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Contraception 83 (2011) 436–440

Contraception

Original research article

Predictors of pregnancy in microbicide trials

Vera Halpern*, Che-Chin Lie, Paul Feldblum, Lut Van Damme[1] and the Microbicide Research Group[2]

FHI, P.O. Box 13950, Research Triangle Park, NC 27709, USA

Received 23 March 2010; revised 24 August 2010; accepted 25 August 2010

Abstract

Background: High pregnancy rates undermine the conduct and interpretation of HIV prevention trials. We performed this analysis to identify baseline participant characteristics associated with increased risk of pregnancy in recent vaginal microbicide trials.
Study Design: We analyzed the data from four recently completed Phase III trials of candidate microbicides for prevention of HIV infection. Cox proportional hazard models, stratified by site nested within study, were used to determine the baseline factors that predict pregnancy. Six thousand seven hundred forty-eight women contributed data for this analysis.
Results: Pregnancies were detected in a total of 1826 (27.1%) women. The hazard of pregnancy was higher for women who had a history of pregnancy, were living with a man or reported more sexual acts not protected by condoms in the week prior to enrollment. The risk of pregnancy was lower in older participants; in women with more years of education; in women who reported more sexual partners at baseline interview; in women who reported using intrauterine contraception, implants, sterilization or injectables and in women who reported use of a condom during their last act of vaginal intercourse.
Conclusions: Our data suggest that current use or acceptance of intrauterine contraception, implants, sterilization or injectables is the most effective approach to reduce pregnancy rates and might be a useful eligibility criterion in future HIV prevention trials.

Keywords: Microbicide; HIV prevention trials; Pregnancy; Risk factors; Contraception

1. Introduction

Clinical trials of HIV prevention drugs for women are often characterized by high pregnancy rates even when counseling and modern contraceptives are provided to participants. Some recently completed HIV prevention trials in Africa observed pregnancy rates ranging from 8 to 64 per 100 woman-years [1,2]. Because of concerns about unknown fetal effects of investigational drugs, most recent trials excluded women who were planning to become pregnant, and required women to discontinue product use, either permanently or for the duration of their pregnancy, if they became pregnant during follow-up. This had a potential to increase their time off product and lead to reduced study power to detect an effective intervention [3]. More importantly, high pregnancy rates raise a number of safety and ethical concerns. In spite of frequent testing, some early, and thus most vulnerable, pregnancies may remain undetected. The associated in utero exposure to some investigational drugs can jeopardize the growth and development of an infant. Abortion is illegal, and thus unsafe, in many countries where HIV prevention trials are being conducted, posing additional threats to the welfare of those participants who decide to terminate their pregnancy. For all of these reasons, reducing the incidence of pregnancy in HIV prevention trials is highly important, although certain issues would be somewhat mitigated if pregnant women were allowed to continue using the investigational drug [4].

One approach to achieving low pregnancy rates in an HIV prevention trial would be to detect, prior to enrollment,

* Corresponding author. Tel.: +1 919 544 7040; fax: +1 919 544 7261.
E-mail address: vhalpern@fhi.org (V. Halpern).
[1] Formerly at CONRAD (Arlington, VA, USA).
[2] Mark Weaver (FHI, Research Triangle Park, NC, USA); Christine Mauck (CONRAD, Arlington, VA, USA); Fernand Guédou (Centre Hospitalier Affilié Universitaire de Québec, Québec, Canada); Florence Mirembe (Makarere University, Kampala, Uganda); Roshini Govinden (HIV Prevention Research Unit, Medical Research Council, Durban, South Africa); Orikomaba Obunge (University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria); Folasade Ogunsola (College of Medicine, University of Lagos, Lagos, Nigeria).

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doi:10.1016/j.contraception.2010.08.018

women who are at high risk of pregnancy and either exclude them from the trial or provide them with effective contraception. We evaluated the relationships between participants' characteristics and the incidence rates of pregnancy in four trials of candidate microbicides in order to identify baseline factors associated with increased risk of pregnancy.

