**EFECTIVENESS AND SAFETY OF A NEW DISPOSABLE VAGINAL DEVICE FOR THE NON-SURGICAL MANAGEMENT OF PELVIC ORGAN PROLAPSE (POP) IN WOMEN**

**Abstract (250 word maximum) currently at 345**

Introduction

both theand effectiveness andadisposable pessary to correct pelvic organ prolapse (POP)The device is inserted vaginally by the user with an applicator, Following insertion, the applicator is removed and discarded and the device may remain within the vagina for up to 7 days

Methods

The study was prospective, multi clinic, single arm, open labelstudy. Following screening and sizing, device usage lasted 45 days, with five office visis. During that time subjects were allowed to use as many devices as they wished, for a period of 1-7 days each. During the device usage period, subjects had to complete a diary, noting usage length, functionality and adverse events.

Four almost identical device models were tested sequentially. Statistical analysis was done on results from all models. The first performance endpoint was the percentage of subjects with an improvement from baseline of at least 1 POP-Q stage.

Results

52 subjects completed the study per protocol in three clinics;altogether there were 94 usage cycles in which 992 devices were used over 3393 usage days, an average of 36.1±5.70 days per subject.

In 100% of the usage cycles, there was a reduction of 2 POP-Q stages and in 97% of the usage cycles that began with stage 3 prolapse (64/66), there were three stages of reduction (p<0.0001). Subjective assessment of POP related symptoms showed mean improvement scores from 29 to 2.7 (P<0.0001). Modified PFIQ-20 QoL scores improved from 33.6 to 5.1 (p<0.0001), and modified PFIQ-7 improved from 24.9 to 0.7 (p<0.0001).

There were 91 device related adverse events (AE’s). almost all mild (98.9%), of short duration and anticipated (87.9%), and included mainly spotting, discomfort and some pain. There were no cases of vaginal infections, and there was only one case of urinary infection.

Conclusion

This new disposable vaginal device for the management of POP was found to be efficacious (with significant objective prolapse reduction and subjective relief of POP symptoms) and safe for use, with minimal mild and anticipated AE’s.KEYWORDS: Intravaginal device, pelvic organ prolapse, disposable vaginal device, non-surgical management.

**ONE-SENTENCE CONDENSATION OF THE PAPER**: A new disposable intravaginal device for the non-surgical POP management performs as intended, well tolerated, and with a safety profile comparable to existing ring pessaries.

**SHORT VERSION OF THE TITLE**: Single-use intravaginal device for management of pelvic organ prolapse is efficacious and safe for use

**Authors - Affiliations and disclosures**

**Elan Ziv MD Urogynecologist**

* Prev. Director, Urogynecology, Assuta Medical Centers, Tel Aviv, Israel
* CEO and Medical Director, ConTIPI Ltd, Caesarea Industrial Park, Caesarea, Israel

Dr Ziv has financial interest at ConTIPI Ltd, who invented and produced the device described in this study, as a shareholder and an employee.

**Tsvia Erlich MsC**

* VP Regulatory and Clinical Affairs at ConTIPI Ltd

Mrs Erlich has financial interest at ConTIPI Ltd, who invented and produced the device described in this study, as a management member and a consultant.

**Joseph May MD OBGYN LLB**

* Prev. senior clinician & Director of Menopause clinic, Meir medical center, Kfar Saba, Israel.
* Consultant OBGYN, Ramat Hasharon, Israel

Dr May has no financial interest at ConTIPI Medical Ltd.

**Simon Dascalu MD OBGYN**

* Prev. senior clinician, Maaynei Hayeshuah medical center, Israel.
* Consultant OBGYN, Hertzelia, Israel

Dr Dascalu has no financial interest at ConTIPI Medical Ltd.

**Introduction**

While minor degrees of POP affect up to 75% of women who have had a vaginal delivery[[1]](#endnote-1), symptomatic POP with descent beyond the hymen affects 3% to 6% of the population[[2]](#endnote-2). Approximately 3.5 million USA women currently suffer from symptomatic POP[[3]](#endnote-3), of them 210,000 - 300,000[[4]](#endnote-4) women undergo surgical interventions, annually. The rest of affected women is managed with vaginal pessaries or not treated at all. Mainly due to aging population, within 30 years, demand for services is expected to grow by 45%, while the population will only grow by 22%[[5]](#endnote-5).

