Treatment with an intravaginal gel containing siliceous dioxide, selenite, and citric acid to promote regression of ASC-US-, LSIL, ASC-H, HSIL, p16/Ki61 status, and improve clearance of hr-HPV in cervical specimens

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ABSTRACT — OBJECTIVE: *An intravaginal gel containing highly disperse siliceous dioxide (SiO_2) and an anti-oxidative combination of citric acid and sodium selenite was tested for its ability to promote the regression of abnormal cytological findings and its influence on the hr-HPV status and tumor markers p16/Ki67 (CINtecPLUS).*

PATIENTS AND METHODS: A historical control study was performed, including women (n=100) diagnosed with conspicuous cervical smears (ASC-US, LSIL, ASC-H, or HSIL). The gel was applied for 3x28 days. After three months, participants were analyzed for Pap status, hr-HPV strains, and expression of tumor markers p16/Ki67. Three months later, Pap testing and p16/Ki67 analysis were repeated. The results were compared to those of 106 women who met the same inclusion criteria but did not obtain any treatment.

RESULTS: After six months, cytological Pap findings were improved in 80.9% of the participants in the treated group, and the clearing of hr-HPV was observed in 53% of cases. Only 5.3% were tested p16/Ki67 positive after six months in comparison to 75.0% at baseline. In the comparison group, 37.1% of the Pap smears and 18.6% of the CinTec results were improved, but no hr-HPV clearance was observed. The improvements were highly significant for the treatment.

CONCLUSIONS: The vaginal gel containing SiO_2 and sodium selenite may support the healing of conspicuous cytological findings and clearance of hr-HPV.

KEYWORDS
Vaginal gel, Pap testing, HPV clearance, Siliceous dioxide.

INTRODUCTION

According to WHO, 311 000 women worldwide died of cervical cancer in 2018[1]. An essential prerequisite for the development of the disease is a persistent infection with one of the "high-risk" strains of Human Papilloma Virus (hr-HPV). These viruses belong to the sexually transmitted pathogens and can infect basal epithelial cells of the cervix. Within the nuclei of infected cells, viral genomes can exist as stable episomes, replicating in low numbers in parallel to

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the cell cycle. This so-called "latent" phase of the viral life cycle may last for decades, but it may also switch to vegetative viral DNA replication. With the help of viral proteins, the cycle arrest and apoptotic mechanisms of infected cells are overcome. Thus, viral DNA and proteins are produced in high copy numbers in the terminally differentiated cells of the upper squamous epithelium, and from here, virions are released during expected cellular degradation. Due to the massive loss of cellular control mechanisms, the neoplastic transformation of the tissue may occur[2,3]. However, HPV infections are often cleared spontaneously by the normal immune response, and all stages of precancerous changes may heal spontaneously. Additional risk factors such as tobacco smoking and infections with other sexually transmitted pathogens play an essential role in enforcing neoplastic changes4. Generally, the development of a cervix carcinoma is a long-lasting process, which is characterized by the occurrence of well-characterized dysplastic precancerous stages. Consequently, screening strategies have been developed that include the examination of cervical cell smears (Pap testing). Cytological findings are classified according to the Bethesda nomenclature, which differentiates between benign and malign results of different cell types, allowing for an evaluation of progression risks and thus enabling the application of adequate treatment strategies[5]. Lower-grade cytological findings like ASC-US (atypical squamous cells of undetermined significance) and LSIL (low grade squamous intraepithelial lesions) spontaneously regress to an inconspicuous state within 1-2 years very often but may also progress to more severe conditions characterized as cervical intraepithelial neoplasia CIN2/3[4,5]. The actual course also depends on additional factors like age, presence of high-risk HPV (hr-HPV) strains, and further risk factors[6-10]. Hence, to prevent over-treatment of low-grade abnormalities, testing for hr-HPV is often included in screening strategies[11,12] in order to estimate the risk for the occluded presence or potential progression to higher-level lesions. A further diagnostic tool for evaluation of lower-level lesions with comparable or even improved specificity and sensitivity is the double detection of tumor marker proteins p16 and Ki67 with the commercially available CinTec test system[13,14].

