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# Mechanisms of action of currently available woman-controlled, vaginally administered, non-hormonal contraceptive products

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***Abstract*:** Woman-controlled, vaginally administered contraceptives offer women discreet, self-administered, and reversible options. This brief report summarizes the mechanisms of action (MOAs) of currently available, woman-controlled, vaginally administered, non-hormonal products, excluding those that need to be fitted by a healthcare provider. MOAs of three general types of contraceptives will be reviewed, including pH modulators, spermicides, and barrier methods. The recently approved vaginal pH modulator (lactic acid, citric acid, and potassium bitartrate) has a non-hormonal MOA, acting as a buffering agent in the presence of alkaline semen and resulting in sperm immobilization. In contrast, spermicides, such as nonoxynol-9, act by lysing sperm membranes, resulting in sperm death. Barrier methods, such as the diaphragm and female condom, prevent sperm from entering the uterus. In addition to their varying MOAs, each woman-controlled, vaginally administered method has different instructions for use, efficacy, side effects, and availability/insurance coverage, thus providing a range of characteristics to fit different needs and preferences.

***Keywords:*** contraceptive, mechanism of action, vaginally administered, woman-controlled

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## Background

While the oral contraceptive pill and female sterilization remain the most utilized birth control methods by women in the United States, many other methods are available to address the needs of this diverse population.[1] Each product has its own set of unique characteristics that women must consider when selecting a contraceptive method that best suits their needs and lifestyle. Although efficacy is a top driver for many women, other important drivers include concerns about hormones, impact on long-term health or fertility, and side effects such as weight gain, changes in bleeding profile, and impact on sex life.[2,3] Flexibility, the ability to maintain control over use, and/or the ability to use a method discretely are also of primary importance for many women. In addition, the desire for non-contraceptive benefits such as suppressing menstruation or protection against sexually transmitted infections (STIs) may be paramount in the decision-making process. Contraceptive needs are not static, and a woman may use multiple types of contraceptive methods simultaneously, sequentially, or in a patchwork depending on their specific circumstance.[4]

Although the mechanisms of action (MOAs) vary, woman-controlled, vaginally administered, non-hormonal contraceptive products share the common features of being discreet, self-administered, and reversible. The hormone-free characteristic might appeal to women who have concerns about the side effects of hormones. Side effects of hormonal contraception can include weight gain, headaches, breast tenderness, irregular periods, mood changes, and decreased sexual desire.[5] However, for some women, these potentially unwanted side effects might be balanced or outweighed by positive side effects such as reduced risk of ovarian and endometrial cancers, lighter menstrual periods or amenorrhea, and improved acne.[6]

The goal of this brief report is to provide an overview of the currently available, woman-controlled,

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**Table 1.** Timeframe of availability of woman-controlled, vaginally administered products.

| Timeframe | Product | Access and insurance |
|---|---|---|
| ~1960s | N-9 gel/film/foam/suppository[a] (e.g. Conceptrol®, Gynol II®, VCF®)[7] | Over-the-counter |
| 2009 | Female condom (FC2®)[8] | Over-the-counter |
| 2014 | Diaphragm (Caya®)[9] | Prescription; no out-of-pocket costs under the ACA[b] |
| 2020 | VPM gel (Phexxi®)[10] | Prescription; no out-of-pocket costs under the ACA[b] |

ACA, Affordable Care Act; N-9, nonoxynol-9; VPM, vaginal pH modulator.
[a]Timing of availability varies by formulation.
[b]Religious and other exemptions may apply.

vaginally administered, non-hormonal products with a focus on their MOAs. This review does not include products that need to be fitted by a healthcare professional, such as the multi-size diaphragm or cervical cap.

## Overview of woman-controlled, vaginally administered, non-hormonal contraceptive products

While formulations of nonoxynol-9 (N-9) have been available to consumers for many years, there are a limited number of new products that have become available recently (Table 1).[7–10] In the 2000s, a female condom and a silicone-based diaphragm became available, and in 2020, the Food and Drug Administration (FDA) granted approval for a vaginal gel. N-9 formulations and the female condom are available to women as over-the-counter products; the diaphragm and vaginal gel are available via a prescription and covered in full under the Affordable Care Act as FDA-approved contraceptives.[11,12]

### *pH modulators*

The MOAs of vaginally administered, non-hormonal products fall into three general groups (Table 2).[8,10,13–16] One group are locally acting, non-hormonal pH modulators, represented by the recently approved vaginal pH modulator (VPM) (Phexxi, formerly known as Acidform). VPM is an on-demand vaginal gel, composed of active buffering ingredients (lactic acid, citric acid, and potassium bitartrate), a humectant (glycerin), gelling agents (alginic acid and xanthan gum), benzoic acid, sodium hydroxide, and purified water.[17] In a woman's vagina with an optimal microbiota, the pH is acidic, ranging from 3.5 to 4.5.[17] Semen is alkaline, ranging in pH from 7.2 to 8.0, and sperm are completely immobilized at pH $\leqslant$ 5.[13] Preclinical testing has shown that VPM maintains the acidic pH of the vagina even in the presence of semen and reduces sperm motility.[13] In addition to acidic buffering, VPM has high viscosity and creates a barrier over the cervix, which further helps to immobilize sperm and prevent pregnancy.[13,17] In a phase 1 clinical study, VPM administered 0–30 min precoitus or 8–10 h precoitus significantly reduced the mean number of progressively motile sperm compared with control cycles.[18]