Vaginal pessaries, mainly ring shape, are the most common non-surgical means of management of all stages of POP[[6]](#endnote-6). Pessaries are considered to be a relatively safe method of managing POP without serious side effects[[7]](#endnote-7),[[8]](#endnote-8),[[9]](#endnote-9) and the ACOG practice bulletin recommends pessary trial use prior to any surgical management[[10]](#endnote-10).

Existing pessaries have several features which limit their widespread use; they are all reusable, hard, resilient large bodies. Insertion and removal are done manually, sometimes difficult, painful or unpleasant[[11]](#endnote-11), most often necessitating a medical practitioner. They are intended for prolonged periods (e.g. 3-12 months™[[12]](#endnote-12),[[13]](#endnote-13),[[14]](#endnote-14)), and may cause irritations, pressure ulcers, infections, foul smell, etc.

Existing pessaries function well, but compliance reduces over time. Reports suggest that 56-73%[[15]](#endnote-15) of women can be successfully fitted within 1-4 pessary trials. However, the median discontinuation rate was found to be 49.1% (range 37-80%)[[16]](#endnote-16). The main reasons for discontinuation were inability to insert and remove the device by the user, failure to retain the pessary, discomfort, desire to move to another mode of treatment (e.g. surgery), and sexual disturbances.

The ProVate™ Device is designed to perform exactly as the existing ring pessary, while reducing or even eliminating most of the problems mentioned above.

* The device is disposable, sterile, and ready for immediate insertion.
* The device is intended to be inserted by the user in a non clinic setting.
* The device is small, compressed in an applicator during insertion, and opens to become a ring pessary once inserted.
* A pull string minimizes size and the device may be removed easily for disposal.
* Insertion resembles that of the menstrual tampon.
* The user may use the device for up to seven days and remove the device whenever she wants (e.g. intercourse) and insert a new device at her disclosure.
* The device is provided in six sizes.

Figure 1 shows the ProVate™ Device in different configurations, compacted and deployed, with and without the applicator, within and outside the body.

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|  | 07.tif |
| Figure 3b-The ProVate™ support, within its applicator, inserted intra-vaginally. | Figure 3a The ProVate™ support, in its compacted mode |
| 09.tif |  |
| Figure 3d-The ProVate™ support in its deployed (ring shape) mode, during use | Figure 3c-The ProVate™ support in its narrow compact mode, without the applicator. |
|  |
| Figure 3e-The ProVate™ support in its narrow compact mode, pulled out of the vagina for disposal |

Figure 1-The ProVate™ Device in different configurations

**Methods**

This study assessed the effectiveness and safety of the *ProVate™* Device. The study was designed to test up to four (4) consecutive *ProVate™* Device models in an iterative fashion***.*** Minor design improvementswere made to each of the models tested, mainly to the applicator system, based on the results of the previous model. The objective of the study was to confirm that the ProVate™ Device performs as intended and is safe for regular use. The study was designed as a prospective, multi clinic, one arm, open label, non-randomized, non-controlled, R&D supporting, home use performance study.

Objective effectiveness was measured by assessing change from baseline in stage of prolapse (while using the POP-Q scale and the Baden- Walker Grading), comparing results at visit 5 (final visit) with baseline staging/grading, and also at all interim visits.

Subjective effectiveness was assessed by using the POP Symptom Alleviation Score which was developed by ConTIPI Medical Ltd (Caesarea, Israel) as an author compiled scoring system to assess change in POP related complaints before and during treatment. POP related complaints (symptoms) were graded 0-4 (0 being “no complaint at all” and 4 being “significant complaint”), and scores during visit 1 (before using the device) and visit 5 (while using the device) were analyzed and compared. Results were normalized to the 100 scale.

