Introduction

Pelvic organ prolapse (POP) is defined as a condition in which vaginal wall support is lost, and various pelvic organs prolapse into the vagina. While minor degrees of POP affect up to 75% of women who have had a vaginal delivery[1], symptomatic POP with descent beyond the hymen affects 3% to 6% of the population [1]. The prevalence of pelvic organ prolapse increases with age until a peak of 5% in 60- to 69-year-old women. Some degree of prolapse is present in 41% to 50% of women upon physical examination, but only 3% of patients report symptoms [2]. Women considering treatment of POP should be offered a vaginal pessary as an alternative to surgery [1].

The NICE guideline on the management of urinary incontinence and pelvic organ prolapse in women recommends that all prolapse treatment options be discussed with patients including lifestyle modification, pelvic floor muscle training, pessaries, and surgery. The NICE guidance recommends that the pessary is removed at least every 6 months but does not recommend where or who should do this [3].

Approximately 71–90% women can be successfully fitted with a pessary for either SUI or POP, with symptomatic relief in 70–90% of the women who undergo a successful pessary fitting [4].

Pessaries have been in the market for many decades, and they are known to be relatively safe for use, involved with minor complications, most of them anticipated. Most women with POP will only require non-invasive management [5]. Vaginal pessaries are the only proven and well-studied noninvasive means of managing POP. A pessary is a device inserted into the vagina to support the walls and related pelvic organs. Modern pessaries are made of hypoallergenic silicone, rubber, or pliable plastic and are indicated for all pelvic prolapse stages [6]. It seems that a significant number of gynecologists prescribe pessaries as a first resort in treating POP [7] [8][9], although training in pessary use is limited and apparently needed [10] [11]. In a recent survey of 1,000 French healthcare providers, 54% felt that pessary prescription should be first line care for POP [12]. Pessaries are experiencing a resurgence in popularity following the problems experienced with surgical solutions (high symptomatic recurrence rate and morbidity with the trans-vaginal mesh implants) [8], and are now again viewed as an option for the management of prolapse for women in any age group [13]. Success or failure will depend on appropriate pessary selection, patient characteristics, provider training and experience, thorough counselling, as well as the achievement of an adequate fit and patient satisfaction [9].

A comprehensive review suggested that around 85% of women with symptomatic pelvic organ prolapse can be fitted successfully with a pessary[14]. The pessary size used should be individually fitted to each patient. There are many instances where devices are used vaginally, yet the clinically manifested vaginitis rate is rather low. The most commonly used long-term vaginal device is the intra-vaginal pessary for POP, followed by vaginal contraceptive rings. Vaginal contraceptive rings have a definite lifetime of 21-28 days in which they remain within the vagina. However, there is no definite or agreed-upon length of use for POP pessaries.

To date, only three types of polymeric material have been used in the fabrication of marketed drug-releasing vaginal rings [4]. All these materials are non-biodegradable and hydrophobic, such that they neither dissolve nor swell when immersed in aqueous media or inserted vaginally [15]. Vaginal microflora is variable and may show marked fluctuations of diverse microorganisms, even on a daily basis. The question of whether vaginal devices cause significant changes in vaginal microflora, and whether such devices may increase the rate of vaginal infection, has been the subject of much research over the past decades [16] [17]. Consensus is, however, that for the most widely used devices, non-hormonal vaginal contraceptive rings and pessaries for POP, vaginal microflora are not greatly affected.

The Provate Device is a new, disposable, self-inserted pessary that may be left in place within the vagina for up to 7 days. The goal of the device is to provide comfortable, safe support of the prolapsed uterus, that a woman can insert and remove herself without the need for a physician’s presence, thus empowering the woman to xxxx. Because this is a new concept in pessary use, a device that is disposable and self-inserted, it is important to establish safety in addition to efficacy. The objective of the study was to confirm that the ProVate Device does not alter vaginal microflora in a clinically significant manner, as compared to a control (commercially available vaginal ring pessary). Specifically, we were examining for significant change from baseline in specific vaginal microflora (*Lactobacillus spp., Gardnerella vaginalis, Candida* morphotypes, or *Staphylococcus aureus*), vaginal symptoms that are bothersome to the participant, or vaginal symptoms that require treatment.

**Methods**

The study population included females aged 21 to 80 years, in good general health diagnosed with POP (POP-Q stages 2-4); 73 subjects were randomized in a 1:1 ratio to groups A and B. Premenopausal women were enrolled only if their menstruation cycles within six (6) months prior to the study were regular and lasted between 26-40 days. The study population consisted of women who have previously used any ring vaginal pessary. The study took place in seven clinic sites, six in the United States and one clinic in Israel.

*Study Design*

The study was designed as a multi-center, open label, prospective, randomized, controlled, statistically powered (non-inferiority), crossover, home-use study. The study had a crossover design with two (2) study groups: A and B. Both groups used the study device and the control device (a commercially available vaginal ring pessary) in a cross-over fashion. The order of the use of the devices was determined based on initial randomization. Each portion of the sequence lasted 30 days (±3 days) for post-menopausal subjects, or the length of subject’s menstrual cycle (±3 days, within the range of 26-40 days) for menstruating subjects.

