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Original Article

Efficacy, safety and acceptability of a benzalkonium chloride spermicide cream in women aged 40 years and over needing contraception: A prospective multicentre study

David Serfaty[a,*], Vera Prilepskaya[b], Olivier Graesslin[c], Jean-Louis Benifla[d], François Aubin[e], François Verriere[f], Yana Mas[f], Julie Escola[f], Erwana Coatantiec[f], Frédéric Carrois[f]

[a] 9 rue de Villersexel, Paris 75007, France
[b] ул. Академика Опарина, д.4, 117997 Moscow, Russia
[c] Centre hospitalier universitaire de Reims, 45 rue Cognacq-Jay, Reims, Cedex 51092, France
[d] Hôpital Lariboisière, 3 avenue de Ambroise Paré, Paris 75010, France
[e] Venn Life Sciences, 63 Boulevard Haussmann, Paris 75008, France
[f] Laboratoire Innotech International, Groupe Innothera, 22 Avenue Aristide Briand, Arcueil 94110, France

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ABSTRACT

Objective: : This multicenter prospective study (BZK40+) aims to determine the efficacy and tolerance of a benzalkonium chloride-containing spermicide as contraceptive among women aged 40 and over.
Procedure: : Fertile women enrolled in this open single-arm study were instructed to systematically use the benzalkonium chloride spermicide before each intercourse. At the end of a 6-month mandatory period, participants were given the option of continuing the study for a further 6 months. The primary endpoint for contraceptive efficacy was the Pearl Index (PI) up to 12 months of typical use.
Main findings: : A total of 151 women (mean age: 45.9 years) were enrolled, 144 (95.4%) completed the initial 6-month period and 63 (41.7%) completed the optional 6-month period. The median number of intercourses ranged from 3 to 5 per month. The spermicide was applied before 96.3% of the 5,895 sexual intercourses. The PI up to 12 months of typical use was 0 pregnancies (95% confidence interval: 0–2.88). The cumulative treatment exposure was 1249.7 women-months.
Conclusion: : This first study in women aged 40 years and over shows that benzalkonium chloride spermicide (Pharmatex®) is effective, well tolerated and well accepted in this population. Although very interesting, these results with a PI equal to zero are surprising and not in accordance with the low efficacy of spermicides in the overall population according to the WHO. So, our results should be interpreted with caution and confirmed by future research.
Clinical trial registration number (EudraCT): 2016–004,188–38

Introduction

Midlife women are the group of women whose specific contraceptive issues receive the least attention [1]. Yet, woman's contraceptive needs change beyond 40 years as fertility gradually declines [2], while comorbidities (e.g. hypertension, diabetes, obesity, cancer) increase with age. These diseases can alter unfavorably the benefit-risk ratio of the birth control method currently used by these women [3]. The risk of maternal-fetal adverse effects is also greatly increased when pregnancy occurs in midlife [4,5]. Contraception is therefore recommended until menopause is confirmed.

All contraceptive methods are considered safe for healthy perimenopausal women and none is contraindicated by age alone [4]. Based on current guidelines, long-acting reversible contraceptives such as copper or levonorgestrel intrauterine devices (IUD) or progestogen-only pills or implants are particularly appropriate contraceptive methods for midlife women regardless of comorbidities, because of their contraceptive efficacy, their good cardiovascular safety profile, and their non-contraceptive benefits on perimenopausal symptoms [6]. Otherwise, barrier methods, like spermicides, may offer some key advantages, particularly in women aged 40 years and over, such as no known contraindication, no systemic effects, full control by the woman herself, ready availability without prescription and moderate cost. However, there is only scant and/or old clinical research data on these methods, and midlife women were not

* Corresponding author.
E-mail address: drserfatyfncgm@aol.com (D. Serfaty).

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included in their eligibility criteria [1,7,8]. Furthermore, estimations of spermicides efficacy are derived from studies focusing mainly on nonoxynol-9 spermicides, for which important safety concerns have been raised in case of frequent use [9]. The development of effective and safer spermicides has thus been the focus of some research over the last decades [10], but to date, no such product has specifically been evaluated in perimenopausal women who may be particularly interested in using such methods.

