Original Research

Contraceptive Efficacy, Safety, Fit, and Acceptability of a Single-Size Diaphragm Developed With End-User Input

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OBJECTIVE: To estimate contraceptive efficacy, safety, acceptability, and fit of a single-size diaphragm used with contraceptive gel.

METHODS: We conducted a multicenter trial in which 450 couples used the single-size diaphragm, 300 randomized to acid-buffering gel and 150 to nonoxynol-9, for at least 190 days and six menstrual cycles. Visits were at enrollment and after menstrual cycles 1, 3, and 6. Study outcomes included pregnancy probability, safety, acceptability, and fit. Pregnancy and safety were compared with an historical control group who used a standard diaphragm with these gels.

RESULTS: Most (439/450 [98%]) women could be fitted with the single-size diaphragm. A total of 421 of 450 (94%) provided follow-up. The 35 study pregnancies yielded 6-month Kaplan–Meier cumulative typical use pregnancy probabilities per 100 women with 95% confidence intervals (CIs) of 10.4 (6.9–14.0) for all users and 9.6 (5.5–13.6) and 12.5 (5.4–19.5) with acid-buffering gel and nonoxynol-9, respectively. Historical control analysis yielded a propensity score–adjusted estimate of this pregnancy probability for the single-size diaphragm of 11.3 compared with 10.7 per 100 women for the standard diaphragm ([rounded] difference 0.7, 95% CI −3.6 to 4.9). Approximately half (51%) reported at least one urogenital event but compared favorably to the standard diaphragm in historical control analysis. Most (282/342 [82%]) liked the diaphragm. Results suggest that if provided by a clinician, 94% (95% CI 92–96%) could insert, correctly position, and remove the diaphragm.

CONCLUSION: The single-size diaphragm was safe, as effective as a standard diaphragm, and acceptable when used with contraceptive gel.

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LEVEL OF EVIDENCE: II

The single-size diaphragm (research name: SILCS single-size contraceptive barrier device) is a one-size, nonlatex female barrier developed by PATH, an international, nonprofit global health organization, in

†*Deceased.*

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Financial Disclosure

Dr. Schwartz, Ms. Callahan, and Dr. Mauck are employees of CONRAD, an organization that contributed to the development of the single-size diaphragm, but will not receive any royalties for commercial sales. Ms. Kilbourne-Brook is an employee of PATH. PATH has a limited royalty interest in commercial sales of the single-size contraceptive barrier device (SILCS) diaphragm to support advocacy for adoption of the SILCS diaphragm in low-resource settings. The other authors did not report any potential conflicts of interest.

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collaboration with CONRAD, a nonprofit entity with the overall goal to improve reproductive health. An innovative, user-centered evaluation of more than 200 prototypes was performed, with the goal of creating a single-size diaphragm that is simple to use, comfortable, and attractive (Fig. 1).

Diaphragms may be feasible and acceptable in low-resource settings.[1–3] Studies in the United States, Dominican Republic, South Africa, and Thailand demonstrated that the single-size diaphragm fits women across a range of body masses and parities and from diverse regions and that women without previous experience can use it.[4–7] The single-size diaphragm creates a barrier to sperm comparable to that of a standard latex diaphragm.[8] As with other diaphragms, the single-size diaphragm may also protect against cervical sexually transmitted infections (STIs) and human immunodeficiency virus (HIV).[9] This report presents the results of a pivotal trial of the safety and contraceptive effectiveness of the single-size diaphragm in 450 couples followed for 6 months. Participants were randomized to the use of an approved contraceptive gel typically used with diaphragms or an acid-buffering gel in development as a possible long-term replacement.

MATERIALS AND METHODS

We conducted a multicenter trial in which 450 couples were followed for at least 190 days and six menstrual cycles at the California Family Health Council, Inc. (Los Angeles and San Francisco Bay Area, California); University of Pittsburgh/Magee-Women's Research Institute (Pittsburgh, Pennsylvania); Johns Hopkins Community Physicians (Baltimore, Maryland); Eastern Virginia Medical School/CONRAD (Norfolk, Virginia); Advances in Health (Houston, Texas); and the University of Pennsylvania (Philadelphia, Pennsylvania). Eighty also participated in a colposcopy and microflora substudy at two sites (Norfolk and Pittsburgh). The study conformed to the principles of the Declaration of Helsinki and was approved by each organization's institutional review board. The participants took part voluntarily and signed informed consent forms.