2. Materials and methods

We analyzed the combined data from four Phase III trials conducted in Nigeria, Ghana, Benin, Uganda, South Africa and India between 2004 and 2007 that evaluated the effectiveness of two potential vaginal microbicide gels — C31G (SAVVY®) and 6% cellulose sulfate (CS). All four trials (SAVVY/Nigeria, SAVVY/Ghana, CS/Nigeria and CS/multicountry) were approved by institutional review boards of the participating institutions, monitored by data monitoring committees, and registered in the ClinicalTrials.gov database. All participants signed written informed consent forms before screening and enrollment. The trials were double-blind, randomized, placebo-controlled and of similar design, and they all used the hydroxyethylcellulose gel as placebo [5].

The admission criteria and study procedures for these trials have been reported in detail elsewhere in accordance with the CONSORT guidelines [2,6,7]. Briefly, women who were HIV seronegative, assumed to be at high risk of HIV, nonpregnant and reportedly not desiring to become pregnant for the duration of the study were enrolled. While definition of "high risk of HIV" differed slightly between the trials, it generally implied very frequent sexual intercourse and multiple sexual partners. Most of the admission criteria were similar between the trials with the exception of age: all four trials restricted enrollment to women 18 years or older, but the CS/multicountry trial did not have an upper age limit whereas the other three trials did not admit women over 35 years. Participants were randomized to use active or placebo gel along with condoms for all acts of sexual intercourse for 12 months. Participants were interviewed, and tested for pregnancy at baseline and during monthly follow-up visits with urine-based rapid pregnancy tests. Women who became pregnant during the study were instructed to stop using the study gel; they could resume using the gel after the completion of pregnancy was confirmed by a negative test. The time off product due to pregnancy still contributed to the overall time-to-event analysis. The three trials in Ghana and Nigeria provided family planning counseling and condoms to all participants and referred those who were interested in using other methods of contraception to family planning clinics. In addition, the CS/multicountry trial provided contraceptive injectables and pills on site. The data from the two sites in India in the CS/multicountry trial were not included in this analysis due to the high prevalence of surgical sterilization and because only two pregnancies were observed in those sites.

An incident pregnancy was defined as a positive urine test for pregnancy at a follow-up visit and a negative test at the previous visit. Time to pregnancy, in days, was computed as the difference between the estimated date of fertilization, calculated crudely using the midpoint between the earliest date that the incident pregnancy was detected through a positive urine test and the date of the previous negative urine test, and the enrollment date, plus one. Cox proportional hazard models, stratified by site nested within study, were used to determine the baseline factors that predict pregnancy. Our resulting model implicitly assumed that associations between baseline factors and risk of pregnancy were consistent across the sites. We evaluated this assumption by testing stratum-by-risk factor interactions for all factors retained in the final model [8]. Only time to first pregnancy was included in the analyses. All models controlled for randomized treatment group and for the most effective contraceptive method reportedly used at baseline. Impacts of potential risk factors were assessed using a series of likelihood ratio tests to arrive at a parsimonious model. Factors were retained in the final model if they were significantly associated with pregnancy at the .05 level.

3. Results

A total of 7059 women were enrolled in the four trials (excluding two sites in India in the CS/multicountry trial), of which 6748 women were tested for pregnancy at least once during the study and contributed pregnancy data to this analysis: 2082 in SAVVY/Nigeria, 2038 in SAVVY/Ghana, 1506 in CS/Nigeria, and 1122 in CS/multicountry. Study populations were relatively homogenous across the three studies conducted in West Africa (Table 1). Participants in the CS/multicountry study generally had higher risk sexual behaviors at baseline and were older than their counterparts in the other three trials (almost a third of participants in this trial were over 35 years of age, contributing 12 pregnancies to the analysis.) In addition, more participants in the CS/multicountry study used effective contraception and cohabited with a man.