The purpose of our study was to assess in a real life setting and in women aged 40 and over the efficacy, safety and acceptability of a benzalkonium chloride-containing spermicide that has long been available in Europe.

Patients and methods

Study design

This open-label, single-arm study (EudraCT number: 2016 −004,188−38) was conducted in 16 centres (France: 10, Russia: 6) between December 2017 and October 2019. The protocol was approved by Health Authorities and Independent Ethics Committees. All women received adequate information about the study and signed their informed consent prior to inclusion.

Patient population

Eligible participants were fertile and sexually active women aged 40 and over.

- Informed about the risks and benefits of all contraceptive methods, particularly at this age.
- For whom contraceptive methods other than spermicides were not possible (intolerance, contraindications or refusal to use).
- Who accept to use a spermicide for at least six months.
- With a negative pregnancy test at inclusion.
- Who have had a normal smear test within three years.

The investigators were asked to appreciate the women's fertility potential as in routine gynecological practice.

The main exclusion criteria were :

- any concurrent disease contraindicating pregnancy,
- any concomitant treatment carrying a risk of teratogenicity,
- any vulvo-cervico-vaginal abnormal results,
- any infectious vaginitis over the last six months,
- any sexually transmitted disease treated over the last three months,
- HIV positivity or risk of HIV infection,
- any unprotected sexual intercourse within the previous seven days,
- more than two previous induced abortions,
- breast-feeding, or
- inability to conform to instructions for use of the spermicide.

Study medication and regimen

The spermicide was a 1.2% benzalkonium chloride cream (Pharmatex®, Laboratoire Innotech International) used as recommended by the manufacturer and as explained by the investigator during the baseline visit (Visit 1-V1, M0). A single dose was to be systematically introduced high into the vagina using an applicator, before each sexual intercourse, regardless of the menstrual cycle phase.

Study visits and evaluations

Study visits took place at 2 (V2) and 6 (V3) months. At the end of this period, participants were proposed to continue the study for an additional 6 months, and a final visit was planned at 12 (V4) months. Participants were contacted by phone at 1, 4 and, if relevant, 9 months (Fig. 1).

A urinary pregnancy test was performed monthly at woman's home and during on-site visits. The self-evaluation diary (including intercourse dates, spermicide use or not, reasons for non-use, concomitant use of other contraceptive methods or medications, spermicide acceptability, compliance, adverse events, menstruation dates) was completed by the woman after every sexual intercourse and checked by the investigator at each visit. Compliance with the tested medication and with the instructions for its use was also assessed by checking the number of empty or partially filled tubes of cream returned, compared to the number of documented sexual intercourses. A global study treatment satisfaction questionnaire was completed by participants and investigators. A questionnaire related