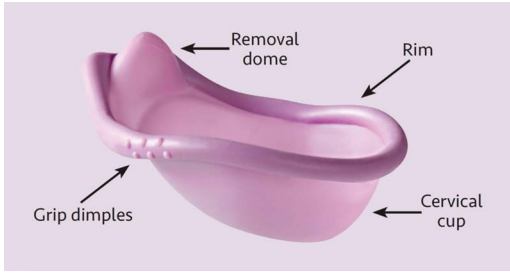

Fig. 1. Single-size diaphragm (current name: Caya). Image courtesy of Kessel marketing, CAYA™ contoured diaphragm.
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Primary objectives were to estimate the cumulative 6-month typical use pregnancy probability and to evaluate safety. Secondary objectives were to estimate the cumulative six-cycle typical use and six-cycle perfect use pregnancy probabilities; compare contraceptive effectiveness and safety of the single-size diaphragm compared with a standard diaphragm (Ortho All-Flex) using an historical control analysis[10]; estimate the proportions who could be fit with the single-size diaphragm and who could correctly insert, position, and remove it on their first attempt using only written instructions; and assess acceptability.

The single-size diaphragm is made of silicone rubber molded over a contoured nylon spring that allows it to fit a range of diaphragm sizes without a tight-wedged fit (Fig. 1). The rim surrounds a contoured membrane with two cup-like structures and a flat area. The larger cup fits over the cervix and the smaller (removal dome) provides an indentation for finger placement for removal. An anterior notch is designed to minimize urethral pressure. The user inserts the single-size diaphragm by squeezing the rim at midpoint "grip dimples," inserting it into the vagina as deeply as possible, then pushing the anterior end behind the pubic bone. The single-size diaphragm for this study was manufactured by Molded Rubber and Plastics Corporation. It received European approval in 2013 and Canadian and U.S. approvals in 2014 and is currently marketed as the Caya contoured diaphragm.

Gynol II contains 2% nonoxynol-9 and was the only spermicide commercially available in the United States for use with a diaphragm at the time the studies were conducted, although this formulation is no longer available. BufferGel (acid-buffering gel) is an investigational aqueous gel containing Carbopol 974P gel formulated at a pH of 3.9. Acid-buffering gel is spermicidal in vitro and contraceptive in rabbits,[11,12] safe in phase I studies in women and men,[13,14] and possibly effective in treating symptomatic bacterial vaginosis.[15] A multicenter contraceptive study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) demonstrated that BufferGel used with a standard diaphragm worked about as well as nonoxynol-9 with that diaphragm (cumulative 6-month typical use probability of pregnancy 10.1/100 women [95% confidence interval (CI) 7.1–13.1] and 12.3/100 women [95% CI 7.7–16.9], respectively[10]). This pivotal study

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was designed to be comparable with the NICHD study so that the latter could be used in an historical control analysis to compare the single-size diaphragm with a standard diaphragm on contraceptive effectiveness and safety.

Healthy, sexually active female volunteers 18–40 years old at risk for pregnancy and desiring contraception but at low risk for HIV and STIs who had normal menstrual cycles, were not pregnant nor desiring pregnancy, and were willing to accept an unknown risk of pregnancy and to engage in at least four acts of vaginal intercourse per cycle were eligible. They were ineligible if they were breastfeeding, within 2 months of last pregnancy outcome, or had an unevaluated abnormal Pap test result, drug or alcohol abuse, toxic shock syndrome, sensitivity to any study products, genital findings suspicious for an STI or a current vaginal infection or urinary tract infection, or contraindication to pregnancy. Male partners had to be at least 18 years old, at low risk for STIs and HIV, and without known fertility problems, vasectomy, or sensitivity to study product components.