During the trial, first-time pregnancies were detected in a total of 1826 (27.1%) women across the four studies, of whom 552 (30.2%) were in SAVVY/Nigeria, 769 (42.1%) in SAVVY/Ghana, 308 (16.9%) in CS/Nigeria, and 197 (10.8%) in CS/multicountry, corresponding to pregnancy rates of 36.9 (95% CI 33.9–40.1), 63.9 (95% CI 59.5–68.6), 28.7 (95% CI 25.6–32.1) and 26.1 (95% CI 22.6–30.1) per 100 woman-years, respectively (Table 2). Across the four trials, 1490 women had one pregnancy and 336 women became pregnant more than once. Among those who became pregnant, the median time to first pregnancy — 127 days across all studies — was similar between the trials. Only two of the four trials collected outcome data for more than 90% of the study pregnancies in a systematic manner: in the CS/Nigeria and CS/multicountry trials, 86% and 56% of

Table 1
Selected baseline characteristics by study and overall

Characteristic	SAVVY/Ghana (*n*=2038)	SAVVY/Nigeria (*n*=2082)	CS/Nigeria (*n*=1506)	CS/multi (*n*=1122)	All (*n*=6748)
Continuous variables (mean±S.D.[a])					
Age in years	22.7±3.6	23.6±3.7	23.4±3.6	30.1±9.4	24.4±5.7
Years of education	7.8±3.4	11.1±3.5	10.5±3.7	8.1±4.0	9.4±3.9
Previous pregnancies	1.5±1.5	1.6±1.5	1.97±1.7	2.5±1.99	1.8±1.7
Sex partners in last 3 months	8.5±29.8	18.9±56.8	19.7±53.7	105±182.2	30.3±90.5
Vaginal sex in average week	9.2±7.3	10.9±11.5	6.99±7.5	13.1±16.5	9.9±10.9
Categorical variables (*n*, %)					
Cohabiting	214 (11)	170 (8)	53 (4)	207 (18)	644 (10)
Contraceptive method:					
Oral hormonal	239 (12)	303 (15)	247 (16)	86 (8)	875 (13)
IUD, implants, sterilization	14 (0.6)	22 (1)	6 (0.3)	98 (9)	140 (2)
Injectables	43 (2)	27 (1)	19 (1)	266 (24)	355 (5)
Condoms	956 (47)	1556 (75)	828 (55)	528 (47)	3868 (57)
None/Other	786 (39)	174 (8)	406 (27)	144 (13)	1510 (22)
Baseline positive STIs[b]	190 (9)	266 (13)	152 (10)	209 (19)	817 (12)
Baseline positive RTIs[c]	1144 (56)	882 (42)	984 (65)	606 (54)	3616 (54)

[a] S.D., Standard deviation.
[b] Sexually transmitted infections (gonorrhea, chlamydial infection, syphilis or trichomoniasis).
[c] Reproductive tract infections (candidiasis or bacterial vaginosis).

pregnancies, respectively, resulted in spontaneous or induced abortion, and 13% and 43%, respectively, resulted in a live birth. Due to the illegal nature of abortion in some of the participating countries, the self-reported data on pregnancy outcome should be interpreted with caution. Despite the high pregnancy rates, of total observed person-time, only about 5% in SAVVY/Nigeria and CS/Nigeria, 10% in SAVVY/Ghana, and 7% in CS/multicountry were off product due to pregnancy.

Of the 20 predefined baseline factors, 10 were found to be significantly associated with pregnancy in the final model (Table 3). Across the four studies, the hazard of pregnancy was higher in women who had a history of pregnancy and/or more deliveries or were living with a man. The risk of pregnancy was lower among women who reported using intrauterine contraception, implants, sterilization or injectables at baseline and for women who reported use of a condom during the last act of vaginal intercourse prior to screening. In accord, having more sexual acts not protected by condoms in the week prior to enrollment was associated with increased risk of pregnancy. In addition, the risk of pregnancy was lower in older participants (for each 1-year increase in age at screening, the hazard of pregnancy decreased by 10%), in women with more years of education (for every one-year increase, the hazard of pregnancy decreased by 2%), and in women who reported having more sexual partners in the 3 months prior to screening (for every 10-partner increase, the hazard of pregnancy decreased by 1%). We found no evidence that any of the associations varied by site.