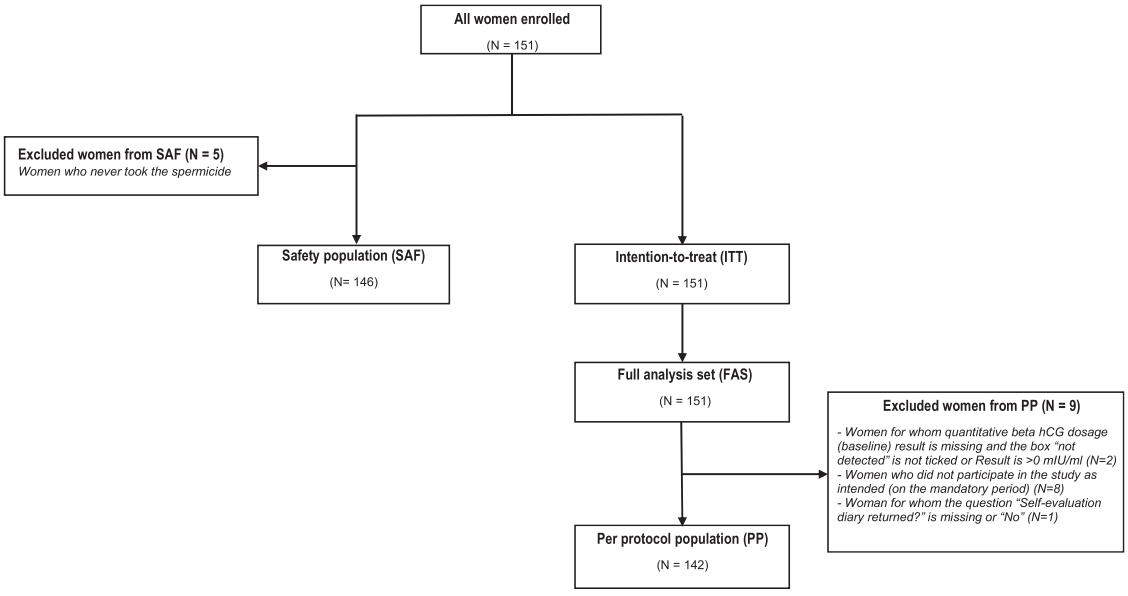

Fig. 1. Flowchart: Disposition of women.

to its lubricating effect was addressed at the last visit to all women reporting this effect.

During the phone contacts, the investigator particularly reminded the women how to correctly use the spermicide and complete the self-evaluation diary.

Study endpoints

The primary endpoint was the contraceptive efficacy of the spermicide determined after up to 12 months of typical use (including incorrect or inconsistent use), as expressed by the Pearl Index (PI), i.e., number of unintended pregnancies/100 women-years of exposure. This index reflects the spermicide's efficacy in a real-world setting.

Secondary efficacy endpoints included the PI determined after 6 months of typical use and after 6 and up to 12 months of perfect use (i.e. systematically correct use of the spermicide), the pregnancy rate during 6 and 12 months of typical and perfect use (i.e. number of pregnancies/100 women), the investigators' and participants' treatment global satisfaction, the spermicide acceptability (based on its continued use throughout the study, its systematic use before each sexual intercourse, its lubricating effect and ease of use) and any adverse events reported.

Statistical analysis

The study was powered to demonstrate a PI for up to 12 months of typical use with an upper limit of its 95% confidence interval (CI) below 22, the accepted contraceptive effectiveness for spermicides by the Haute Autorité de Santé (HAS) in France [10] at the time of study initiation.

On the assumption that the spermicide would achieve a mean PI of 6.33 in a population of women aged 40 and over, representative of "real-life" users in terms of age distribution [11] (i.e., 2/3 women ≥ 45 years with a PI of 5 and 1/3 aged 40–44 with a PI of 9), computer simulations were performed to assess the study's power with different sample sizes. Based on these simulations, a sample size of at least 62 woman-years, i.e., 124 subjects followed for 6 months, would be required to demonstrate with a 90% power a PI with an upper limit of its 95% CI below 22 assuming a theoretical PI of 6.33. Assuming a potential dropout rate of 20%, the planned study population comprised 150 women.

Four analysis populations were defined. The intent-to-treat (ITT) population included all women having participated in the study. The full analysis set (FAS) consisted of the entire ITT population except for women with a pregnancy confirmed after the start of the study and corresponding to a conception date preceding the study. The per protocol (PP) population comprised all women of the FAS population presenting no major protocol deviation. The safety population (SAF) incorporated all women having used the spermicide at least once.

The primary efficacy analysis was conducted on the FAS population after the last woman had completed the 12-month period. Any women lost to follow-up or deciding to stop contraception before 12 months were to be included in the analysis on the basis of the data available up to the date of the last contact or the last use of the product, respectively.

Results

Recruitment, participants and populations analysed

Out of the 151 women enrolled and included in both the ITT and FAS populations, 144 (95.4%) completed the mandatory 6-month period and 65 (45.1%) accepted to participate in the additional 6-month period (55.3% of women aged 40–44, 40.2% of those ≥45), of whom 63 (41.7%) completed this additional period (Fig. 1, Fig. 2). Seven (4.6%) women withdrew from the study before V3, a further two withdrawing during the additional period. All discontinuations were motivated by personal decision.

Participants' characteristics

Demographics and baseline characteristics for the FAS population are shown in Table 1. Barrier methods comprised the most common contraception used before the study (62.7% in the 40–44-year age group, 69.7% in the ≥ 45 years age group). Only a few women, all over 45 years, were spermicide users (6%).