Each female was seen at enrollment and at visits 2, 3, and 4 (after menstrual cycles 1, 3, and 6). After eligibility assessment and randomization to gel, each participant underwent a fit and position, insertion, and removal test using the single-size diaphragm with their assigned gel. Women who could not be fitted or could not successfully insert, position, and remove the single-size diaphragm within three tries were discontinued as were those who were also unsuccessful at visit 2. Participants were called 2 weeks after enrollment to discuss any problems. Early discontinuers were seen 2 weeks postdiscontinuation for pregnancy testing.

Participants were to insert the single-size diaphragm before intercourse as their only contraceptive method for at least 190 days and six menstrual cycles. Approximately 1 teaspoon of study gel was to be placed into the large cup and a small amount spread around the cervical rim before insertion. Additional gel was to be applicator-inserted if the diaphragm had been in place for more than 2 hours before the first act or before each additional act of intercourse. If no acts occurred within 8 hours, the diaphragm was to be removed, cleaned, and reinserted with fresh gel if sex was still anticipated. The diaphragm was to remain in place for at least 6 hours after intercourse and no more than 24 hours. Emergency contraception was offered per local practice. Participants recorded menses, product use, device or gel problems, and use of other contraception on a study-supplied diary.

Randomization to gel used the permuted blocks method, stratified by center, with an overall two-to-one ratio (acid-buffering gel:nonoxynol-9) to match the NICHD study. Allocation sequences were generated by a statistician not otherwise involved in the study using a validated SAS program. Gel was packaged in individual, identical tubes labeled with letter codes (ie, A, B, C) with more than one letter for each gel type to preserve blinding. Allocation to letter code was provided in sequentially numbered sealed opaque tamper-evident envelopes and assigned by site staff after confirmation of the couple's eligibility. Sample size was calculated to provide a reasonable level of precision in estimating the true cumulative 6-month typical use pregnancy probability. If 28% discontinued early for reasons other than pregnancy, a sample of 450 would allow estimation with a precision of 2.4–4.0 percentage points over a range of likely probabilities.

Per plan, the primary analysis population is the treated population who provided follow-up data. The treated population pregnancy population is the subset who used the device at least once and whose last day in the effectiveness analysis was not before enrollment (for example, women who conceived before enrollment were not included) (Fig. 2). Historical control analysis was conducted on women eligible for the given analysis (pregnancy, safety) in their respective studies, implementing preplanned exclusions to enhance comparability given study design differences (for example, differences in inclusion and exclusion criteria).

The cumulative 6-month typical use pregnancy probability and 95% CI were calculated for the treated population pregnancy population using the Kaplan-Meier method with Peto standard errors.[16] A cumulative 12-month typical use pregnancy probability was extrapolated by estimating the probability of pregnancy during the second 6-month period as 75% that of the first[17] and then applying standard survival analysis methods assuming constant hazard. We computed an emergency contraception-adjusted cumulative six-cycle typical use pregnancy probability using a standard life-table method that included the estimated number of pregnancies that would have occurred if emergency contraception had not been used, based on the probability of pregnancy, relative to the day of ovulation, for days on which risky act(s) took place.[18]

A perfect use cycle was one of standard length in which the woman was at reasonable risk of pregnancy (predefined as a cycle with at least four coital acts, one of which had a high probability of fertilization) and the