A sensitivity analysis was performed by excluding women over 35 years in the CS/multicountry trial due to their potentially lower fecundity. The estimates remained very similar for all the factors in our final model and we would have reached similar conclusions (data not shown).

Factors for which we found insufficient evidence of association with the risk of pregnancy included self-reported use of oral contraceptives and condoms for contraception at baseline (compared to using no method), number of vaginal acts of intercourse in the last week or in an average week, anal or oral sex, positive results at screening for sexually transmitted or reproductive tract infections and histories of douching or using spermicide.

Table 2
Pregnancy data by study and overall

	SAVVY/Ghana	SAVVY/Nigeria	CS/Nigeria	CS/multi	All
Total number of women with detected pregnancy	940	663	369	218	2190
First-time pregnancies	769	552	308	197	1826
Repeated pregnancies	171	111	61	21	364
Days from enrollment to first pregnancy (median)	105.0	137.5	115.75	135.5	127.0
Person-years off product due to pregnancy (% of total person-time)	150.9 (10%)	88.1 (5%)	60.4 (5%)	56.4 (7%)	355.8 (6%)

4. Discussion

All four trials reported high pregnancy rates. The variability of pregnancy rates between the trials was due in part to various prevalence of baseline contraceptive use and provision of contraception in the trial. While frequent testing with sensitive pregnancy tests administered to the participants in the four trials could contribute to the high pregnancy rates by detecting subclinical, or "chemical," pregnancies,

Table 3
Hazard ratio of incident pregnancy for various risk factors

Risk factor	No. of women	No. of events	Percentage with events	Hazard ratio (95% CI)[a]
Primary contraceptive method:				
Injectables	355	51	14.4	0.45 (0.33–0.61)
IUD, implants, sterilization	140	6	4.3	0.21 (0.09–0.48)
Oral hormonal	875	875	30.1	0.94 (0.81–1.10)
Condoms	3868	1039	26.9	0.96 (0.84–1.10)
None/other/emergency	1510	467	30.9	1
Age[b]				0.90 (0.89–0.92)[c]
>23	3028	660	21.8	
≤23	3720	1166	31.3	
Living with man				
Yes	644	195	30.3	1.20 (1.03–1.40)
No	6103	1630	26.7	1
Years of school completed[b]				0.97 (0.96–0.99)[c]
>10	3066	700	22.8	
≤10	3682	1126	30.6	
Ever been pregnant				
Yes	5274	1456	27.6	1.32 (1.15–1.51)
No	1474	370	25.1	1
No. of pregnancies[b,d]				1.05 (1.01–1.10)[c]
>1	3279	893	27.2	
≤1	3467	932	26.9	
No. of vaginal deliveries[b,d]				1.19 (1.12–1.27)[c]
>0	2878	827	28.7	
≤0	3861	996	25.8	
Condom use during last sex act prior to screening				
Yes	3731	931	25.0	0.88 (0.79–0.99)
No	3016	895	29.7	1
No. of different partners in last 3 months before screening (in tens)[b]				0.99 (0.98–1.00)[c]
>40	2713	699	25.8	
≤40	4034	1127	27.9	
No. of acts unprotected by condoms in last 7 days prior to enrollment[b]				1.03 (1.01–1.05)[c]
>0	1350	342	25.3	
≤0	5398	1484	27.5	

[a] From final model; as a last test, the final model was compared to a model that included all 20 predefined baseline factors using the likelihood ratio test (p value=.649, indicating adequate fit of the final model).

[b] Continuous risk factors were split at the median for purposes of presenting pregnancy data by subpopulations.

[c] Hazard ratio estimates represent unit changes for continuous risk factors.