The safety and efficacy of VPM was assessed in the single-arm, open-label, phase 3 AMPOWER study.[19] In 1384 healthy women who were at risk of pregnancy, the seven-cycle cumulative pregnancy percentage with VPM was 13.7% with typical use and 9.99% with perfect use.[19,20] Adverse events ($\geqslant$2%) included vulvovaginal burning sensation (20.0%), vulvovaginal pruritus (11.2%), urinary tract infection (5.7%), vulvovaginal pain (3.8%), vulvovaginal mycotic infection (2.9%), bacterial vaginosis (2.8%), and nasopharyngitis (2.6%). Overall, less than 2% of women discontinued due to any adverse events and less than 1% discontinued due to genitourinary symptoms.[19]

VPM is FDA approved for the prevention of pregnancy and has also received clearance for use as a personal lubricant.[17] VPM should be inserted immediately before or up to 1 h before each act of vaginal intercourse.[10] After coitus, there is no need for a woman to remove VPM or take any other action. In addition to its use as a contraceptive, the acid-buffering properties of VPM might make it

**Table 2.** Characteristics of woman-controlled, vaginally administered, non-hormonal products available in the United States.

| | Product description | Mechanism of action | Systemic absorption | Effective time frame and instructions for use | Removal after coitus | Common side effects |
|---|---|---|---|---|---|---|
| Non-hormonal | | | | | | |
| VPM (Phexxi)[10,13] | Gel containing lactic acid, citric acid, and potassium bitartrate | Non-hormonal, short-acting pH modulator that maintains the acidic vaginal environment even in the presence of alkaline semen, causing immobilization of the sperm; thick viscosity of gel offers barrier over cervix | No | On-demand; apply ⩽1 h before every act of intercourse; one-time use | No need to remove | Vaginal burning/ itching, vaginal yeast infection, urinary tract infection, vaginal area discomfort, bacterial vaginosis, and vaginal discharge |
| N-9[14,15] | Gel/film/ foam/ suppository containing nonoxynol-9 [nonylbenzene with a nine-membered poly (ethylene glycol) moiety] | Non-hormonal short-acting spermicide that damages a sperm's cellular membrane resulting in its immobilization and death; as a surfactant that damages cell membranes, N-9 can increase risk of HIV infection | No | On-demand; apply before every act of intercourse (⩽1 h prior to intercourse for gel/foam; ⩾15 min to ⩽3 h prior to intercourse for film; ⩾10 min to ⩽1 h prior to intercourse for suppository); one-time use | No need to remove | Vaginal irritation, allergic reactions, and urinary tract infection |
| Diaphram (Caya)[15,16] | Flexible shallow dome made of silicone | Non-hormonal, short-acting barrier method | No | On-demand; apply before every act of intercourse; reusable | Remove 6–24 h after intercourse | Vaginal irritation,[a] allergic reactions,[a] and urinary tract infection[a] |
| Female condom (FC2)[8,15] | Nitrile sheath and outer ring, polyurethane inner ring; pre-lubricated with silicone | Non-hormonal, short-acting barrier method | No | On-demand; apply before every act of intercourse (most women insert the female condom between 2 and 20 min before intercourse); one-time use | Remove after intercourse | Discomfort or pain during insertion or sex, burning sensation, rash, and itching |

N-9, nonoxynol-9; VPM, vaginal pH modulator.
[a]Common side effects when used with a spermicide.

effective in the prevention of STIs since an acidic vaginal environment is thought to be protective against infections.[21–23] VPM is currently being studied for prevention of chlamydia and gonorrhea, with one phase 2b/3 clinical trial recently completed[24] and one phase 3 trial on-going (NCT04553068).

### *Spermicides*

Locally acting, non-hormonal spermicides, represented primarily by N-9, are the second group of vaginally administered products. Surfactants such as N-9 are widely used in detergents, emulsifiers, wetting agents, and other compounds. N-9 spermicide has been in use in the United States since the 1960s and is available in a variety of formulations, including gel, film, suppository, or foam. It is chemically composed of nonylbenzene with a nine-membered poly(ethylene glycol) moiety. N-9 interacts with the lipids in the membranes of the sperm, resulting in the lysing of the sperm membranes and the immobilization and death of the sperm.[14]

Despite the long history of use of N-9, data on the efficacy of N-9 formulations when used alone is limited. In one trial of 1536 women, five different formulations of N-9 (52.5 mg gel, 100 mg gel, 150 mg gel, film, and suppository) yielded 6-month, typical-use pregnancy rates of 22%, 16%, 14%, 12%, and 10%, respectively.[25] Adverse events included vulvovaginal candidiasis, bacterial vaginosis, vulvar or vaginal irritation with concurrent infection, urinary tract infection or symptoms, culture-proven symptomatic urinary tract infection, and partner side effects.