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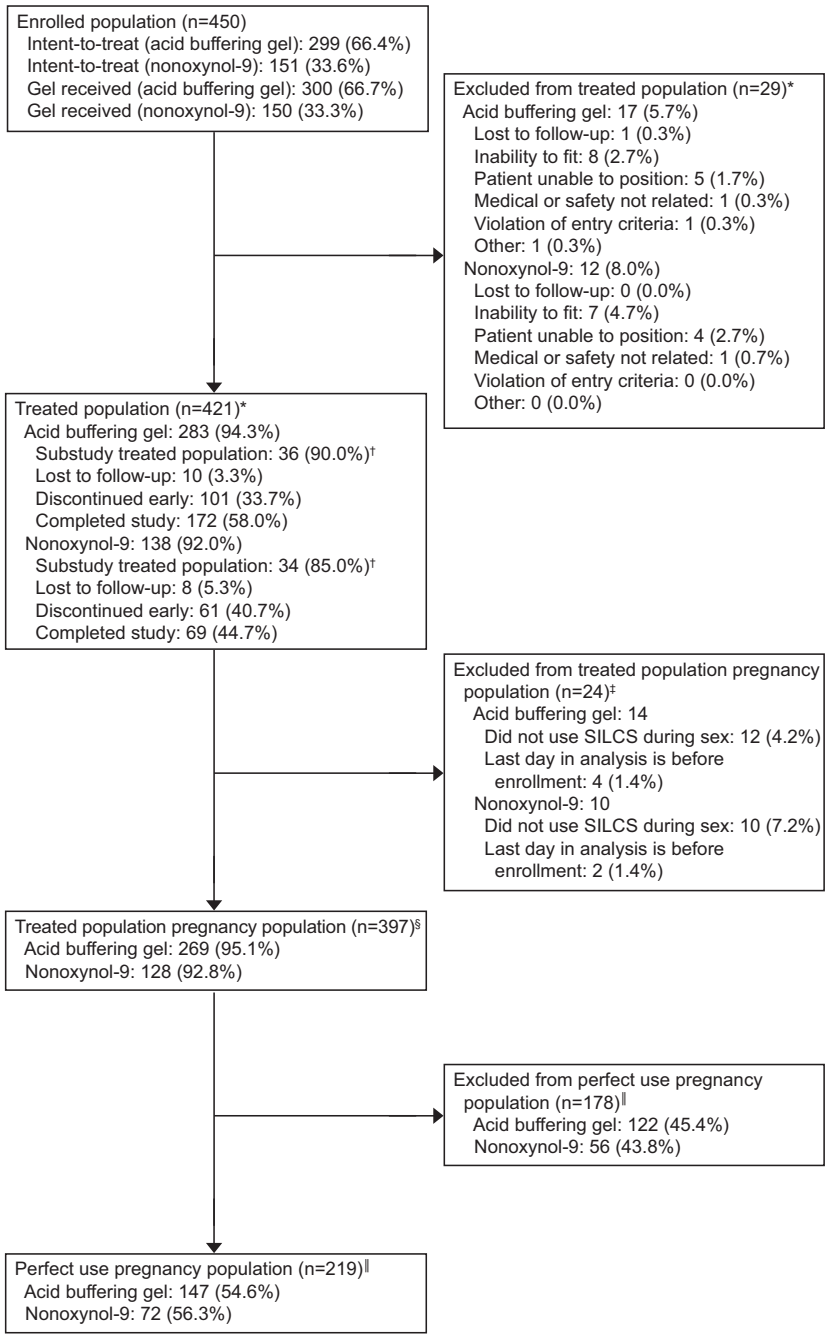

Fig. 2. Population tree. Contraceptive efficacy trial of the single-size diaphragm used with acid-buffering gel or nonoxynol-9. Enrolled population includes all participants inserting the single-size diaphragm. Treated population includes enrolled population women providing follow-up data classified by gel received. Treated population pregnancy population includes treated population women who used the device at least once during intercourse and whose last day in the effectiveness analysis is not before enrollment. Perfect use pregnancy population includes women with at least one cycle of perfect use and a reasonable risk of pregnancy. Substudy treated population includes colposcopy and microflora data from substudy participants in the treated population. *Unless otherwise stated, denominator for percentages, enrolled population for given gel-received group. †Denominator for percentages, enrolled population from centers conducting substudy. ‡Four couples met criteria for both exclusions. §Denominator for percentages, treated population for given gel-received group. ‖Denominator for percentages, treated population pregnancy population for given gel-received group. SILCS, single-size contraceptive barrier device.

Schwartz. Single-Size Diaphragm. Obstet Gynecol 2015.

single-size diaphragm and study gel were reportedly used correctly and without additional contraception for all acts. Cumulative six-cycle pregnancy probabilities were computed for perfect use cycles using the life-table method.

Planned safety subendpoints were urogenital adverse events (symptomatic urinary tract infections, urogenital symptoms, abnormal bleeding, Pap test result changes, and symptomatic vaginal and cervical infections) and product-related adverse events. Urogenital, serious, or possibly product-related adverse events for male partners were also collected.