The first usage phase started following a 14 to 16 days washout period in which subjects were requested to refrain from using any vaginal device. Between the test phases of the two studied devices there was again a washout period of 14 to 16 days for post-menopausal subjects or one menstrual cycle for pre-menopausal subjects. Size fitting of each pessary type was performed at the beginning of each phase, followed by regular use of the chosen size for the rest of the ~30 usage days, or the length of the subject’s regular menstrual cycle. There were seven scheduled visits to the study clinic for each subject over an X period; one screening visit and three additional visits for each pessary tested (baseline/size fitting, size confirmation and end-of-phase visits). Randomization took place during Visit 2 prior to the use of the pessary.

Vaginal Microflora test samples were taken for all eligible subjects during four different study visits:

* Visit 2 - baseline of first usage period of study (either ProVate or Control device, based on the study group A or B). The sample was taken prior to the use of the tested device.
* Visit 4 - end of the first usage period;
* Visit 5 - baseline of the second usage period of the study (either ProVate or Control Device). The sample was taken prior to the use of the second tested device.
* Visit 7 - following second round of study (either ProVate or Control Device), any study device.

***Ethics approval***

***Microflora Analysis***

Four key microorganisms were evaluated during the study: *Gardnerella vaginalis, Lactobacillus spp., Staphylococcus aureus* and *Candida* morphotypes. *Lactobacillus spp.* and *Gardnerella vaginalis* were evaluated by Gram stain using the Nugent semi-quantitative scale based on the Isenberg Handbook of Clinical Microbiology (ASM), third edition. *Candida* morphotypes were evaluated by Gram stain using semi-quantitative scale. *Staphylococcus aureus* was evaluated using a semi-quantitative blood agar culture method. Counts of *Lactobacillus* and *Gardnerella* were assessed using the Nugent Score. The Nugent Score is a [Gram stain](http://en.wikipedia.org/wiki/Gram_stain) scoring system developed to diagnose bacterial [vaginosis](http://en.wikipedia.org/wiki/Vaginosis) [18]. The score is calculated by assessing the presence of large [Gram-positive](http://en.wikipedia.org/wiki/Gram-positive) [rods](http://en.wikipedia.org/wiki/Rod-shaped_bacteria) ([*Lactobacillus*](http://en.wikipedia.org/wiki/Lactobacillus) Morphotypes, scored as 0 to 4), small Gram-variable rods ([*Gardnerella vaginalis*](http://en.wikipedia.org/wiki/Gardnerella_vaginalis) morphotypes; scored as 0 to 4), and curved Gram-variable rods (Prevotella, [*Mobiluncus*](http://en.wikipedia.org/wiki/Mobiluncus)*spp*. morphotypes; scored as 0 to 2) and can range from 0 to 10.

Failure was defined if:

1. There were significant changes in vaginal microflora (i.e., significant meaningful change in *Lactobacillus spp, Gardnerella vaginalis, Candida spp*, or *Staphylococcus aureus* levels from baseline), where a significant change was defined, according to common clinical practice, as: a) Nugent score < 7 at baseline (Visit 2/5) for whom the end-of-treatment Nugent score (Visit 4/7) is ≥ 7; or b) > 1 scale unit increase in *Staphylococcus aureus*; or c) > 1 scale unit increase in *Candida* morphotype.
2. Failure parameter #2 - bothersome vaginal symptoms
3. Failure parameter #3 - vaginal symptoms that require treatment.

*Data Analysis*

Sample size calculations for the current study were based on the primary endpoint, namely the proportion of patients that reported unit increases of microflora growth over the course of usage. Based on a previously conducted study with the TIPI vaginal device for stress urinary incontinence (TIPI 007), we initially expected that 14.6% of patients would have a significant change in *Gardnerella vaginalis* and *Lactobacillus spp* following the use of ProVate. Furthermore, based on the same study, we expected that approximately 2.4% of patients would have a significant increase in *Candida spp* following the use of ProVate, whereas this proportion would be 3% for *Staphylococcus aureus,* based on the PT 103 clinical safety and efficacy study to evaluate the ProVate Device. To be conservative, we assumed that the subjects with a significant change in any of the microorganisms of interest would be mutually exclusive, therefore 20% of the total sample would have a significant change in the microflora. Based on the literature, we also expected that approximately 5% (2% to 8%) of subjects would have an infection with the microorganisms of interest and would, therefore, require treatment. Finally, using data from the PT103 study we expected that up to 17% of subjects would experience bothersome vaginal symptoms related to infection. Assuming a failure rate in the control group of 30%, based on the information above, and an actual difference in failure rate between groups of zero, a sample size of 54 subjects would achieve 80% power at a significance level of 0.025 using a one-sided non-inferiority test of correlated proportions (McNemar test assuming 10% discordant pairs), and a non-inferiority margin of 15% [19] [20].