Change in Quality of life (QoL) was assessed utilizing applicable parts of the PFDI-20 and PFIQ-7 [[17]](#endnote-17) QoL questionnaires. As the entire validated PFDI-20 & PFIQ-7 questionnaires include questions on various pelvic floor disorders which are beyond the scope of this study, subjects were requested to respond only to questions that are pertinent to POP. In the modified scores, 10/20 questions of the original PFDI-20 questionnaire were utilized. Possible scores in this questionnaire were 0-4, where 0=not at all, 4=very much. Results were normalized to the 100 scale. In the PFIQ-7 questionnaire subjects were requested to respond only to questions regarding POP (Modified PFIQ-7). Possible scores in this questionnaire were 0-3, where 0=not at all, 3=very much. Results were normalized to a scale of 0-100. Both modified QoL questionnaires were provided to subjects in English and in Hebrew, and were filled out at baseline visit and during final visit (V5).

Safety was assessed by recording the following:

1. Rate and incidence of anticipated Adverse Events (AE), which include vaginal wall trauma (e.g. erosions, abrasions, ulcerations), vaginal/urine infections, pain, spotting, discomfort, de-novo or worsening urinary incontinence and constipation.
2. Rate and incidence of Serious Adverse Events (SAE); rate and incidence of all AE’s (anticipated and non-anticipated, serious and non-serious, related and unrelated to the study device), and rate and incidence of device intactness.

Adverse events were reported in one of the following methods: daily diary, scheduled meeting with the investigator, non-scheduled call from the subject, and scheduled weekly telephone call to the subject.

Study population included: females, aged 21-80 years with symptomatic sensation of vaginal prolapse, clinical demonstration of POP-Q stage 2 – 4 prolapse in one or more sites along the vaginal wall, able to use both hands and insert a device into the vagina. The 61-91 mm pessary was well fitted and retained.

Exclusion criteria included previous inability to accommodate tampons or vaginal pessaries; current participation in another clinical study; co-morbid condition(s) or severe systemic disease that could limit the subject’s ability to participate in the study; pregnancy, suspected pregnancy or intention to be pregnant during the course of the study, abnormal vaginal bleeding in the past six months, previous vaginal surgery during the last three months, severely atrophic vagina, existing vaginal or vulvar laceration, symptomatic vaginal or urinary tract infection as determined by physical examination and lab results, recurrent urinary tract infections and abnormal cervical cytology.

Subjects were recruited from three community clinics (Gynecology & Urogynecology) in Israel.



*Figure 2- Study timeline*

During visit 1 (screening, baseline) subjects were screened for eligibility to participate in the study, and completed initial POP symptoms score and QoL questionnaires. During visit 2, screening was completed by ensuring that a 61-91mm ProVate™ Device was well fitted and retained. An ultrasound scan was conducted to estimate capacity of Post Voiding Residual (PVR) urine. Subjects were instructed as to how to insert the device by themselves and were sent home for 40-80 hours, and seen again during visit 3, thereby confirming correct size. If size were too small (expulsion) or too large (discomfort) then subject was refitted. The usage periodbegan at the end of visit 3 and ended on visit 5 – where visit 4 was a mid-study visit designed to ensure compliance with study restrictions and assess for AEs. During the study period, subjects were instructed to use the device at will for at least 28 days within a period of 45 days, and complete a daily usage diary. During each clinic visit, subjects were examined vaginally, to exclude signs of infection, bleeding and vaginal wall trauma. Subject completed the POP symptoms score and QoL questionnaires, as well as other questionnaires dealing with usage, satisfaction and ease of use. Both at baseline (visit 3) and post usage (visit 5).

The full analysis set (FA) included all eligible subjects who inserted at least one device (even if the insertion process was never completed). The FA analysis set served as the main analysis set for safety assessments. The per-protocol analysis set (PP) included all subjects from the FA analysis set who used the study device models for at least 20 days, with no major protocol deviation. The PP analysis set served as the main analysis set for the effectiveness and performance analyses.

Statistical analyses were performed using SAS v9.4 (SAS®, SAS Institute Cary, NC USA) software. The required significance levels of findings werep≤ 0.05..