Samples for semiquantitative vaginal culture were collected and genital colposcopy was performed in all participants in the substudy at enrollment and at all scheduled follow-up visits. A colposcopy substudy event was either a noniatrogenic finding first detected after randomization or a baseline finding that

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worsened during follow-up. Vaginal flora was evaluated by changes in colony counts from baseline and the proportion of women with an adverse change. Acceptability was assessed by 1) proportion discontinuing for personal reasons related to the single-size diaphragm or gel, 2) proportion of coital acts in which the single-size diaphragm was reportedly used, 3) nonmedical problems with the single-size diaphragm or gel, and 4) acceptability questionnaire.

A standard propensity score–adjusted historical control analysis compared the single-size diaphragm study group with the NICHD study group. A propensity score is the model-derived probability that a given person is in a particular study group based on relevant baseline characteristics. Controlling for propensity score simultaneously controls for all baseline covariates in the model. The null hypothesis was that the propensity score–adjusted single-size diaphragm 6-month typical use pregnancy probability was more than six absolute percentage points higher than that of the standard diaphragm (ie, the single-size diaphragm was inferior). Rejection of the null (one-sided $\alpha=0.025$) indicates that the single-size diaphragm effectiveness was noninferior to (at least as good as) the standard device. No statistical comparison between gels was planned.

We compared the single-size diaphragm group with the standard diaphragm group on three safety endpoints: 1) moderate or severe urogenital adverse events, 2) moderate or severe product-related adverse events, and 3) moderate or severe urinary tract infections calculated as the between-group differences (and their 95% CIs) in propensity score–adjusted cumulative 6-month event probabilities. For consistency, adverse events from the NICHD study were coded along with the single-size diaphragm events. A planned interim analysis was reviewed by an independent data monitoring committee who recommended study continuation.

RESULTS

A total of 450 women (300 acid-buffering gel; 150 nonoxynol-9) were enrolled (Fig. 2) from February 4, 2008, to February 13, 2009. The last participant visit was October 22, 2009. Four hundred twenty-one of 450 (94%) met inclusion criteria for the treated population; of these, 397 of 421 (94%) were included in the pregnancy population with most exclusions resulting from not having used the single-size diaphragm during intercourse. In the pregnancy analysis, 219 of 397 (55%) had at least one perfect use cycle.

The vast majority (92%) of the treated population had never used a diaphragm. Approximately two thirds would have required a size 70- to 75-mm standard diaphragm. There were no important differences in baseline characteristics between gel groups (Table 1).

Approximately 54% of the treated population completed the study (Fig. 2). Most early discontinuations were for personal reasons not related to the device, followed by pregnancy. Loss to follow-up was low (approximately 4%) (Fig. 2).

There were approximately 22,348 reported coital acts with the single-size diaphragm. Exposure to the single-size diaphragm and study gel could be calculated for 375 couples. The per-couple monthly average number of coital acts was 13.3 (standard deviation 12.2, median 10.5). There were 40 pregnancies, of which 35 met the prespecified definition of a study event (estimated date of fertilization after enrollment and before the last day in the pregnancy analysis). The Kaplan–Meier cumulative 6-month typical use pregnancy probability for the single-size diaphragm was 10.4 per 100 women (95% CI 6.9–14.0) (Table 2) extrapolated to 12 months 17.8 (95% CI 12.0–23.6). Pregnancy probabilities of the two gels used with the diaphragm are shown in Table 2. No noticeable differences between the two gels were observed.

Historical control analysis yielded a propensity score–adjusted estimate of the cumulative 6-month typical use pregnancy probability for the single-size diaphragm of 11.3 compared with 10.7 per 100 women for the standard diaphragm ([rounded] difference 0.7, 95% CI −3.6 to 4.9; Table 3). Because the upper 95% confidence bound was less than 6.0, the null hypothesis was rejected; that is, the single-size diaphragm was noninferior to (at least as good as) the standard diaphragm for contraception. All three propensity score–adjusted comparisons on safety endpoints showed statistically significantly lower cumulative 6-month probabilities in the single-size diaphragm group: moderate-to-severe urogenital adverse event (−23.6, 95% CI −29.1 to −18.1), moderate to severe product-related adverse event (−24.0, 95% CI −28.3 to −19.6), and moderate to severe urinary tract infection (−6.4, 95% CI −8.9 to −4.0) per 100 women. The estimated cumulative six-cycle typical use pregnancy probability adjusting for 34 emergency contraception users was approximately 0.5 (per 100 women) higher than that without adjustment (Table 2). The 680 perfect use cycles yielded a cumulative six-cycle perfect use pregnancy probability of 7.9 (95% CI 1.7–14.0) and extrapolated to 12 months 14.0 (95% CI 3.0–23.6).

