

# Vaginal Leakage: An Unappreciated Influence on Effectiveness of Agents in Vaginal Gels

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## Background

Vaginal gels are being developed and tested for their effectiveness in preventing HIV and other sexually transmitted infections, unintended pregnancies, and both. Most recently, research has demonstrated the partial effectiveness of a vaginal tenofovir gel in preventing HIV and herpes simplex virus [1]. In light of these encouraging results and the fact that other vaginal products are moving down the research pipeline, the art of improving vaginal drug delivery deserves renewed attention.

Studies of vaginal gels have noted differences in how much the products leak from the vagina after application. Several studies suggest that vaginal leakage may be associated with individual differences in leakage propensity and that products with higher osmolality may leak more [2–4]. In the present study, we determined the amount and variability of leakage for three vaginal gel products with moderate hyperosmolality. We also evaluated whether leakage was associated with osmolality or with several other individual factors. Understanding the reasons for variability in leakage could help increase both the acceptability and the effectiveness of vaginal drugs.

## Methods

This analysis was based on primary data from a Phase I randomized clinical trial conducted by CONRAD and partners to test the safety of a 6% cellulose sulfate (CS) vaginal gel [5]. The study included 48 healthy women ages 18–50 who were randomly allocated to receive one of the following products: 2.5 ml of Conceptrol, 2.5 ml of KY Jelly, 2.5 ml of 6% CS, or 5.0 ml of 6% CS. Women had pelvic exams and were tested for cervicitis and vaginitis prior to enrollment. The gels were applied only during nonbleeding days of the menstrual cycle, and women were asked to abstain from sexual intercourse during the study.

Each woman was given a single dose of gel, a one-use plastic applicator, and a resealable plastic bag containing a pre-weighed sanitary pad. She was asked to insert the gel before bedtime, wear the pad for 10 hours, and return the pad to the study clinic the next day. Vaginal leakage was measured by 1) the overnight change in pad weight and 2) each woman's subjective assessment of leakage (none, very slight, slight, moderate or severe).

We performed a secondary analysis of the data using nonparametric measures. The Wilcoxon rank-sum test and Kruskal-Wallis one-way analysis of variance (ANOVA) test were used to compare median changes in pad weight between the groups of women. We then used simple linear regression to determine whether history of vaginal delivery, time wearing the pad, age, or product osmolality was associated with gel leakage. All statistical analyses were performed using STATA 11.1 (Stata Corp, College Station, TX). The level of significance for all tests was  $p < 0.05$ .

## AUTHOR AFFILIATIONS

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## Results

The participants' demographic characteristics are shown in Table 1. The median age of the participants was 33 years (range, 19–47 years). Most of the women (66%) were Caucasian, and most (55%) had had at least one vaginal delivery.

TABLE 1. Demographic characteristics of the participants (n=47\*)

Characteristic	No. of women (%)
<b>Age</b>	
18–24 years	11 (23)
25–35 years	16 (34)
36–50 years	20 (43)
<b>Race</b>	
Caucasian	31 (66)
Black	12 (26)
Hispanic	3 (6)
Asian	2 (1)
<b>Prior vaginal deliveries</b>	
No	21 (45)
Yes	26 (55)

\* N=47 because one woman from the group receiving 5.0 ml of cellulose sulfate dropped out of the study.

The median duration of pad use was 10.0 h (range, 6.5–16.8 h). For all women, the median change in pad weight was 1.93 g (range, 0.03–6.2 g). However, the amount of leakage differed between products. When compared with women who received 2.5 ml of Conceptrol, those who received 2.5 ml of CS and those who received 5.0 ml of CS had significantly greater changes in pad weight ( $p=0.031$  and  $p=0.024$ , respectively) (Table 2).

We also found substantial variation in leakage between women, ranging from almost no leakage to leakage that was more than twice the amount of the gel inserted (Figure 1). Assuming two-fold dilution and looking at only the 2.5-ml doses, mean amounts of leakage for women in the lowest and highest quintiles were 10% and 71%, respectively, of their administered doses. The women's perceptions of vaginal leakage did not correlate with changes in pad weight, as most women (82%) reported only a slight or very slight amount of leakage (Table 2).

We did not identify associations between leakage and any of the factors we evaluated. No significant differences were found in the median change in pad weight between women who had had a vaginal delivery and those who had not. We also found no significant difference in vaginal leakage by time wearing the pad, age, or product osmolality.

## DISCLOSURE

FHI 360 holds a patent on a vaginal drug-delivery device composed of soft, pliable, non-woven textile materials. The device is being designed as a low-cost, single-use, ready-to-use female health insert that is pre-saturated with a gel for contraception, HIV prevention, or the delivery of treatments for vaginal infections.

