • Perinatal HIV Research Unit • University of California at San Francisco (UCSF) • University of Zimbabwe (UZ)-UCSF
United States	diaphragm and ACIDFORM™/Amphora™ gel or BufferGel™ or K-Y Jelly®	safety	<ul style="list-style-type: none"> • Eastern Virginia Medical School • Magee Women's Hospital • University of Pennsylvania
United States	diaphragm and BufferGel™ or Gynol II	efficacy, feasibility, user acceptability	<ul style="list-style-type: none"> • California Family Health Council • Columbia University • Eastern Virginia Medical School • Magee Women's Hospital • RWJ School of Medicine • University of Cincinnati • University of Colorado

+ Includes recently completed, ongoing, or planned trials.

* Listed alphabetically by country.

TABLE 2. TRIALS EVALUATING CERVICAL BARRIERS FOR STI/HIV PREVENTION*⁺

LOCATION	PRODUCT	PURPOSE/ENDPOINT	RESEARCHERS/SPONSOR
United States	SILCS diaphragm with K-Y Jelly® compared to SILCS with N-9	barrier effectiveness, fit, safety, and user acceptability	<ul style="list-style-type: none"> • CONRAD • Eastern Virginia Medical School • University of Pittsburgh Medical Center
United States and Dominican Republic	BufferGel Duet®	performance, safety, user acceptability	<ul style="list-style-type: none"> • CONRAD
United States, South Africa, Zimbabwe	diaphragm	provider perceptions of diaphragm and willingness to recommend use	<ul style="list-style-type: none"> • Ibis Reproductive Health • UCSF • NICHD
Zimbabwe	diaphragm and cellulose sulfate/CS (Ushercell) gel	safety	<ul style="list-style-type: none"> • CONRAD • UCSF • UZ-UCSF
Zimbabwe	diaphragm and K-Y Jelly®	compliance, user acceptability for contraception and STI/HIV prevention	<ul style="list-style-type: none"> • UCSF • UZ-UCSF

⁺ Includes recently completed, ongoing, or planned trials.

* Listed alphabetically by country.

issues that might justify further inquiry and, therefore, new studies. For example, it is widely assumed that the clinician fitting and prescribing required by current diaphragm labeling is essential for safe, effective, and acceptable use, even though there is evidence suggesting that this clinical dependence might not really be necessary.⁸ It might also be counterproductive from a user perspective, since providing the same size diaphragm to all women would simplify supply and access to the device for a potentially much larger population of users. For this reason, the new methods being tested are either one-size-fits-most or one-size-fits-all devices.

Another question of interest is whether diaphragm users should be encouraged to use the diaphragm continuously and only remove it for cleaning every 24 hours. The premise here is that such a use pattern might increase user adherence and decrease the need for coital dependence; in other words, women would not have to decide to insert the device immediately before sex but would instead have the diaphragm already in place.

Finally, although without exhausting the universe of other unknowns, further research is needed to determine whether cervical barrier methods used without N-9 are effective contraceptives. Some studies have attempted to answer this question,

but a definitive conclusion has not been reached. Of course, all these questions become far more urgent if cervical barriers are, in fact, shown to be effective in reducing STI and HIV transmission. However, at this time, we do not know the answer to this critical question so will have to watch and wait for the results of the ongoing Phase 3 clinical trials.

For more information about cervical barrier research, visit the website of the Cervical Barrier Advancement Society (CBAS) at www.cervicalbarriers.org. You can also subscribe to the CBAS newsletter, which includes regular research updates, by emailing info@cervicalbarriers.org.

⁸ Mauck C, Lai JJ, Schwartz J, Weiner DH. Diaphragms in clinical trials: is clinician fitting necessary? *Contraception* 69: 263-6, 2004.