For the 31 (31/40 [78%]) pregnancies with outcome data, 15 (48%) resulted in 16 live births (one set

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Table 1. Baseline Characteristics in the Single-Size Diaphragm–Treated Population

Demographic	Acid-Buffering Gel (n=283)	Nonoxynol-9 (n=138)	Total (n=421)
Age (y)	28.7±6.0	29.2±6.0	28.9±6.0
Race			
Caucasian	134 (47.3)	67 (48.9)	201 (47.9)
Black	97 (34.3)	50 (36.5)	147 (35.0)
Asian	6 (2.1)	4 (2.9)	10 (2.4)
Other	26 (9.2)	7 (5.1)	33 (7.8)
More than one	20 (7.1)	9 (6.6)	29 (6.9)
Ethnicity			
Hispanic or Latina	39 (13.8)	14 (10.1)	53 (12.6)
Education (y)	13.9±2.7	14.3±2.5	14.1±2.6
Living with partner	215 (76.0)	103 (74.6)	318 (75.5)
BMI (kg/m^2)	28.8±8.4	30.2±8.1	29.2±8.3
Contraceptive use, past 6 mo			
Male condom	216 (76.3)	95 (68.8)	311 (73.9)
Combined oral, injectable, patch, ring	40 (14.2)	14 (10.4)	54 (13.0)
Spermicide alone	30 (10.8)	14 (10.8)	44 (10.8)
Diaphragm	10 (3.6)	7 (5.3)	17 (4.2)
Female condom	6 (2.2)	3 (2.3)	9 (2.2)
IUD	5 (1.8)	3 (2.3)	8 (2.0)
Contraceptive sponge	6 (2.2)	0 (0.0)	6 (1.5)
Progestin-only implant	2 (0.7)	0 (0.0)	2 (0.5)
Nulliparous	81 (28.6)	43 (31.2)	124 (29.5)

BMI, body mass index; IUD, intrauterine device.
Data are mean±standard deviation or n (%).

of twins), 11 (35%) had induced abortions, and five (16%) had spontaneous abortions. No newborn serious adverse events or nonserious birth complications were reported.

Nearly all (415/421 [99%]) of the treated population had an opportunity to report an adverse event. Among them, 257 (62%) reported at least one (Table 4). Approximately 51% experienced urogenital symptoms and 38% had at least one product-related event. Genital pruritus was the most frequently cited. Deleterious changes in Pap test results were seen in 4% (Table 4). There were four serious adverse events, all unrelated to the study product (postsurgical infection, hospitalization for pneumonia-like condition, suicide, myocardial infarction resulting in death). There were five serious adverse events among four male partners, all unrelated to the study product.

Table 2. Pregnancy Probabilities,* Pregnancy Population

	Single-Size Diaphragm		
Estimate	With Acid-Buffering Gel (n=269)	With Nonoxynol-9 (n=128)	Total Single-Size Diaphragm (n=397)
Typical use, 6 mo	9.6 (5.5–13.6)	12.5 (5.4–19.5)	10.4 (6.9–14.0)
Typical use, 6 cycles†	10.9 (5.3–16.5)	14.0 (2.8–25.1)	11.9 (6.8–17.0)
Typical use, 6 cycles, adjusted for emergency contraception	11.3 (5.6–17.0)	14.5 (3.2–25.8)	12.4 (7.2–17.6)
Perfect use,‡ 6 cycles	4.4 (0–10.0)	14.9§ (0.2–29.7)	7.9 (11.7–14.0)

Data are pregnancy probability (95% confidence interval).
* Per 100 women.
† Cycle-based calculations exclude cycles of nonstandard length or considered incomplete per rules in the analysis plan. By eliminating time when women may have had lowered fecundity, cycle analysis was expected to produce somewhat higher pregnancy probabilities than the cumulative 6-month method.
‡ n=219.
§ This perfect use probability is somewhat higher than the cumulative six-cycle typical use pregnancy probability. This is the result of a few cycles in which the expected reduction in pregnancies during perfect use was outweighed by a larger reduction in the number of eligible cycles, which increases the cycle-specific, and thus the cumulative, probability.