Different therapeutical approaches have been tested to promote the regression of low-grade lesions or prevent progression. They include the application of 5-fluorouracil, curcumin, imiquimod, interferons, Vitamin D, and others[15-17]. Also, the effect of probiotics was assessed[18]. However, up to date, no convincing strategy was established for those medical approaches. Recently, a vaginal gel was developed, which is based on a combination of citric acid and sodium selenite with anti-oxidant properties. Oxidative stress, i.e., the occurrence of reactive oxygen species, has the potential to cause DNA damage and is a carcinogenic co-factor per se. In addition, several studies have suggested a connection between oxidative stress and the outcome of an HPV infection: higher levels of reactive oxygen species seemed to be associated with a higher risk of viral persistence or progression, and also the assembly of virions appears to be dependent on the local redox gradient[19]. The redox potential of selenite in acidic solutions is comparatively low, and the resulting high anti-oxidative potential may be useful in different pharmaceutic applications[20]. The vaginal gel further contains highly disperse siliceous dioxide (SiO_2) particles that may bind proteinaceous particles. In a preliminary study, intravaginal application of the gel improved the cytological status of women with abnormal cell smears compared to non-users within a 16-week trial[21]. In the present study, it was aimed at further characterizing the effect of the gel.

PATIENTS AND METHODS

Study Design

A controlled study was performed to evaluate the influence of an intravaginal gel containing highly disperse siliceous dioxide (SiO_2) and a combination of citrate/selenite on conspicuous cytological findings in cervical smears.

The study included 206 women with 100 patients in the treatment group and 106 participants in the control group. They were aged 25 to 60 years, who had a cytological diagnosis of ASC-US (atypical squamous cells of undetermined significance), LSIL (low grade squamous intraepithelial neoplasia) ASC-H (atypical squamous cells of undetermined significance and cannot exclude HSIL) or HSIL (high grade squamous intraepithelial neoplasia) according to Bethesda classification. Participants had signed informed consent, had a negative pregnancy test, and used an adequate contraceptive method throughout the course of the trial. Women with oncological carcinoma or immunological diseases, chronic viral infections (including hepatitis), immunosuppressive treatment, pregnancy, known allergy to any of the components of the gel, or colposcopy findings suspicious for invasive carcinoma were excluded from the clinical trial.

Eligible individuals underwent cytological screening, testing for tumor markers p16/Ki67, and hr-HPV status (see below) for baseline data. Women in the treatment group were then advised to apply 5 ml of the intravaginal gel (DeflaGyn®) for 3 x 28 days by utilizing single-use applicators. Menstruating patients were advised to pause the application interval upon bleeding (3-5 days per cycle).

After three months, cytological status, expression of tumor marker proteins p16/Ki67, and hr-HPV status were analyzed as before. Additional three months later ("6 months"), during which no treatment was performed, cervical smears were examined for their cytological status and expression of p16/Ki67.

The endpoint of the study was treatment success as measured by the regression of cytological findings to lower-grade lesions or complete remission to NILM and the clearance of hr-HPV. Also, p16/Ki67 expression was evaluated. Safety of DeflaGyn® vaginal gel was assessed by documentation of adverse events and determination of systemic selenium absorption.

Test Material

DeflaGyn® vaginal gel (Deflamed DEFLAMED International s.r.o., Prague, Czech Republic) is based on an aqueous solution and contains highly dispersed SiO_2 (2 mg/ml), which may adsorb pathogens and other particles as well as the anti-oxidant sodium selenite pentahydrate (0.166 mg/ml; equivalent to 250 µg selenium in the daily dose of 5 ml) and is acidified by citric acid (4.96 mg/ml) thus reaching a pH of 3.0. Other components that serve as preservatives or chelators are hydroxyethyl cellulose and potassium sorbate and sodium benzoate, respectively.

Sampling and Analytical Methods

At baseline, after three and six months, cervix smears were taken from the participants, stained according to Papanicolaou, and evaluated in accordance with the Bethesda classification. Additionally, the samples were tested for expression of tumor marker proteins p16 and Ki67 utilizing the CINtec® PLUS test (Roche Diagnostics). With this test, double staining indicates the oncogenic transformation of cells. HPV testing was performed using cobas® 4800 test (Roche Molecular Systems, Inc., Branchburg, NJ, USA), a PCR-based test system that detects HPVs DNA from the high-risk strains 16 and 18 as well as 12 additional high-risk types. For assessment of selenium absorption, the serum concentration of selenium was determined at baseline, and after three months.

For descriptive data evaluation, Microsoft Office Excel was used. Statistical analysis was performed using the software "Quickcalcs" (https://www.graphpad.com/quickcalcs/; GraphPad Software, San Diego, CA, USA). Fisher's exact test with two-tailed p-value was utilized to calculate the significance of the association between treatment with DeflaGyn® vaginal gel and improvement of cytological findings, HPV clearance, and the outcome of CinTecPlus testing.

