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Performance of a vaginal self-collection device versus clinician collected cervical samples for the detection of high-risk human papillomavirus

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ABSTRACT

Objective: Screening for cervical cancer requires the participation of target women. Human papillomavirus (HPV) testing can be performed on vaginal self-samples and self-sampling can improve this participation. This study aims to validate the performance of the vaginal self-sampling device (Vitroveil®) to detect high risk human papillomavirus (hrHPV) in comparison to clinician collected samples and evaluate the degree of acceptability of the Vitroveil® device.

Methods: A cross-sectional observational study was carried out in a cohort of 385 participating women (median age of 44 ± 10.47 years) attending primary care centers and cervical pathology services of Granada, Spain. Two paired samples (vaginal self-sample and clinician collected cervical sample) where collected from each participant to compare the detection of HPV with the Vitro HPV Screening assay (Vitro, Granada, Spain). A questionnaire was also provided to the participants to analyze the degree of satisfaction with the device and the preference for sampling method.

Results: Overall concordance for hrHPV detection was substantial (κ 0.804). The prevalence of any hrHPV infection was higher in self-collected samples (30.6%) than in clinician-collected samples (24.3%). The participants found the self-sampling device easy to use and preferred self-collection as the collection method.

Conclusion: The Vitroveil® self-sampling device enables safe and accruable hrHPV testing, obtaining equivalent results to those of the clinician collected samples. High acceptability of the device has been demonstrated among women in the study. Nevertheless, additional studies are necessary to verify the efficacy and reliability of the device's performance.

1. Introduction

The strategy endorsed by the World Health Organization (WHO) in 2020 (World Health Organization, 2020a) towards the elimination of cervical cancer comprises three measurable targets: vaccination, screening, and treatment, that should be completed by 2030.

Screening is a secondary prevention activity that can bring several benefits for the population and the health system, being the most important one the reduction of cervical cancer incidence and mortality. It was 2003 when the European Union recommended the Member States to introduce or scale up organized population-based breast, cervical and colorectal cancer screenings, also establishing the criteria to perform them (European Commission, 2003). Since then, many European countries have implemented screening programs (von Karsa et al., 2008). In Spain, with the second lowest incidence and mortality rates for cervical cancer (Luengo Matos and Muñoz van den Eynde, 2004), the National Health System Cancer Strategy also recommends the screening (Ministerio de Sanidad y Consumo, 2009). For women over 30–35 and up to 65 years, HPV-based screening every 5 years is the preferred option (Torné et al., 2022).

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In Spain 60 % to 70 % of women diagnosed with cervical cancer had not been screened in the previous 10 years (Castillo et al., 2016; Ibáñez et al., 2015). Different barriers can contribute to the low participation on the screening; one of the main ones is the requirement to undergo a speculum examination (Hawkes et al., 2020). In this sense, HPV-based screening allows the participants to collect their own sample, overcoming some of the known barriers for participation. HPV testing through self-sampling has gained attention for its potential to increase screening participation (Di Gennaro et al., 2022). The WHO strongly recommends the use of self-sampling to achieve cervical cancer control by 2030 (World Health Organization, 2020a; World Health Organization, 2022). Additionally, different studies have shown that self-sampling, when using a polymerase chain reaction (PCR)-based HPV test, is as accurate as clinician collected samples to detect cervical precancer (Arbyn et al., 2018).

Vitroveil® (VITRO SA, Granada, Spain), is a vaginal self-collection device that is minimally invasive, the special design covering the hole vaginal cavity guarantees the quality and reliability of the sample obtained by the women themselves. The veil sample is collected in a dedicated vial containing the transport medium capsulated inside the cap, which avoids chemical risks for the woman during the manipulation and that makes the sample stable during the transport and storage. The unique format of the transport vial allows its entry into the high throughput automation flow of the laboratory without pre-analytical preparation modules. All these unique features represent a very useful solution for its introduction in population screening programs.

The present study aimed to evaluate the performance of Vitroveil® against paired clinician-collected cervical samples, for the detection of high-risk HPV types (hrHPV) with the Vitro HPV Screening assay (VITRO SA, Granada, Spain) and the extended genotyping with the HPV Direct Flow CHIP test (VITRO SA, Granada, Spain). The acceptability of Vitroveil® device among women participating in the study was evaluated.