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Table 3. Comparison of Pregnancy Probabilities, National Institute of Child Health and Human Development Study and Single-Size Diaphragm Study, Both Used With Acid-Buffering Gel or Nonoxynol-9

Estimate	Single-Size Diaphragm	Standard Diaphragm
6-mo typical use from trial publication		
Acid-buffering gel	9.6 (5.5–13.6)	10.1 (7.1–13.1)
Nonoxynol-9	12.5 (5.4–19.5)	12.3 (7.7–16.9)
Total (acid-buffering gel and nonoxynol-9)	10.4 (6.9–14.0)	NA
Historical control analysis: propensity score–adjusted estimate of 6-mo typical use pregnancy probability*		
Total (acid-buffering gel and nonoxynol-9 combined)	11.3†	10.7

NA, not available.
Data are pregnancy probability (95% confidence interval) unless otherwise specified.
* Based on participants in the single-size diaphragm and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development study meeting criteria for inclusion in the historical control analysis.
† The difference was 0.7 (differences resulting from rounding) (95% CI = −3.6 to 4.9). Because the upper bound of the 95% CI was less than the predefined margin of 6.0 percentage points, the null hypothesis was rejected, indicating the single-size diaphragm was noninferior to the standard diaphragm.

Colposcopy findings were minimal, consisting of erythema, petechiae, ecchymosis, and grossly white findings; there was no deep epithelial disruption. Most women did not develop an adverse change in microflora. Approximately one third had a decrease in lactobacillus H_2O_2+ colony count, one fourth had an adverse change in each of Gardnerella, ureaplasma, *Escherichia coli,* or all of these colony counts, and less than 10% had an adverse change in candida (Table 4). There were no important differences between gel groups in colposcopy or microflora.

Almost all (439/450 [97.6%], 95% CI 95.7–98.8%) women could be fitted with the single-size diaphragm. On one attempt after reading written instructions only, more than three fourths (76%, 95% CI 72.0–80.1%) of participants were able to insert, correctly position, and remove the device and thought accurately that the position was correct. However, with coaching and up to three attempts, almost all (94%, 95% CI 91.9–96.4%) participants could insert, correctly position, and remove the device. Of the 39% (162/421) who discontinued early, only 12% discontinued for personal reasons related to the single-size diaphragm or gel (data not shown).

Couples reported a high proportion of coital acts with the single-size diaphragm (median 97%). Approximately two thirds (225/342 [66%]) reported 573 device or gel problems, most commonly device shift or dislodgment (13%; data not shown). Most women who completed questionnaires (282/342 [82%]) liked the single-size diaphragm, 40% would choose it as a contraceptive if it was available and effective, and 91% would recommend it to a friend (data not shown).

DISCUSSION

This pivotal study assessed the safety and contraceptive efficacy of the new single-size, nonlatex diaphragm. Participants were young, most were of proven fertility, and almost all were naïve to diaphragm use. The single-size diaphragm provided contraceptive protection comparable to the standard, as demonstrated by per-gel pregnancy probability point estimates similar to those in the NICHD trial[10] and a historical control analysis showing a cumulative 6-month typical use pregnancy probability well within the planned noninferiority margin.

The single-size diaphragm appeared to be safe and acceptable with no serious product-related adverse events. Deleterious Pap test result changes were rare, colposcopic findings minimal, and most did not experience adverse change in microflora. The probabilities of experiencing moderate to severe urogenital or product-related adverse events or urinary tract infections were significantly lower among the single-size diaphragm users than standard diaphragm historical controls, which may reflect device design improvements including a reduction in urethral pressure.