**Results**

In the Initial part of the study (part A, using the first model), 44 subjects enrolled and tried the device at least once (FA set)l 33 subjects completed this part of the study per protocol (PP set). Minor amendments were then made to the applicator system, and this was tried during part B of the study wherean additional 20 subjects who also participated in part A tried two slightly amended applicator system models. All 20 subjects completed the study. The revised product was retested by 47 subjects (22 who participated in at least one previous part and 25 new recruits) and 41 participants completed . Subject disposition may be seen in Figure 3.

87 new subjects were screened, 18 of them were screen-failures, and a further 17 prematurely discontinued the study. Reasons for premature termination included Adverse Events (3), inability to insert the device (2), wish for surgery (1), inability to be fitted with available device’s size (8), and protocol violations (3). Altogether, 52 subjects completed the study in the 3 clinics. 24 completed one part of the study, 14 completed 2 parts, and 14 used the device during 3 parts. Subjects who participated in the study more than once were considered re-confirmed subjects, hence altogether 129 subjects were screened and 111 enrolled (figure 3).

****Altogether, in the Per Protocol set, there were 94 usage cycles in which 992 devices were used over 3,393 usage days, an average of 36.1±5.70 days per subject. In the Full Analysis set (safety), 1,592 devices were used over 3558 study days.

Figure 3-Subject disposition within the PT103 study

The mean age of the participants (N=111) was 60.4±9.72, with the majority of the participants between 61-70 (52.3%). Their mean BMI was 25.8±4.46. Of the 151 births reported by the participants, 108 were spontaneous vaginal deliveries, 39 instrumental, and 4 cesarean section. Almost all of the participants (81.1%) were postmenopausal; 13 subjects were using systemic HRT, and 6 used vaginal estrogen cream.

Objective effectiveness – reduction of POP stage

In the PP group, at baseline, in 28 usage cycles there was POP-Q stage 2 prolapse, while in 66 usage cycles there was POP-Q stage 3 prolapse. Following device insertion , prolapse was reduced substantially and immediately, (Table 1) and by visit 5, in 90 usage cycles there was no prolapse (POP-Q stage 0), and in two usage cycles there was POP-Q stage 1 prolapse. in all usage cycles (100%) there was at least 2 POP-Q stages reduction while using the device and in 64/66 of cases with POP-Q stage 3 prolapse (97%) there was even 3 POP-Q stages reduction while using the ProVate™ Device (<0.0001)..

This improvement was demonstrated at all three study sites with no statistically significant difference among sites; hence all study sites data were pooled.

Comparable results were achieved while using the Baden & Walker Halfway Grading system as well.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Visit** | **POPQ stage 0** | **POPQ stage 1** | **POPQ stage 2** | **POPQ stage 3** | **POPQ stage 4** |
| **Screening** |   |   | ***35 (31.5%)*****28 (29.8%)** | ***76 (68.5%)*****66 (70.2%)** |  |
| **Visit 3** | *93 (96.9%)*89 (96.7%) | *3 (3.1%)*3 (3.3%) |   |   |   |
| **Visit 4** | *93 (96.9%)*91 (96.8%) | *1 (1.0%)*1 (1.1%) | *2 (2.1%)*2 (2.1%) |   |   |
| **Visit 5** | *90 (97.8%)***90 (97.8%)** | *2 (2.2%)***2 (2.2%)** |   |   |   |

*Table 1 - Comparison of POP-Q stages before (screening) and while using the device, at the different visits (FA (red) PP (black), p<0.0001)*

Subjective effectiveness – reduction of POP stage

Figure 4-Comparison of POP related symptoms average scores before using the ProVate™ Device and while using the device (PP, All Cohorts, p<0.0001)

Figure 4 shows results for the POP Symptom Alleviation Score Mean total scores of all POP related complaints were significantly reduced (from 29 to 2.7; p<0.0001).