2. Methods

2.1. Study design

The project was approved by the Research Ethical Committee CEIM/CEI of Granada (Reference 240222/0222). All women participating in the study signed the written informed consent forms. The study met the institution's guidelines for protection of human subjects concerning safety and privacy. A total of 385 women were included in the study. The women were invited to participate when attending a public primary care health center for opportunistic cervical cancer screening or when attending a follow-up check at a cervical pathology service. Samples were collected between June 2022 and January 2023. Information about the study and their participation, and a proper informed consent was given and signed by each woman prior to collecting the samples. Self-collection was performed by the woman herself immediately prior to the clinician collected sample by either a primary care doctor and/or midwives in the primary care health centers and by gynecologists in the cervical pathology units.

Vitroveil® includes a tampon-like class I medical device (*veil*) (Nodjikouambaye et al., 2019a; Nodjikouambaye et al., 2019b) with a plastic applicator and an empty tube with transport medium sealed int its pierceable lid (Fig. 1). The sample is collected by inserting the veil into the vaginal cavity for 2 min. Afterwards, the veil is removed, inserted into the dedicated vial which drops the transport medium over the veil after closing.

Cervical samples were taken by the clinician using a cervical brush and rinsing it into 20 mL ThinPrep® PreservCyt media (ThinPrep, Hologic,Marlborough, MA, USA). This sample was used for routine molecular detection of hrHPV and cytological analysis. Self-samples were used only for hrHPV testing. All clinical follow up was managed according to Spanish guidelines, and the results of the self-collected sample did not affect clinical follow up.

Cervical smear slides were Pap-stained, and histo-technicians interpreted the results following the Bethesda 2001 classification. Histological analysis of colposcopy-guided biopsy was performed in case of cytological abnormalities (Solomon et al., 2002).

The samples were stored and transported at room temperature (18–24 °C) to the laboratory for analysis (Hospital Universitario Clínico San Cecilio, Granada, Spain).

2.2. HPV testing

Both self-collected and clinician collected samples were directly processed using the automatic MAIS system (VITRO SA, Granada, Spain) and the RNA/DNA Pathogen Extraction assay (VITRO SA, Granada, Spain). No pre-analytical manipulation was required for the veil sample. Once it was received in the laboratory, it was automatically processed without opening the vial, as its cap is pierceable. The MAIS system performs the nucleic acids extraction and the PCR plate set up, allowing 480 samples to be processed in one working day.

The hrHPV detection was performed with the Vitro HPV Screening assay, a real-time multiplex PCR assay using primers and fluorescent probes targeting L1 conserved region of the HPV genomes. It specifically identifies HPV genotypes 16 and 18 in separate fluorescent channels and 12 hrHPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) as a pool in the same channel. In the same reaction the human beta-globin gene is detected by a different fluorochrome as a control for the whole

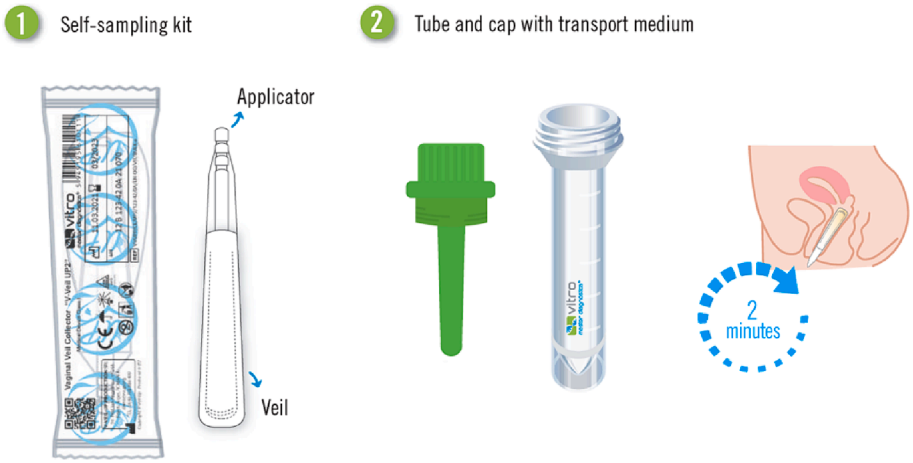

Fig. 1. Vitroveil® device and transport vial.

process. Results are expressed as negative or positive for HPV16, HPV18 or other hrHPV. Cutoff for positivity is ≤ 40 cycle number. When neither beta-globin nor HPV is detected, the result is invalid. The amplification was carried out in a Vitrocycler equipment (VITRO SA, Granada, Spain) and the results were automatically analyzed with OVTS software (VITRO SA, Granada, Spain).