Ethical approval

Ethical approval of the main study was given by the Multicenter Ethics Committee (Medical Chamber Check Republic February 2017) and the Local Ethics Committee (Brno/Vsetin, Olomouc, Prague, October 2017). The main study was registered in the ISRCTN registry with the ID ISRCTN11009040 (https://doi.org/10.1186/ISRCTN11009040). The current work represents a sub-analysis of the data collected during the preliminary trial.

RESULTS

Cytological Results

One hundred women with abnormal cervical smear were included in the group that received treatment with a vaginal gel containing SiO_2, selenite, and citric acid. Of those, 22% were diagnosed with ASC-US, 58% as LSIL, 9% as ASC-H, and 11% with HSIL diagnosis (Figure 1; left chart; black bars). In the group to which the experimental results were compared (non-treated group), the findings showed an equal distribution at baseline: From 106 women, 23.6%% were diagnosed with ASC-US, 55.7% as LSIL, 16% as ASC-H, and 4.7% as HSIL (Figure 1, right chart, black bars).

There were no dropouts during the first three months of the study. However, six women from the treatment group and one participant of the control group did not complete the three months follow-up period.

After treatment with the vaginal gel for three months, 75% of the participants had improved cytological findings (determined as complete resolution of lesions or change to lower grade lesions). After six months, the improvement was seen in 80.9% of them. As shown in Table 1, 56% of cervical smears were classified negative for intraepithelial lesion or malignancy (NILM), 34% had low-grade lesions (ASC-US and LSIL) 3% were classified as HSIL after three months with further improvements after six months. In detail (Table 2), 79.3% of LSIL and 76.2% of ASC-US findings had improved, while 4.8% and 5.2% of them had progressed to higher-level findings after six months. 100% of ASC-H findings and 88.9% of HSIL improved after six months.

In the group that did not have any treatment, less pronounced changes were observed (Figure 1 and Table 3). After completing the trial (6 months), 37.1% of the participants had improved Pap results. In detail, 16.2% had inconspicuous findings, while 71.4% still was diagnosed with lower-grade lesions (ASC-US or LSIL) and 12.4% with higher-grade lesions ASC-H or HSIL. From low-grade lesions at baseline, ASC-US and LSIL, 25% and 23.7% had improved,

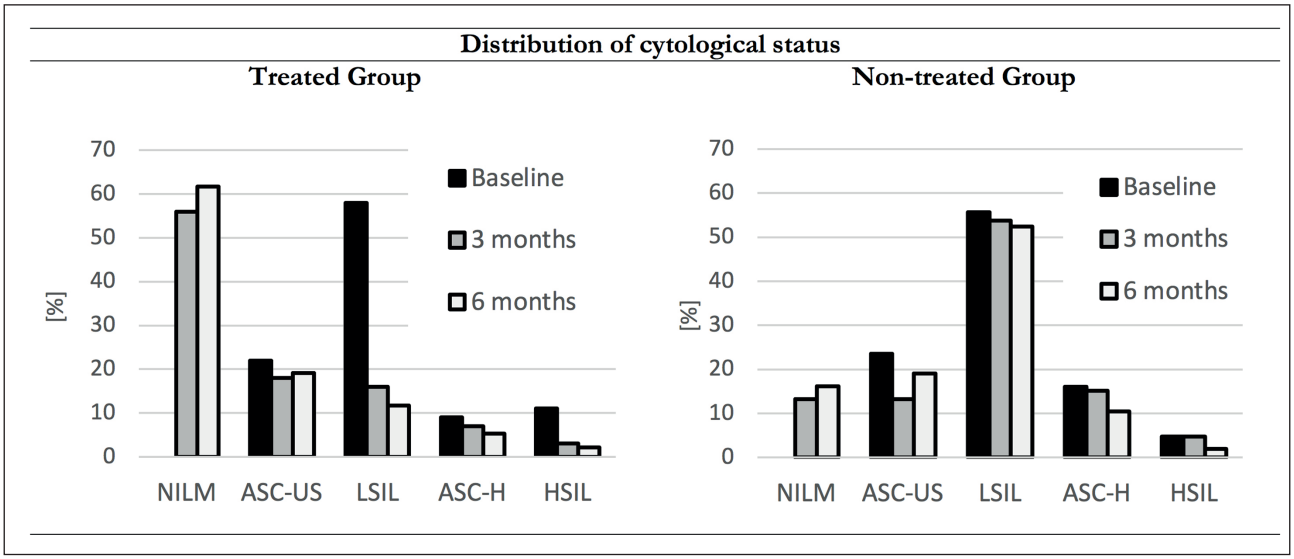

Figure 1. Cytological findings in cervical smears. Percentage distribution is given. Smears were taken at baseline (black bars), after 3 months (grey bars) and after 6 months (white bars). One group of women were treated with the selenite-SiO_2-containing vaginal gel for 3 months (left chart; n=100 at baseline and 3 months and n = 94 after 6 months); the comparison group did not receive treatment (right chart; n=106 at baseline and after 3 months and n= 105 after 6 months). During the following 3-month period, no treatment was performed.