Follow-up data

During the two study periods, the median length of the menstrual cycle was about 29 days in both age groups. Participants reported

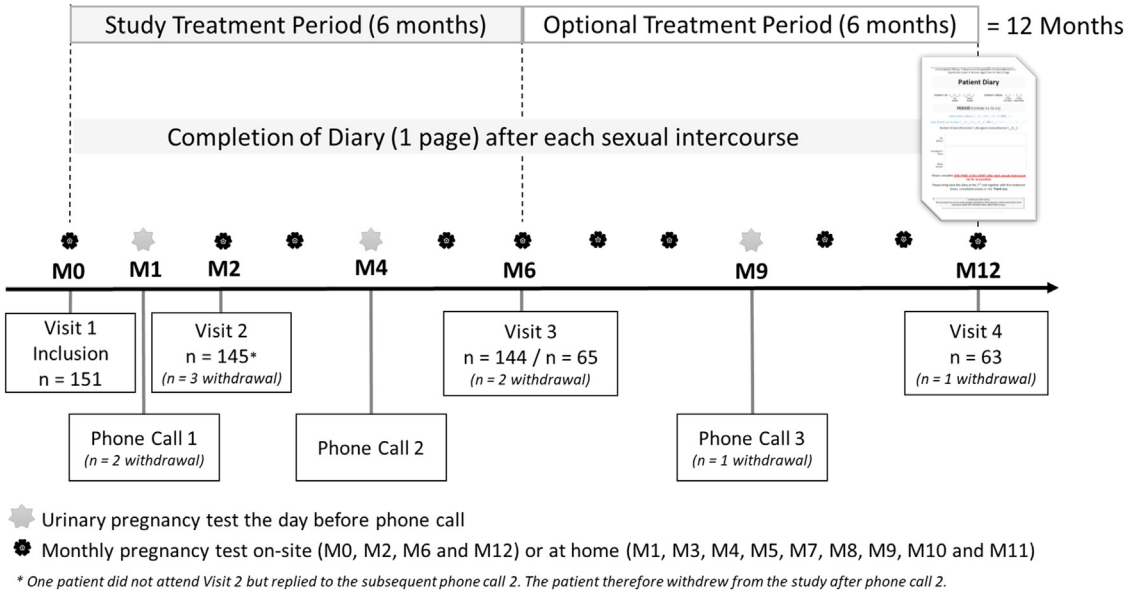

Fig. 2. Diagram of the study visits, phone calls and disposition of enrolled women through the study.

Table 1
Participants demographics and baseline characteristics.

Parameters	Total (*N* = 151)	40–44 years (*N* = 51)	≥45 years (*N* = 100)
Mean age, years (SD)	45.9 (3.8)	41.9 (1.3)	48.0 (2.8)
Mean BMI, kg/m^2 (SD)	24.6 (4.2)	23.3 (3.1)	25.3 (4.5)
BMI in classes (kg/m^2)			
<18.5	5 (3.4)	3 (5.9)	2 (2.1)
[18.5–25[	89 (60.1)	36 (70.6)	53 (54.6)
[25–30[	35 (23.6)	9 (17.6)	26 (26.8)
>=30	19 (12.8)	3 (5.9)	16 (16.5)
Median time between the last menstrual period and inclusion, days (Q1; Q3)	14.0 [9.0; 21.0]	12.0 [8.0; 16.0]	16.0 [9.5; 24.5]
Result of urinary pregnancy test *Negative, n (%)*	151 (100.0)	51 (100.0)	100 (100.0)
Smear test available within 3 years *normal, n (%)*	151 (100.0)	51 (100.0)	100 (100.0)
Gynecological examination performed (i.e., inspection of genital area and vagina per speculum examination)			
Normal, n (%)	147 (97.4%)	50 (98.0%)	97 (97.0%)
Abnormal – not clinically significant, n (%)	4 (2.6%)	1 (2.0%)	3 (3.0%)
Abnormal – clinically significant, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean number of pregnancies during lifetime (including all miscarriages, spontaneous abortions and deliveries) (SD)	2.3 (1.3)	2.2 (15)	2.3 (1.2)
Mean number of induced abortions during lifetime (miscarriages and spontaneous abortions are not included) (SD)	0.5 (0.7)	0.5 (0.7)	0.6 (0.8)
Last contraceptive method used (number of women and%)	150 (99.3%)	51 (100%)	99 (99%)
Hormonal contraception (LNG IUD excepted)	13 (8.6%)	4 (7.8%)	9 (9.1%)
Copper and levonorgetrel IUD	14 (9.3%)	6 (11.7%)	8 (8.0%)
Barrier methods (female and male condom, diaphragm, cervical cap, sponge)	101 (66.9%)	32 (62.7%)	69 (69.7%)
Natural family planning	21 (13.9%)	10 (19.6%)	11 (11.1%)
Spermicides	6 (4.0%)	0 (0.0%)	6 (6.0%)

intercourse at regular intervals (median: 3–5 and 4–5 per month during the mandatory and additional periods, respectively).