Instructions for use of N-9 differ slightly depending on the formulation. The N-9 gel and foam can be applied immediately or up to 1 h prior to each act of vaginal intercourse. The N-9 film should be inserted at least 15 min prior to each act of vaginal intercourse to allow time to dissolve and, once inserted, is effective for up to 3 h. The N-9 suppository should be inserted at least 10 min prior to each act of vaginal intercourse and is effective for up to 1 h after insertion. After coitus, N-9 formulations do not need to be removed.

N-9 can damage cell membranes of the vaginal wall, and frequent use of N-9 has been associated with genital lesions that increase the risk of human immunodeficiency virus (HIV) infection.[7] N-9 is therefore not recommended for those at risk for STIs or HIV.[7,14]

### *Barrier methods*

The third group comprises barrier methods that prevent sperm from entering the uterus and fertilizing the egg. This group includes diaphragms, which are shallow silicone domes that are inserted over the cervix. It is recommended that contraceptive gels be used with the diaphragm.[9] The Caya diaphragm is a one-size-fits-most, contoured diaphragm that does not require a traditional fitting by a healthcare provider. In a phase 2/3 trial of 450 couples, the six-cycle typical- and perfect-use pregnancy rates with the Caya diaphragm, when used with a contraceptive gel, were 11.9% and 7.9%, respectively.[26] The most common urogenital adverse events (⩾10%) were pain/irritation/pruritus (36.4%), abnormal bleeding (14.2%), and symptomatic vaginal infection (12.8%); other urogenital adverse events included symptomatic urinary tract infection (3.4%), deleterious Pap test result change (3.7%), and symptomatic cervical infection (1.2%). The diaphragm with contraceptive gel can be inserted up to 2 h prior to vaginal intercourse; if more than 2 h elapse, women should reapply the contraceptive gel.[16] Post-coitus, women should wait at least 6 h, but not longer than 24 h, to remove the diaphragm.[16] Diaphragms do not protect against STIs or HIV.[16]

The second type of barrier method is the female or internal condom (FC2), which is a loose-fitting sheath that lines the vagina and is held in place by a closed inner ring at the cervix and an outer ring that stays outside of the vagina.[8] The female condom, which is pre-lubricated with silicone, is indicated for prevention of both pregnancy and STIs and should be removed after intercourse.[8] Although no efficacy trials have been performed on the current version of the female condom, based on a previous version of the female condom (FC1), the 6-month, typical-use pregnancy rate is 12.4% and perfect-use pregnancy rate is 2.6%.[27] In a crossover trial of 276 women that compared the functionality of FC2 to FC1, adverse events with FC2 included discomfort during or after insertion (13% and 1.9%, respectively), pain after insertion (2.3%), burning/rash/itching (2.3%), and device uncomfortable to use (2.3%).[28]

Several other women-controlled, vaginally administered, non-hormonal contraceptives are in development, including polyphenylene carboxymethylene (PPCM), a topically applied polymer in early-stage development for contraception and STI prevention. In addition, an intravaginal,

monthly, self-administered ring (Ovaprene®), which employs chemical and physical mechanisms to prevent fertilization, has completed a postcoital clinical trial (NCT03598088).[29]

## Implications for practice and/or policy

A variety of woman-controlled, vaginally administered contraceptives are currently available with distinct instructions for use, efficacy characteristics, side effect profiles, non-hormonal MOAs, and differing access/insurance characteristics. Although the exact side effect profiles vary, the adverse events are all generally localized in nature rather than systemic. Pregnancy percentages with typical use range from 10% to 22% and with perfect use from 2.6% to 9.99%. STI protection is variable in this group of contraceptives, with the female condom approved for this indication versus N-9 and the diaphragm, which do not offer such protection.

To meet the needs of our diverse population, a wide range of contraceptive choices are required. Woman-controlled, vaginally administered contraceptives are discreet, self-administered, and reversible; thus, offering women autonomy over their reproductive lives. By employing a shared decision-making model, providers should partner with patients to identify which characteristics fit their needs, and subsequently tailor patient education to ensure that patients integrate the relevant information to enable informed decisions.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Author contributions

BTC, BLG, and BH all contributed equally to the literature review and analysis, and all authors were involved in drafting and critically revising the manuscript. BTC, BLG, and BH reviewed the final manuscript together and all authors gave approval for submission.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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