Table I. Cervical smear findings of women treated with the vaginal gel. Shadings indicate different cytological changes: black: progression to higher grade lesion; grey: persistence; light grey: regression to lower grade lesion; white: non-conspicuous finding (remission). After 6 months, different baseline values ("base 2") are given, since some participants had dropped out.

Base 1		3 months					Base 2	6 months				
		NILM	*ASC-US*	*LSIL*	*ASC-H*	*HSIL*		*NILM*	*ASC-US*	*LSIL*	*ASC-H*	*HSIL*
0	***NILM***	**0**	0	0	0	0	0	**0**	0	0	0	0
22	***ASC-US***	**17**	4	0	1	0	21	**16**	4	1	0	0
58	***LSIL***	**34**	7	12	4	1	58	**36**	10	9	2	1
9	***ASC-H***	**4**	4	0	1	0	6	**4**	2	0	0	0
11	***HSIL***	**1**	3	4	1	2	9	**2**	2	1	3	1
100		**100**	**56**	**18**	**16**	**7**	94	**58**	**18**	**11**	**5**	**2**

Table II. Change in cervical smear findings of women without treatment. Shadings indicate different cytological changes: black: progression to higher grade lesion; grey: persistence; light grey: regression to lower grade lesion; white: non-conspicuous finding (remission).

		3 months				6 months			
		Remiss. [%]	Regress. [%]	Persist. [%]	Progres. [%]	Remiss. [%]	Regress. [%]	Persist. [%]	Progres. [%]
Treated Group	**ASC-US**	77.3	0.0	1.0	4.5	76.2	0.0	19.0	4.8
	LSIL	58.6	12.1	20.7	8.6	62.1	17.2	15.5	5.2
	ASC-H	44.4	44.4	11.1	0.0	66.7	33.3	0.0	0.0
	HSIL	9.1	72.7	18.2	0.0	22.2	66.7	11.1	0.0
No Treated Group	**ASC-US**	16.0	0.0	32.0	0.6	25.0	0.0	29.2	45.8
	LSIL	10.2	8.5	76.3	5.1	10.2	13.6	67.8	8.5
	ASC-H	17.6	41.2	35.3	5.9	23.5	58.8	11.8	5.9
	HSIL	20.0	20.0	60.0	0.0	20.0	80.0	0.0	0.0

Table III. Remission, Regression, Persistence and Progression of cervical lesions. Percentage changes of ASC-US, LSIL, ASC-H and HSIL findings after 3 and 6 months are given. Remission: complete healing; Regression: change to lower-grade lesion; persistence: no change in finding; Progression: change to higher-grade lesion.

Base 1		3 months					Base 2	6 months				
		NILM	*ASC-US*	*LSIL*	*ASC-H*	*HSIL*		*NILM*	*ASC-US*	*LSIL*	*ASC-H*	*HSIL*
0	***NILM***	0	0	0	0	0	**0**	0	0	0	0	0
25	***ASC-US***	4	6	7	8	0	**24**	6	7	7	4	0
59	***LSIL***	6	5	45	2	1	**59**	6	8	40	4	1
17	***ASC-H***	3	3	4	6	1	**17**	4	4	6	2	1
5	***HSIL***	1	0	1	0	3	**5**	1	1	2	1	0
106		14	14	57	16	5	**105**	17	20	55	11	2

and 45.8% and 8.5% progressed to higher-grade. All the HSIL findings at baseline were improved and 82.4% of ASC-US. However, 1 ASC-H had progressed to HSIL (Table 2). According to statistical evaluation with Fisher's exact test of independence, the association between treatment with vaginal gel and overall improvement of cytological findings was highly significant when compared to the non-treated group (p<0.0001).