Use of the spermicide was reported by each woman in her diary, all diaries being collected after completion. Based on these diaries, no contraceptive method other than the spermicide was used in over 98% of the recorded sexual intercourses. The instructions for use of the spermicide were systematically respected by more than 80% of women during the mandatory period, and by at least 95% during the additional period.

Efficacy outcomes

Primary efficacy endpoint

The spermicide had a 12-month typical-use PI of 0 (no unintended pregnancy) in the FAS population (1249.7 women-months at risk) (Table 2). The upper limit of the 95%CI (2.88) was well below both the hypothetical value of 22 and the PI values reported for spermicides in the overall population [12–14].

A sensitivity analysis was performed on the FAS population (n = 151) excluding 4 women with a cervical medical/surgical history that could have a negative effect on fertility and for whom no element was provided by the investigator to justify the woman's fertility post cervical treatment (n = 147). The results of this analysis confirmed the spermicide's contraceptive efficacy with an upper limit of the 95%CI of 2.95, so below 22.

Secondary efficacy endpoints

The PIs after 6 months of typical use, and after 6 and up to 12 months of perfect use, were similarly 0 in the FAS and PP populations (Table 3). As no pregnancy occurred, pregnancy rates at 6 and 12 months are 0, whatever the population considered.

Other key secondary endpoints

The median number of sexual intercourses per woman and per month, ranged from 3 to 5 during the mandatory period and from 4 to 5 during the optional period. Most women reported having used this spermicide for each sexual intercourse (97.2% and 94.2% of women in the FAS between V1 and V2, and between V2 and V3 respectively). In most cases, Pharmatex® was used as the only contraceptive method (mean [SD] 98.9% [9.6%]). Less than 1% of intercourses were reported with concomitant use of this spermicide and another contraceptive method and only 0.7% of intercourses were reported without Pharmatex®.

Nearly all women and investigators said they were at least somewhat satisfied with the spermicide (99.3% after the mandatory period, 100% after the supplementary period). Its ease of use during the 12-month period was reported as being slightly acceptable,

Table 2
Primary efficacy endpoint results: Contraceptive efficacy over up to 12 months of typical use expressed by the Pearl Index (PI) in the FAS population.

Overall Pearl Index (PI)	Total (*N* = 151)	40–44 years (*N* = 51)	≥ 45 years (*N* = 100)
Number of unexpected pregnancies	0	0	0
Cumulative treatment exposure (women-months)	1249.71	436.53	813.17
PI [95% CI]	0.00 [0.00 - 2.88]	0.00 [0.00 - 8.24]	0.00 [0.00 - 4.42]

The higher upper CI limit observed in the younger age group compared to the older age group of women results from the shortest cumulative length of exposure to treatment in the younger group (due to the smaller size of the group).

Table 3
Secondary efficacy endpoint results: Contraceptive efficacy over up to 6 months of perfect and typical use and 12 months of perfect use, expressed by the Pearl Index (PI) in the FAS and PP populations.

	FAS (N = 151)	PP (N = 142)
12 months PERFECT use		
Number of unexpected pregnancies	0	0
Cumulative treatment exposure (women-months)	1230.06	1211.60
PI [95% CI]	0.00 [0.00 - 2.92]	0.00 [0.00 - 2.97]
6 months TYPICAL use		
Number of unexpected pregnancies	0	0
Cumulative treatment exposure (women-months)	869.29	847.84
PI [95% CI]	0.00 [0.00 - 4.14]	0.00 [0.00 - 4.24]
6 months PERFECT use		
Number of unexpected pregnancies	0	0
Cumulative treatment exposure (women-months)	853.03	840.61
PI [95% CI]	0.00 [0.00 - 4.21]	0.00 [0.00 - 4.28]

acceptable or perfectly acceptable with respect to 98.6% of the reported sexual intercourses. This trend was similar in both age groups. The vast majority of women (> 95%) considered the ease of use of the spermicide to be either acceptable (≈2/3) or perfectly acceptable (≈1/3) during most of sexual intercourses. The lubricating effect of the spermicide was considered appropriate by 96.1% of women reporting this effect (87.0% of women aged 40–44 and 89.7% of those ≥ 45 years) (Fig. 3).