Quality of Life (QoL) Questionnaires

Figure 5 demonstrates substantial decrease in all modified PFDI-20 items scores The difference between visit 1 and visit 5 of 28.52 (SD=20.31) in mean total score of the modified PFDI-20 questionnaire is statistically significant (p<.0001).

Figure 5-Comparison of the Modified PFDI 20 average Score before using the ProVate™ Device (Visit 1) and while using the device (Visit 5) (PP, All Cohorts, p<0.0001)

The percent of subjects reporting that “not at all” for specific items of the modified PFDI-20 questionnaire) ranged from 5.3% to 76.6% at baseline, but increased to 80.6% through 98.9% at the end of usage period.

PFIQ-7 (modified)

Figure 6 demonstrate substantial decrease in all modified PFIQ-7 items scores. The mean total modified PFIQ-7 score was 24.9 at visit 1 and 0.7 at visit 5, (P<0.0001), demonstrating significant reported improvement in QoL.

Figure 6-Comparison of PFIQ-7 scores from before and while using the ProVate™ Device. (PP, All Cohorts, p<0.0001)

The percent of subjects reporting no symptoms at all while using the device increased from between 33.0% and 81.9% to 95.7% at least from the screening to visit 5.

*Adverse Events*

General safety analyses were conducted on the Full Analysis Population (FA).

e. .In the FA set, 124 adverse events were reported. Table 2 shows the breakdown of AE’s into Non-Device Related (NDRAE 33, 26.7%) and to Device-Related (DRAE 91, 73.3%) AEs.

|  |  |  |  |
| --- | --- | --- | --- |
| Population | Total AE | Non-Device Related AE(NDRAE) | Device Related Adverse Events (DRAE) |
| Remotely | Possibly | Probably | Total DRAE |
| All Cohorts | 124 | 33 (26.7%) | 8 (6.5%) | 17 (13.7%) | 66 (53.2 %) | 91 (73.3%) |

*Table 2-Number & percentage of device-related and non-device related adverse events (FA, All Cohort)*

In the All Cohorts population (FA set) there were 91 device-related adverse events while using **1592** devices over **3558** usage days. The most common AE’s were discomfort and spotting,. Vaginal wall trauma was only seen at part A of the study, not seen again following proper training by the investigators. The largest part of the AE list consists of sporadic AE’s, usually of 1-2 complaints each.

In the 91 potentially device-related AEs, 33 (36.3%) were reported during sizing phase and 58 (63.7%) during the device usage phase.

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Figure 7-Frequency of potentially Device Related AE’s within All Cohorts, (FA)

As with other vaginal devices, a learning/accommodation period, during which subjects become accustomed with the device, was expected. Most (anticipated) AEs occurred during the sizing phase (where the subjects became aware of the new device) and during the beginning of the usage phase (where subjects became accustomed with the device). It was clear that AEs were reduced while subjects became more experienced with device usage. Most of the device-related adverse events occurred within one week after visit 3 (58.9%,(Figure 8), within use of the first 5 devices (75.5%, Figure 9).

Weeks from visit 3

AEs

Figure 8-Break down of Device Related AE’s by weeks from visit 3 (FA, all cohorts)

Figure 9-Break down of Device Related AE’s by the number of device in the study (FA, all cohorts)

Specific Safety points: vaginal infections, UTI and urine retention

There were no signs or symptoms of vaginal infections (by self-report and/orvaginal exam). There was one case of UTI, treated with antibiotics, and one case of presumptive UTI where the subject was treated by her physician without a lab test or reporting to the PI.

Post-Void Residual (PVR) urine volume was studied by ultrasound scan before insertion of the first device, and with the device deployed within the vagina (visit 4). There was no significant difference in PVR before (15.0±15.56 ml (range 0-53.5 ml)) and while using the ProVate™ Device. (14.1±21.9 ml (range 0-90.7 ml).

**Discussion**

 Vaginal ring pessaries have been used effectively for the non-surgical management of POP for many years, and function well in most cases, substantially reducing vaginal wall prolapse. However, usage may be cumbersome and even bothersome. Multiple re-use of the device signifies constant cleaning and replacement and are associated with vaginal discharge, odors and infections, perception of aging and disability, and functional sexual disturbances.