Determination of hr-HPV and p16/Ki67

The clearance of hr-HPV was assessed to evaluate the efficacy of the vaginal gel. In the treated group, 87.0% of cytological samples were found hr-HPV-positive at baseline. The value declined to 41% hr-HPV positive after three months, corresponding to a clearance rate of 53% (Table 4). Figure 2 depicts the distribution of HPV positive findings and its clearance for each cytological group. Obviously, most lesions that resolved to NILM or regressed to ASC-US also became HPV negative within three months (Figure 3). Most higher-grade lesions remained hr-HPV positive.

In the comparison group, no HPV clearance was observed. In contrast, the percentage of HPV positive findings increased by 6% within three months (83.0% *vs.* 78.3% at baseline; Table 4). This finding is consistent with the observation that there was less overall improvement in cytological findings. Also, 50% of the unsuspicious findings (NILM) and 64.3% of ASC-US were diagnosed as hr-HPV positive (*vs.* 14.3% and 27.8% in the treated group, respectively).

The effect of treatment with the vaginal gel on overall HPV clearance was highly significant, according to Fisher's exact test (p<0.0001).

Correspondingly, also CINtecPLUS positive findings declined in the group treated with the gel. In Figure 3, the results are displayed for baseline, after three months, and after six months. In the group treated with the vaginal gel, CTP test was positive in 75% of all cases at baseline. About 90% of the higher-grade lesions (ASC-H and HSIL) had a positive CTP result, and for lower-grade lesions, CTP was positive in 69.0% (LSIL) and 77.3% (ASC-US). After three months, only 12.0% of all findings remained CTP positive, which further decreased to 5.3% after six months. A reduction was observed in each cytological group.

The comparison group had a higher percentage of CTP positive results at baseline (91.5%), and until the end of the study, the overall amount of CTP positive findings decreased to 75.2%. Here, the reduction of tumor marker expression was confined to lower-grade cytologic results ASC-US and LSIL (Table 5). The overall effect of treatment with the vaginal gel on CTRP findings was highly significant after 3 and 6 months (p<0.0001) when compared to the non-treated group. Generally, however, the amount of CTP positive findings was unusually high in this group, even in lower grade lesions. Thus, these results may be biased by some other effects.

Table IV. HPV positive findings in correlation to cytological status. Percentage values of hr-HPV positive findings are given for each cytological group and for the total number of participants.

		Baseline [%]	3 months [%]
Treated Group	**NILM**	0.0	14.3
	ASC-US	100.0	72.2
	LSIL	81.0	81.3
	ASC-H	88.9	71.4
	HSIL	90.9	66.7
	All Groups	**87.0**	**41.0**
Non-treated	**NILM**	0.0	50.0
	ASC-US	56.0	64.3
	LSIL	94.9	93.0
	ASC-H	58.8	87.5
	HSIL	60.0	100.0
	All Groups	**78.3**	**83.0**