**Results**

The study was conducted in seven sites, six in the United States and one in Israel, between August 2017 and September 2018. All eligible randomized women participants reported POP that had been assessed by vaginal examination. At screening, prior to introduction of any vaginal device, 21 (36.2%) of the 58 subjects had POP-Q stage 2 prolapse, 35 (60.3%) had POP-Q stage 3 and 2 (3.4%) had POP-Q stage 4 prolapse. The mean age was 64.5±10.57 (range 36-77 years), and the largest age group was between 71-80 years of age. (Table 1). The vast majority of the subjects, 52 (89.7%) reported various co-morbidities (not an exclusion criterion,) like metabolic and cardiovascular conditions. All 58 subjects (100%) had reported at least one delivery, and average parity was 2.7±1.11 deliveries. No deliveries nor pregnancies were reported within 12 months prior to screening. Four (6.9%) subjects were premenopausal, four of the postmenopausal subjects were using systemic Hormone Replacement Therapy (HRT), and five reported using vaginal hormone therapy. All subjects had used a vaginal ring pessary, whether commercially available ring and/or the ProVate Device. The duration of usage of the pessaries varied between one month and 15 years; 17 subjects (29.3%) used a ring pessary on a continuous basis, while 41 (70.7%) had non-continuous use.

The total number of subjects who met at least one failure criterion was comparable between the ProVate and control devices (Table 2); the rate of failure as defined using the above mentioned three failure parameters was nine (15.5%) for ProVate and nine (15.5%) for Control (lower than the 30% expected during the design of the study), with a one-sided 97.5% upper limit of 13%, which was within the non-inferiority limit of 15%. There were two cases of bothersome vaginal complaints (failure parameter 2) and one case which also required treatment (failure parameter 3) for vaginal infection within the control group, and none with the ProVate group.

Failure criterion 2 involved bothersome vaginal complaints, suggesting vaginal infection, while failure criterion 3 also involved treatment for a diagnosed vaginal infection. With the Control device, there were two cases of bothersome vaginal complaints and one case which required treatment for overt vaginal infection, in a subject who presented with bothersome malodorous vaginal discharge during Visit 7. On examination she had a malodorous infectious discharge and inflammation of vaginal walls and was treated with metronidazole. There were no reported vaginal complaints potentially related to vaginal infections while using the ProVate Device.

Laboratory findings and symptoms and signs of vaginal infection are comparable between the existing marketed vaginal Control Device and the new ProVate Device (Table 10).

**Conclusion**

The objective of the study was to confirm that the ProVate Device does not alter vaginal microflora in a clinically significant manner, as compared to a control (commercially available pessary). Analysis of results showed that both devices encouraged similar rates of microflora growth, therefore confirming that our device does not alter vaginal microflora significantly. Results of specific item or microorganism, namely changes in Nugent’s score, levels of *Staphylococcus aureus* and *Candida* morphotypes, and rates of bothersome vaginal symptoms and symptoms which require treatment, were found to be comparable between ProVate and the control. Further, the study demonstrated lower growth rates than expected, based on other microflora research [21] [22].

Vaginal microflora is unstable and continuous sampling may show marked variability in the presence and level of various vaginal microorganisms, in the same woman, even on a daily basis. This is true in both pre- and post-menopausal women. Constant natural fluctuations in the vaginal microflora limit the value of laboratory results alone in the assessment of vaginal infections (SOURCE).

These fluctuations make studies like this very difficult to interpret as results of the microbial samples may change very often, regardless of the studied device. This may lead to wrong assumptions as to the presence or absence of various microorganisms. Therefore, in a clinical study, attention should be aimed at signs and symptoms of a possible vaginal infection rather than be limited to laboratory results, due to the expected microflora fluctuations discussed above. Though our sample was small and the difference was not significant, it is still interesting to note that there were no signs of infection or bothersome complaints that required treatment with the ProVate Device, as compared with the five cases when using the control device. Explanations for this

In many of the articles which discuss adverse events related to vaginal pessaries, one may find a substantial number of cases of vaginal infection or vaginitis. Significant discharge, itching, and genital ulcers have been reported [23]. Alperin and colleagues found that 6% of pessary users had vaginitis diagnosed within the first three months after initial pessary placement, and that vaginitis was documented in 35% of patients throughout the nine year follow-up period [24]. However, we have no data comparing the use of a fresh-clean device at every insertion versus a device which is in constant use for years and is removed, cleaned, and immediately re-inserted, such as is the common practice for currently available pessaries. Since a large portion of pessary users cannot remove the ring pessary by themselves and need the help of a medical practitioner, removal and cleaning is performed every few weeks or even few months.

Results from this study show that with the ProVate Device, the rate of microflora changes and vaginal complaints which are bothersome or requiring treatment is relatively low and comparable to an existing market-available vaginal ring pessary. Adverse events related to the ProVate Device were minor, non-serious, and all resolved completely. There were no vaginal or urinary infections.

Due to the minimal microflora changes and absence of clinical vaginal infections, the ProVate Device demonstrates comparable minimal impact on microflora compared to the Control pessary with no additional safety concerns.

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