 In most cases of pessary usages, the user is unable to insert or remove the device by herself. In a study among 496 British gynecologists, many of these practitioners stated that 10.7% of the users discontinued usage because of “dislike of the changing procedure”15.

The ProVate™ Device is a disposable flexible vaginal ring pessary designed to overcome many of the faults of existing ring pessaries. Although POP diagnosis, size fitting, size confirmation and routine follow up are performed by the physician. this design allows the users to insert and remove the sterile device by themselves, anywhere, at their own discretion, with no cleaning. The procedure is intuitive to many women (like insertion and removal of a menstrual tampon), and removal is instantaneous with a pull of a string. The ProVate™ Device, therefore, allows women to take control over their POP management, and over their intimate behavior (ability to remove the device prior to intercourse and insert a new one.). Disposable home self-use devices, such as the ProVate™ device, may allow women to use the device when they choose, and for their preferred allowed length of time. Our participants described this as ;freedom to decide‘ The ability to control POP management was noted verbally by the study subjects during the visits to the clinic including the ability to have unhindered intercourse. In addition, the ability to have some “device free intervals”, – waiting to insert a new device while still enjoying of POP-symptom-free periods, was also noted by the participants.. This is the first device of its kind to allow women these types of freedom when treating POP non surgically.

Success of any POP management may be discussed in two ways: anatomical reduction of prolapse and alleviation of prolapse symptoms. There are many cases in which anatomical correction does not alleviate prolapse symptoms, hence the importance of recording both points.

In our study, reduction to stage zero (0) was achieved in over 94% of the study cycles, and in the rest (~6%), there was reduction to stage one (1),.

The POP symptoms alleviation score regarding POP interference before the study and while using the ProVate™ Device were compared and a significant improvement was noticed while using the device,

Quality of life has increased considerably and significantly while using the ProVate™ Device. This was reflected by employing the modified versions of two validated Pelvic Floor QoL Questionnaires – PFIQ-7 and PFDI20.

The medical literature cites conflicting data on the prevalence of AE’s within groups of pessary users. While Hanson et al[[18]](#endnote-18) report only 14.5% of any complaintsBai et al[[19]](#endnote-19) reporedt 73.1% adverse events, while West & Moore21 found 56% AE’s This huge variability may reflect a difference in reporting. An ongoing daily/weekly follow-up of complaints and findings among users, as was employed in this study, will likely lead to a larger proportion of complaints, as compared with retrospective reporting.

Vaginal wall trauma, a well-known and described AE, occurs in 19.3% of pessary users[[20]](#endnote-20) (range 3-24%[[21]](#endnote-21).) In our study, there were seven cases of erosions, (?%) in the initial phase of the study only, which were noted by the investigator only (not the subjects), and were believed to be caused by the initial trials to insert the device. Following better instructions as to how to insert the device, no traumas were further noted.

Urogenital infections are rather common in women. However, in our study, there were no subject’s complaints or clinical signs and symptoms of vaginal infection. In our study there was only one case of symptomatic UTI, and one case of presumed UTI, which may or may not be attributed to the ProVate™ Device. These figures are rather low as a survey of 2000 women in the US found that 10.8% of women >18 years reported at least 1 presumed UTI during the last 12 months[[22]](#endnote-22).

Our study shows that the ProVate™ Device:

–fulfills its function, the anatomical correction of prolapse and the alleviation of POP symptoms, while being

Safe for use, comparable in effectivessnessexisting ring pessaries while offering the new aspect of self insertion of a disposable device.

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Conflict of Interest: Authors A & D have financial interest at ConTIPI Medical Ltd. Authors B&C declare that they have no conflict of interest.

**General comments:**

1. **All figures need to be removed from manuscript, saved in jpg format in separate files and figure titles need to be included at end of manuscript before references. Only 6 tables/figures can be included and the more figures the less text we can include. If quality of life is the main success point here, needs to be strengthened in discussion section and compared to other pessary studies more .**
2. **Font should be times new roman. Line numbers should be removed.**

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