Safety outcomes

Compliance with the spermicide was good with a median of 7.9 doses used per tube, respecting the recommended maximum of 11 per tube.

Forty-six (31.5%) women of the safety population experienced at least one adverse event. In the 40–44 and ≥ 45 age groups, 3 (6.3%) and 7 (7.1%) women reported at least one treatment-related adverse event. The most frequent adverse drug reactions were vulvovaginal pruritus (n = 3 in women aged 40–44, n = 5 in women aged ≥ 45) and vulvovaginal discomfort (n = 2 in women aged 40–44, n = 1 in women aged ≥ 45). No hypersensitive reactions were reported. No increase in the number of women with gynecological lesions was observed compared to baseline. No serious adverse drug reactions and no adverse events leading to study discontinuation occurred. No woman reported that her partner had experienced any adverse effects.

Discussion

Our study was the first to investigate the efficacy of this benzalkonium chloride-containing spermicide in menstruating and sexually active women aged 40 years and over, who represent a significant proportion of the patients seen in consultation seeking a contraceptive method. In comparison to previous investigations conducted with other spermicides, recruitment was completed rapidly and the continuation rate of participants was high [12]. Finally, the lost-to-follow-up rate was well below the 20% level suggested to lead to questionable results [13].

The PI up to 12 months of typical use of the spermicide and the upper limit of its 95% CI were well below the hypothetical value used to calculate the required sample size [10]. It was also well below 9, the PI upper value of an effective contraceptive in the overall population according to the WHO [14]. This result is even more significant in that the self-reported monthly coital frequency of the participants was high, potentially putting them at risk of pregnancy.

The efficacy results of this study are consistent with those of a clinical trial on a benzalkonium chloride gel that yielded a net cumulative rate of pregnancy of 1,7 at 6 months [15] but it was an “optimized” benzalkonium chloride and it refers to women of childbearing age and not specifically to women aged 40 and over, subject of our study. Our results are also consistent with those of the meta-analysis of Marmor et al. on different pharmaceutical forms of benzalkonium chloride reporting a typical-use PI of 2,42 [16] but this meta-analysis included very old studies, with a low number of patients and short durations. Here too, it concerned women of childbearing age and not only women aged 40 and over. In fact, the PI of benzalkonium chloride cream in women aged 40 years and older was unknown until our study. Several study design and participant-related factors may have contributed to our result. The rigorous monitoring of women during the study through visits and phone calls, as well as the adequate counselling provided, probably contributed to the correct and consistent use of the tested spermicide according to the instructions. The fact that most participants were familiar with barrier methods and therefore might have been particularly aware of the