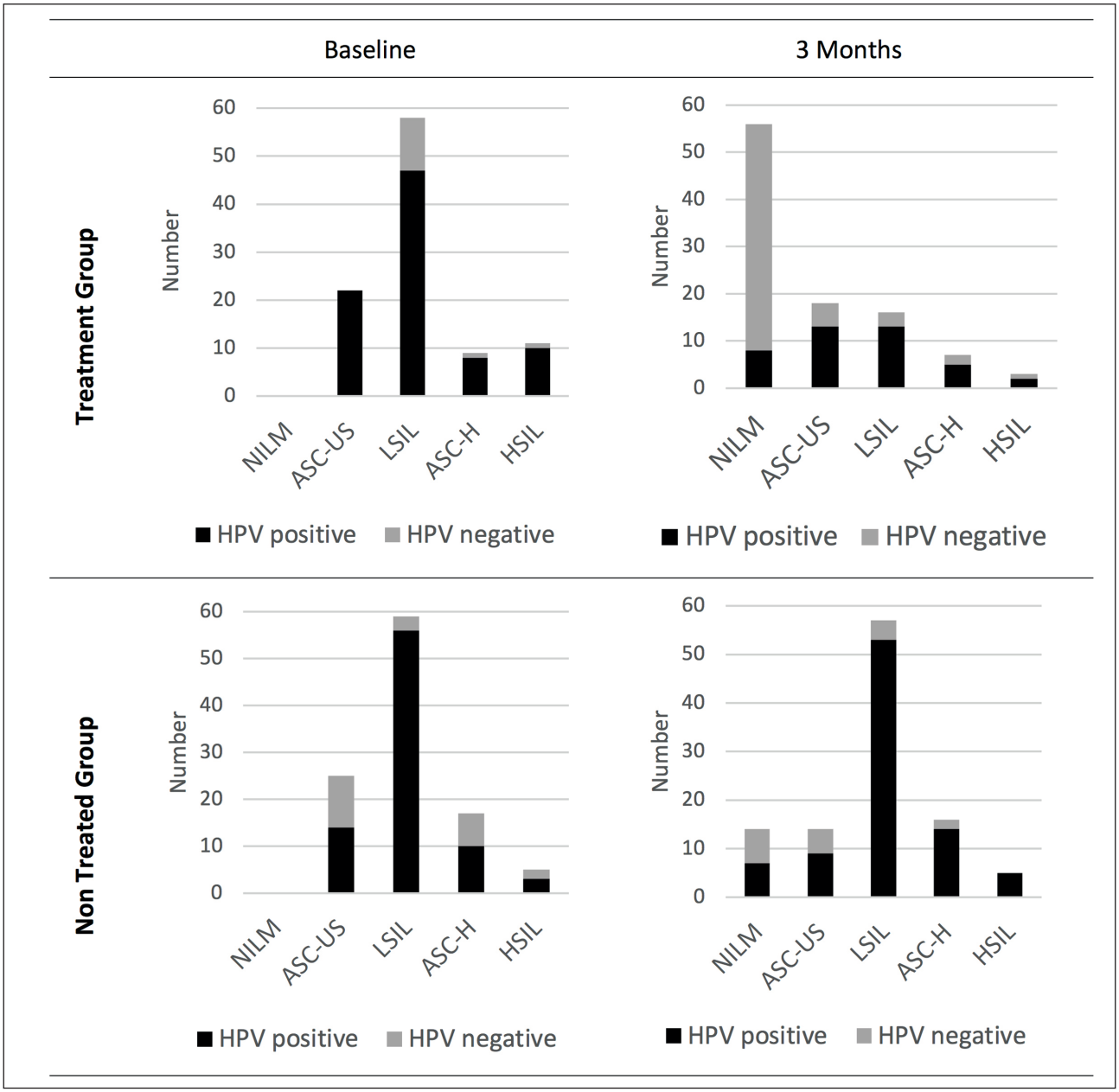

Figure 2. hr-HPV status in relation to cytological findings. Results are shown for treated group (upper row) or non-treated group (lower row) at baseline (left column) and after 3 months (right column).

Safety of the vaginal gel

From the participants in the group treated with the vaginal gel, 42 adverse events were reported. Of those, 12 were reported by four patients and were probably not causal or not known to be related to the usage of the device. Most reported events were mild or moderate and comprised vaginal itching or burning, bloody discharge, increased vaginal bleeding, vaginal mycosis or herpes, or slight abdominal cramps. Termination of treatment was not necessary, and no serious, possibly device-related adverse events were reported.

Selenium serum concentration was measured in the treatment group after three months of treatment. Since no elevation of selenium concentration was measured, it was confirmed that no systemic absorption had occurred.

DISCUSSION

For women treated with the vaginal gel, about ¾ of LSIL and ASC-US findings were improved, i.e., either regressed to lower-level findings or became inconspicuous after six months. In a comparable group of patients, the improvement was seen in about ¼ of LSIL and ASC-US. For higher-grade lesions, success was comparable (90-100%) between the groups,