Participants were randomized to the use of an approved contraceptive gel typically used with diaphragms or an acid-buffering gel in development as a possible long-term replacement. Given that the goal of the study was to evaluate the single-size diaphragm, no statistical comparisons were planned between the gels; however, there did not appear to be any noticeable differences between the gels.

The single-size diaphragm fit almost all users. The results suggest that if the single-size diaphragm were provided in a clinic setting to first-time diaphragm

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Table 4. Safety Subendpoints in the Single-Size Diaphragm–Treated Population

Women With	Acid-Buffering Gel (n=278)*	Nonoxynol-9 (n=137)*	Total (n=415)*
At least 1 adverse event	169 (60.8)	88 (64.2)	257 (61.9)
Urogenital adverse event	137 (49.3)	75 (54.7)	212 (51.1)
Pain, irritation, pruritus	103 (37.1)	48 (35.0)	151 (36.4)
Abnormal bleeding	38 (13.7)	21 (15.3)	59 (14.2)
Symptomatic vaginal infection	37 (13.3)	16 (11.7)	53 (12.8)
Symptomatic urinary tract infection	7 (2.5)	7 (5.1)	14 (3.4)
Deleterious Pap test result change†	8 (3.4)	5 (4.3)	13 (3.7)
Symptomatic cervical infection	1 (0.4)	4 (2.9)	5 (1.2)
At least 1 product-related adverse event	106 (38.1)	50 (36.5)	156 (37.6)
Vaginal flora, adverse change from baseline at final visit	n=31‡	n=28‡	n=59‡
Lactobacillus H_2O_2+	12 (38.7)	9 (32.1)	21 (35.6)
Gardnerella vaginalis	9 (29.0)	7 (25.0)	16 (27.1)
Ureaplasma	8 (25.8)	8 (28.6)	16 (27.1)
Escherichia coli	7 (22.6)	7 (25.0)	14 (23.7)
Candida	3 (9.7)	1 (3.6)	4 (6.8)

Data are n (%).
* Number asked about adverse events at least once after enrollment.
† A significant change from baseline and includes atypical squamous cells of undetermined significance (2), atypical squamous cells of undetermined significance human papillomavirus-positive (4), low-grade squamous intraepithelial lesions (4), and high-grade squamous intraepithelial lesions (3). Denominator for percentages is treated population with postenrollment Pap test.
‡ Denominator for percentages is substudy treated population with microflora data at final visit.

users, almost all women would be able to insert, correctly position, and remove it; if provided over the counter, approximately three fourths of purchasers would be successful users. Approximately 12% would potentially use an improperly positioned device, putting themselves at increased pregnancy risk. Improved instructions have been developed.

Strengths of this trial included its rigorous design, successful recruitment, and low loss to follow-up. The study was limited by reliance on self-report of product use, common to all trials of user-controlled contraceptives, and that participants were not randomized to a diaphragm group. However, the study was designed for maximum similarity to the historical control trial, strengthening the validity of comparisons from historical control analysis.

The use of diaphragms globally has declined dramatically in recent decades as a result of lack of marketing and an increase in hormonal contraceptive products. However, although diaphragms are associated with urogenital events such as pruritus and there are more effective methods available, hormonal methods and intrauterine devices do not meet the needs of women who desire a pericoital method. The single-size diaphragm has features to improve fit and ease of use compared with the traditional diaphragm and also has been shown to be associated with fewer urinary symptoms than standard diaphragms. Its single size removes the need for a pelvic examination and fit assessment, simplifying provision and access. The single-size diaphragm also has potential as a multipurpose prevention technology for the prevention of pregnancy and STIs by being a physical barrier as well as a delivery system for microbicidal drugs. For all of these reasons, the single-size diaphragm has the potential to be more widely used than traditional diaphragms.

PATH has licensed the single-size diaphragm design to Kessel Medintim GmbH of Frankfurt, Germany, and it has been launched in over 10 European countries as Caya to be used with a lactic acid-based gel, Contragel. It has also been cleared for marketing by the U.S. Food and Drug Administration. The single-size diaphragm appeared to be safe, effective, and acceptable when used with a contraceptive gel in this study.

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