[d] Although number of pregnancies and number of vaginal deliveries were correlated, there was no indication that multicollinearity affected the interpretations of the estimated hazard ratios.

the reported numbers, especially in Ghana, are nonetheless alarming. They interfered with the interpretation of the results by increasing the overall time off product in all four trials, thus reducing each study's statistical power to detect a treatment effect. In addition to methodological implications, the high pregnancy rates raise serious safety concerns associated with early terminations as well as potential use of investigational product in early pregnancy.

Most women in the four trials reported using some form of contraception at enrollment and all expressed no desire to become pregnant for the duration of the study. However, the observed high pregnancy rates testify to the ineffectiveness of standard screening questions (e.g., "Do you want to become pregnant in the next 12 months?") to exclude women who were likely to become pregnant. The apparent lack of protective effect of the self-reported use of oral contraceptives and condoms for pregnancy prevention at baseline underscores the low predictive value of the self-reported data and/or inconsistent use of these methods. We could not evaluate whether continuous use of contraception was associated with the risk of pregnancy because none of the four trials collected data on contraceptive use during the trial in a systematic way.

Our results suggest that women who are young, less educated, living with a man, or not using condoms may be more likely to become pregnant during a trial. These findings are in accord with the results of previous research [9]. However, not all baseline characteristics that were found to be associated with significantly higher risk of pregnancy during the trial are likely to be clinically important (i.e., the pooled dataset was so large as to be able to detect as statistically significant differences that were clinically uncertain or meaningless). For instance, the practical implications of the counter-intuitive finding that women who reported more sexual partners at baseline interview had lower risk of pregnancy, are unclear. Of course, because the study participants were not randomly sampled from any larger population, this and all other findings might simply be artifacts of the selected study populations.

Future HIV-prevention trials could consider modifying admission criteria to exclude women likely to become pregnant (e.g., women who are young, less educated, live with a man or use condoms), but recruitment would be more difficult. Also, such modifications would probably yield lower HIV incidence cohorts because some of the baseline characteristics that were correlated with higher or lower risk of pregnancy in our analysis are also associated with increased (e.g., cohabitation) or decreased (e.g., use of condom) risk of HIV [10]. An alternative would be to focus pregnancy prevention efforts on those women identified as likely to become pregnant. However, the wisdom of such a selective approach was previously debated [11]. None of the associations in our analysis, aside from the use of effective contraceptives, were clinically meaningful. Therefore, concentrating special efforts only on the participants at high risk of pregnancy might not be sufficient to substantially decrease pregnancy rates. Provision of effective contraceptive methods to all participants seems more prudent.

Current use of intrauterine contraception, implants, sterilization or injectables was strongly associated with the lower risk of pregnancy and, thus, might be a useful eligibility criterion for future HIV prevention trials. Although extensive use of contraception in trials may affect trial outcomes (e.g., if contraceptive use somehow modifies microbicide effectiveness) or alter the perceived generalizability of the results [3], it nonetheless appears to be the most effective approach to reducing pregnancies. In addition, our findings provided additional evidence that women at risk of

an unplanned pregnancy are often simultaneously at risk for STIs, indicating a need in multipurpose prevention technologies that will allow people to avoid more than one adverse health outcome [12,13].

Acknowledgments

These trials were funded by the United States Agency for International Development; the CS/multicountry trial received partial funding from the Bill and Melinda Gates Foundation. Leigh Peterson, a principal investigator of the SAVVY/Ghana trial, was the main lead for the protocol development, supervised the implementation of the study and reviewed the manuscript. William Ampofo and Baafuor Kofi Opoku, Adesine Adeiga and Rashidi Bakare, Michel Alary, Suniti Solomon, Marissa Becker and Gita Ramjee, respective site investigators of the SAVVY/Ghana, SAVVY/Nigeria and CS/multicountry trials, supervised the implementation of the studies at the sites. Doug Taylor, Wes Rountree and Chin-Hua Wang, lead biostatisticians, helped to design the studies, participated in data analysis and contributed to the interpretation of the pregnancy results.

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