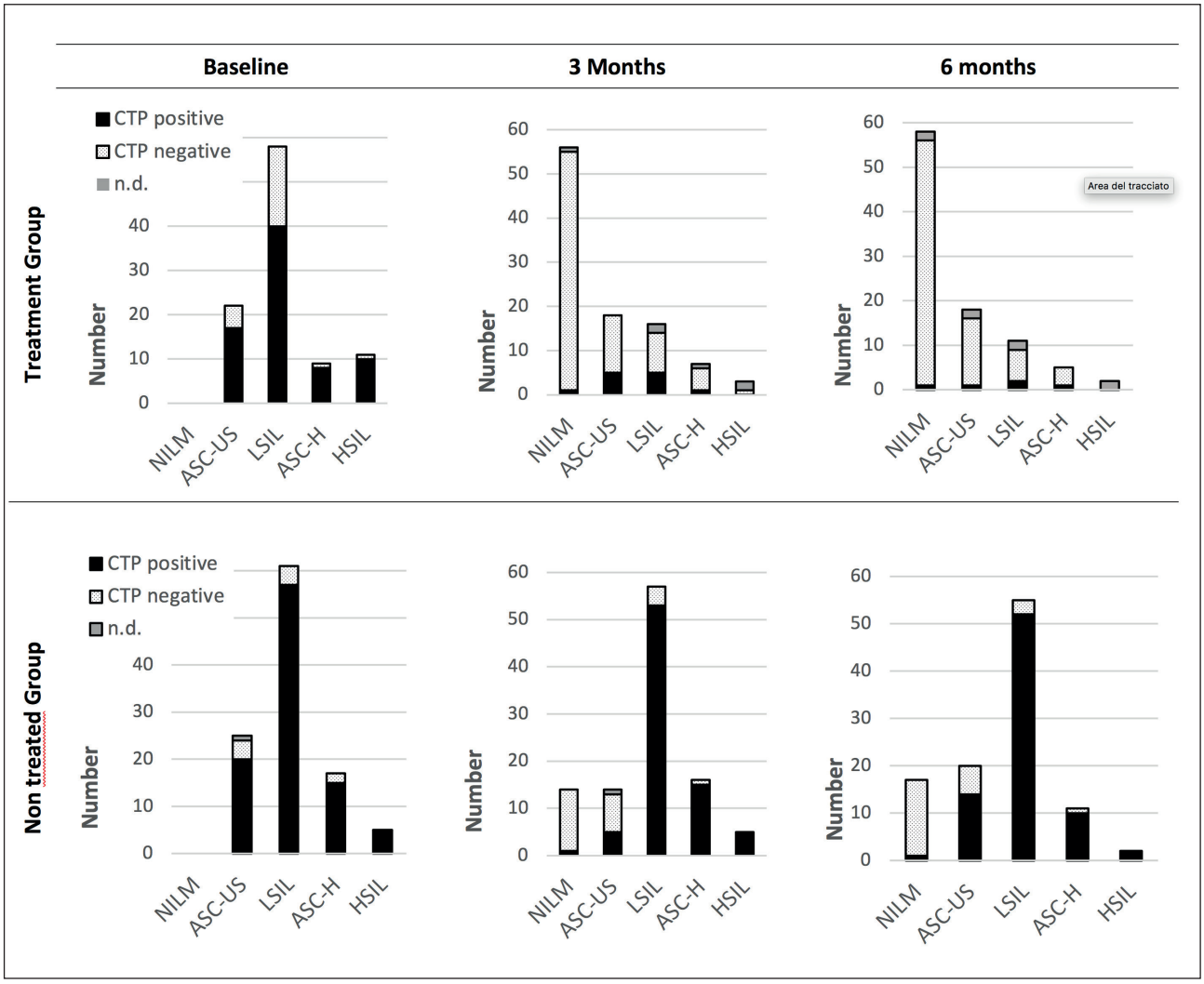

Figure 3. P16/Ki67 (CINtecPLUS) positive results in relation to cytological findings. Results are shown for the treated group (upper row) and the non-treated group that was analysed for comparison (lower row) at baseline, after 3 and 6 months.

but the case numbers were relatively low. Generally, low-level lesions show high spontaneous regression rates of 70% to 90% of cases, depending on the study design and length of the observational period[10,20,22,23]. For six months periods, a 50% regression rate of ASC-US and LSIL was reported in the literature but may take up to 26 months[10]. However, progression to CIN2+ lesions may occur in about 10% to 29% of the cases[7,20,24]. The persistence of ASC-US or LSIL findings significantly increases the risk of further dysplastic development[7,8,22]. Hence, promoting the regression of these lesions may be beneficial. Several factors contribute to progression to higher-level lesions[25-27], but the most crucial progression risk factor is the persistence of hr-HPV strains[9,10,24,26-28].

In the present study, hr-HPV clearance was observed in 53% of the cases after three months of treatment with the vaginal gel. Negative screening results were obtained mainly for NILM and ASC-US findings. Clearance of HPV infections depends on several co-factors like, for example, age, parity use of condoms, or additional vaginal infections and is also different between the hr-HPV strains[24,29]. Hence, the clearance rate in women with normal cytology findings is described with 43% within four months or an average duration of 224 days, and up to 90% of HPV infections are believed to resolve within two years (24,29-31). For abnormal cervical smears, HPV clearance rates are usually lower (24), and 2-year cumulative regression rates between 35% and 53%[32] are reported. Thus, clearance of hr-HPV seemed to be promoted by treatment with the vaginal gel. This view is supported by the results obtained from the comparison group, where no clearance of hr-HPV was observed at all within the three months period (Table 4). Thus, treatment with the SiO_2-containing vaginal gel may promote the clearance of HPV.