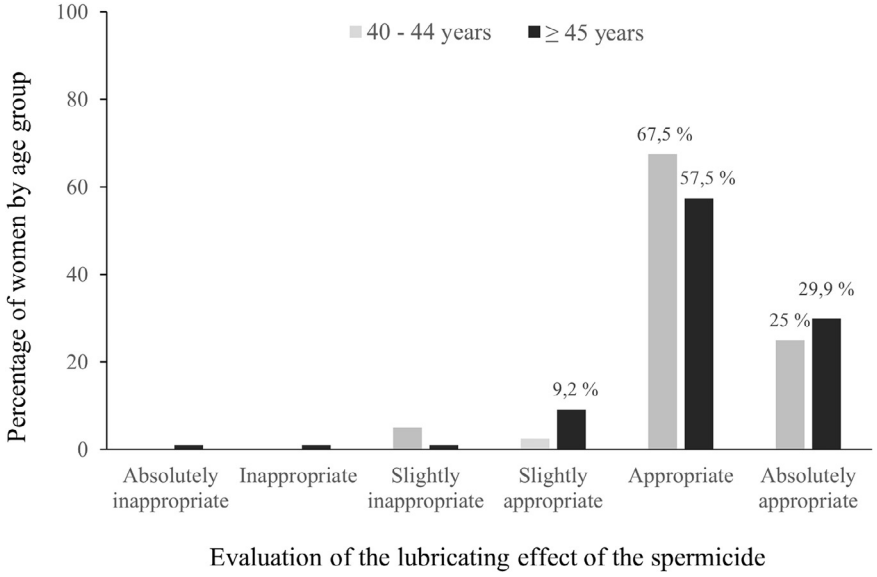

Fig. 3. Perceived lubricating effect of the investigated spermicide over the study among women reporting this effect.

importance of the appropriate use of such an "on-demand" user-dependent contraceptive to optimize its efficacy, likely also favored the correct use of the spermicide. Likewise, the age of users could have been a positive contributor to the adherence. Indeed, the age is known to play a striking role in contraceptive failure and thus contraceptive effectiveness, with the youngest users experiencing failure rates up to 10 times higher than older women for certain methods [17]. Finally, almost all women had achieved their family size and their strong motivation to avoid pregnancy could have been a major driver of their consistent use of the spermicide. The fact that numerous women voluntarily accepted to prolong their study participation up to 12 months also suggests their strong adherence to the spermicide and confidence in this contraceptive, probably reflecting its perceived safety and acceptability. No women discontinued the study because they changed their minds after more careful consideration of the risk of pregnancy, as previously observed [18], or because of safety concerns. However, it is not known to what extent the efficacy of this spermicide also reflects the declining fertility of the participants, one third of whom were aged 40–44 and two thirds of whom were aged 45 or over. Indeed, data from naturally fertile populations showed that age-related fertility loss increases rapidly after the age of 40, with half of women infertile at about age 41 and nearly 90% by age 45 [19]. This is nevertheless an average and for any individual woman the chances of conceiving beyond 40 may be higher or lower depending on certain characteristics. For example, in a study conducted in 36 women aged 45–53, the authors found that 33% of them and 61% of the 177 menstrual cycles recorded were potentially fertile [20]. This age distribution was deliberately chosen in order to assess the efficacy of the spermicide in a sample population that was as representative as possible of the profile of spermicide users observed in France [11]. In keeping with our intention to assess participants as they are in routine gynecological practice, no tests were also conducted to determine the current fertility status of participants before enrolment. The fertility of women who volunteered to participate in the study was left to the appreciation of the investigators who carried out this assessment as they usually do in their daily practice with women over 40 years of age presenting for contraception. According to current guidelines on the clinical evaluation of hormonal contraceptives, comparative studies are not generally requested and single-arm, open-label, historically controlled trials are considered sufficient to establish contraceptive efficacy [21,22].

Overall, our study has several strengths including the rapid recruitment of participants, their low discontinuation rate, their significant level of sexual activity, their strong adhesion reflected in the significant number of women who continued the study for an additional 6 months. But, it also has some limitations: the absence of a control group, a relatively small number of patients, a short study duration, a high number of women aged 45 years and over.

Conclusion

This study provides for the first time evidence supporting the efficacy, safety and well acceptance of benzalkonium chloride spermicide (Pharmatex®) in women aged 40 years and over. Nevertheless, the efficacy of this spermicide, according to our study, is surprising and not in accordance with the low efficacy of spermicides in the overall population according to the WHO [14]. So, although very interesting, our results have to be interpreted with caution, and should be confirmed by further independent research with an improved methodology (higher sample size, longer study duration, smaller number of women aged 45 and over and, if possible, a control group...).

Disclosure of interest

Dr. Serfaty and Prof. Prilepskaya, principal investigators in France and Russia respectively and members of the study scientific committee, declare no financial or non-financial competing interests.

Prof. Graesslin and Prof. Benifla, members of the study scientific committee, also declare no competing interests.

F. Aubin is an employee of VennLife Sciences, contracted by Laboratoire Innotech International to provide statistical and methodological support for the study.

F. Verriere Y. Mas, J. Escola, E. Coatantiec, F. Verriere and F. Carrois are employees of Laboratoire Innotech International, the study sponsor and manufacturer of the spermicide evaluated.

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