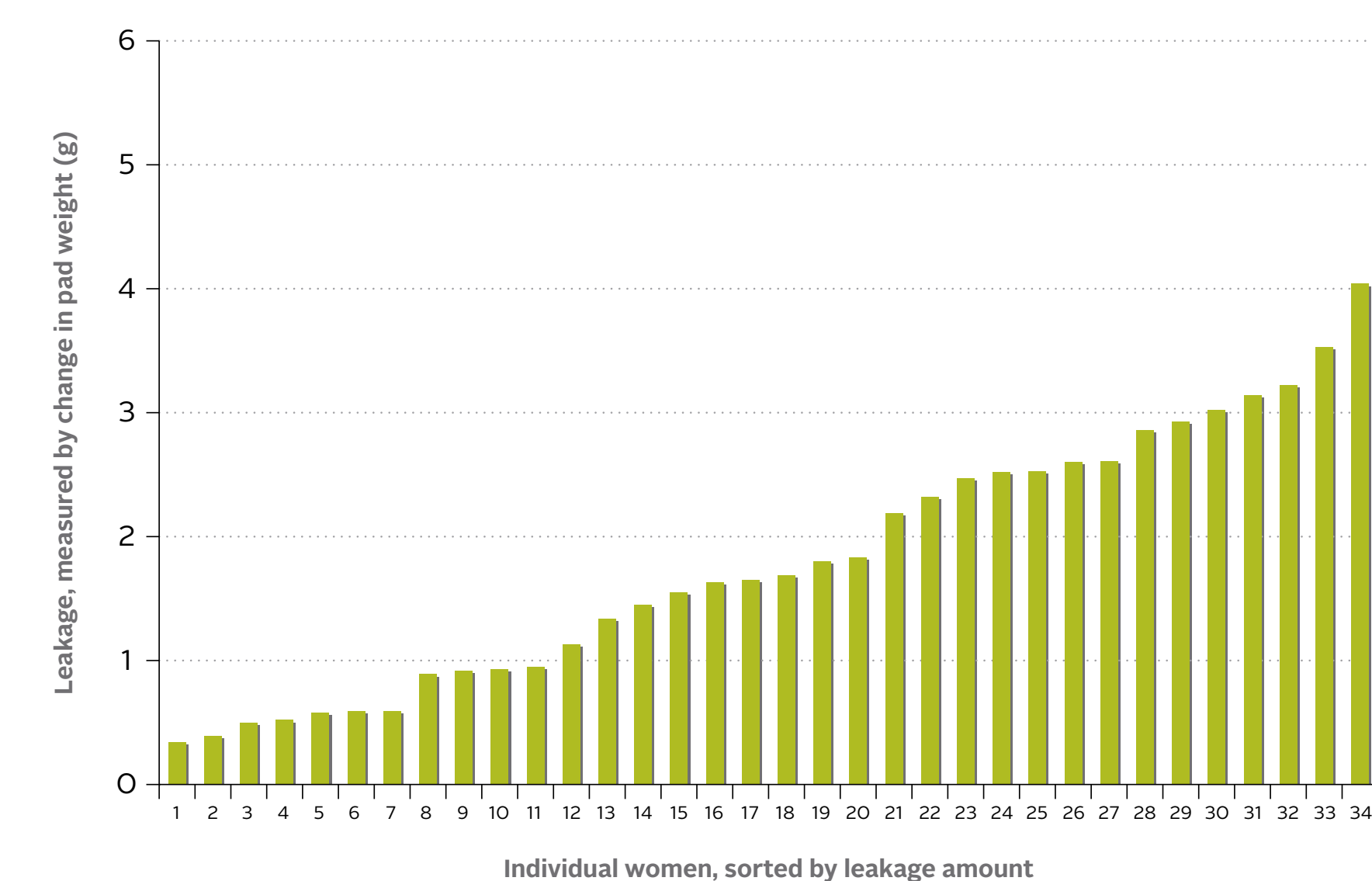
TABLE 2. Objective and subjective measures of leakage by product

Measure of leakage	Product and osmolality			
	2.5 ml CS 1195 mOsm/kg (n=12)	2.5 ml Conceptrol 1257 mOsm/kg (n=12)	2.5 ml KY Jelly 2424 mOsm/kg (n=12)	5.0 ml CS 1195 mOsm/kg (n=11)
<b>Median change in pad weight* (range)</b>	2.4 g (1.1–5.7 g)	0.9 g (0.4–3.2 g)	1.6 g (0.3–4.0 g)	2.9 g (0.0–6.2 g)
<b>Self-reported severity of leakage (No. of women)</b>				
None	2	1	0	0
Very slight	3	3	4	4
Slight	7	6	7	5
Moderate	0	2	1	2

CS = cellulose sulfate

\* For aqueous products, 1 g = about 1 ml

FIGURE 1. Individual variation in leakage for a 2.5-ml dose of gel



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## Discussion

Objective measures of vaginal leakage showed that leakage was significantly higher among women receiving CS (osmolality of 1195 mOsm/kg) than among women receiving Conceptrol (osmolality of 1257 mOsm/kg), suggesting that osmolality was not the major factor influencing leakage. Objective measures were highly variable among individual women within product groups.

Differences in anatomy and in levels of physical activity could have accounted for some of the differences in leakage. However, the number of vaginal deliveries was similar among the women (so their anatomy was likely similar) and the gel was inserted before bed (so physical activity should have been relatively limited and uniform). Another possibility is that gel viscosity, which was not measured in the study, affected leakage.

Unfortunately, the objective and subjective measures of leakage were in poor agreement. Self-reported severity of leakage may have been unreliable, as it is hard for women to accurately estimate how much leakage they have if they are wearing a pad (which absorbs the leakage). A potential limitation of the original study is that although many of the women used the gel products for five additional days without a pad, the women were not asked about leakage on those days.

Overall, we found that leakage of vaginal gels is variable and difficult to explain. And although not demonstrated in our small study, it is clear that extremely high osmolality may lead to severe vaginal leakage [4]. If the bioavailability and effectiveness of a gel are related to its persistence and concentration in vaginal tissues [6], then variation in leakage between products and between individuals is an important issue to address.

Additional research is needed to better evaluate the uniformity of vaginal drug delivery and to explore the use of alternative approaches for delivering vaginal gels. In addition to current work on vaginal rings, low-cost non-woven drug delivery devices, such as FHI 360's feminine health insert, should be evaluated for their ability to reduce variability in vaginal drug delivery.

## REFERENCES

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