Due to the generally high prevalence of hr-HPV infections in ASC-US findings, which do not necessarily hint at the existence or development of high-

Table V. p16/Ki67 positive findings in correlation to cytological status. Percentage values of CTP positive findings are given for each cytological group and for the total number of participants.

		Baseline [%]	3 months [%]	6 months [%]
Treated Group	NILM	0.0	1.8	1.7
	ASC-US	77.3	27.8	5.6
	LSIL	69.0	31.3	18.2
	ASC-H	88.9	14.3	20.0
	HSIL	90.9	0.0	0.0
	Total	**75**	**12.0**	**5.3**
Non-treated	NILM	0.0	7.1	5.9
	ASC-US	80.0	35.7	70.0
	LSIL	96.6	93.0	94.5
	ASC-H	88.2	93.8	90.9
	HSIL	100.0	100.0	100.0
	Total	**91.5**	**74.5**	**75.2**

er grade histologic lesions[33], other diagnostic tools like double detection of tumor marker proteins p16 and Ki67 are increasingly used for the evaluation of ASC-US and LSIL findings in order to differentiate between (post-)inflammatory and real precancerous states, i.e., CIN2/3 lesions[34-40]. The corresponding CinTec test has also been applied in the present study and revealed unusual high values of CinTec positive results at baseline (Table 4). Whereas in literature, about 25-30% of ASC-US and 25-52% of LSIL findings are reported p16/Ki67 positive, thus hinting at higher-grade lesions[23,35,39] up to 80% of ASC-US and 96% of LSIL findings were diagnosed positive in the present study at baseline. Also, in the inconspicuous findings after 3 and 6 months, up to 7.1% were tested p16/Ki67 positive. Values were generally higher in the group that did not obtain any treatment. The high percentage of p16/Ki67 positive results correlated to the unusually high amounts of HPV positive results in lower-grade cytologic findings with ASC-US and LSIL (Table 4). In the group treated with the vaginal gel, a striking decline in p16/Ki67 positive results was observed, while they remained on a high level for the comparison group. Although this finding supports those of hr-HPV screening and Pap testing, the correlation between CinTec results and Pap findings does not seem adequate. It is widely accepted that Pap testing is of a highly subjective nature, which leads to high interobserver variabilities[40-42]. Thus, in the present case, the under-diagnosis of Pap smears may have occurred. Nevertheless, both hr-HPV and CinTec testing also shows a clear tendency towards improvement after treatment with the gel. The putative mode of action is based both on the adsorbing properties of SiO_2 and on the anti-oxidative effect of the selenite compound. Adsorption of viruses to surfaces or (nano-)particles is a process that is influenced by different biochemical and biophysical parameters and is subject to intense research for many years[43]. Virus adsorption has also been investigated in the context of medical applications (e.g.,[44,45]). For HPV, no exact adhesion mechanism to disperse SiO_2 in the vaginal milieu can be described up to now, but the adhesion of proteinaceous particles has been demonstrated. The anti-oxidative effect of the included acidified selenite may help to create a favorable vaginal environment, which prevents infection of epithelial cells with new pathogens, diminishes oxidative stress, and thus supports the endogenic immune response[19]. Thus, the application of the vaginal gel containing SiO_2, selenite, and citric acid may promote hr-HPV clearance, prevent the progression of cervical lesions, and promote remission of suspicious smears.

CONCLUSIONS

An intravaginal gel containing highly disperse SiO_2 and an anti-oxidative combination of citric acid and sodium selenite showed after six months an improvement of cytological Pap findings in 80.9% of the participants the clearing of hr-HPV was observed in 53% of cases. Only 5.3% were tested positive for p16/Ki67 after six months. Therefore, the examined vaginal gel may support the healing of conspicuous cytological findings and clearance of hr-HPV positive findings.

Ethics approval and consent to participate:
Ethical approval of the main study (46) was given by the Multicenter Ethics Committee (Medical Chamber Check Republic February 2017) and the Local Ethics Committee ((Brno/Vsetin, Olomouc, Prague, October 2017). The present work represents a sub-analysis of the results from the study.

Consent for publication:
All authors have consented for publication.

Availability of data and material:
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Authors' contributions:
Pedro-Antonio Regidor and Manuela Sailer were responsible for the practical realization of the study. Anna Müller was responsible for the analysis of the data and writing the manuscript.

Conflicts of interest:
Pedro-Antonio Regidor, Manuela Sailer, and Anna Müller are employees of Exeltis Healthcare.

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