All samples positive for the pool of 12 high-risk genotypes were genotyped with the HPV Direct Flow CHIP assay. This complementary assay allows to perform an extended genotyping to individually identify the genotypes by reverse dot blot hybridization onto the HPV CHIP with an automatic platform (HS24PCRauto, VITRO SA, Granada, Spain). The results were analyzed automatically with hybriSoft™ software (VITRO SA, Granada, Spain). A flow chart of the process is shown in Fig. 2.

The clinical performance of the Vitro HPV test as primary assay for cervical cancer screening has been assessed on ThinPrep-collected cervical samples according to Meijer's guidelines (Bellosillo, B., et al., 2024, unpublished manuscript), The study has demonstrated that the Vitro HPV Screening assay is valid for cervical cancer screening.

2.3. Statistical analysis

We evaluated whether hrHPV testing on self-collected vaginal samples was as accurate as hrHPV testing on a cervical sample taken by a clinician. As the Vitro HPV Screening assay allows us to detect and identify the genotypes 16 and 18, and a pool of other hrHPV genotypes, we evaluated the agreement of the results obtained between the two different samples for these genotypes individually.

Concordance between the results obtained with the two different collection methods was determined by creating a 2x2 contingency table. The concordance corrected by chance was determined using the Kappa (κ) value. Interpretation of the κ values followed the proposed standards of Landis and Koch: slight (0–0.20); fair (0.21– 0.40); moderate (0.41–0.60); substantial (0.61–0.80); and almost perfect (0.81–1.00). The standard error of the estimate is represented next to point estimate, representative of the uncertainty that the confidence interval has at the time of the determination of the parameter under study. All confidence intervals were at 95 % confidence. McNemar's test was used to compare the detection rate for the two sampling methods in terms of the number of positive patients. A P value < 0.05 was considered statistically significant.

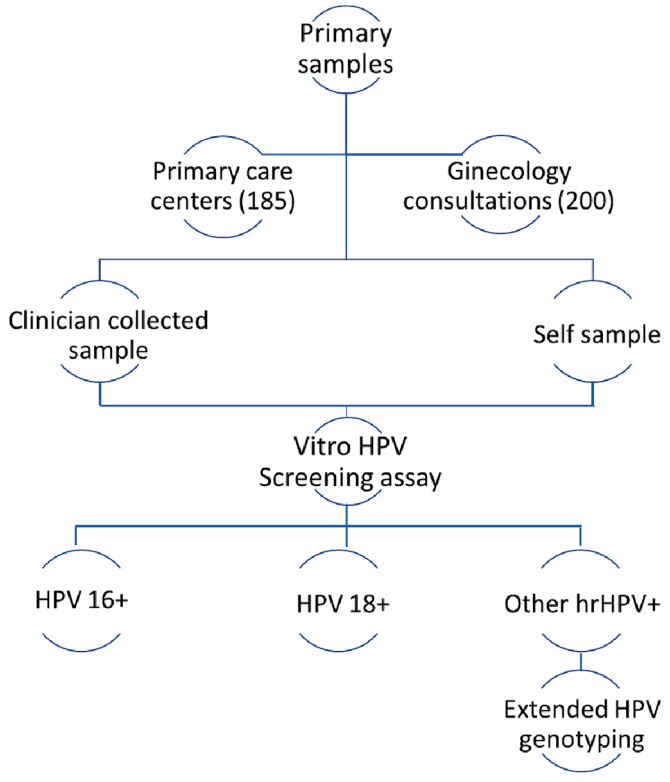

Fig. 2. Workflow of HPV analysis for the samples included in this study.

2.4. Questionnaires

All the women enrolled in the study were asked to fulfill an anonymous questionnaire with seven questions about self-sampling acceptability, sampling preference and understanding of instructions. The degree of agreement with each of the questions was measured with a 4-point Likert scale were 1 means the woman strongly disagrees with the statement and 4 means that she strongly agrees.

3. Results

3.1. Study population characteristics

Women between 23 and 73 years old were included in the study. The median age was 44 years (SD 10.47); 90.64 % (349/385) of study participants were within the recommended target age for HPV-based cervical cancer screening (30–65 years old).

A total of 385 paired self-collected vaginal samples and clinician-taken cervical samples were collected for the study. 185 paired samples were collected from primary care centers and 200 paired samples were collected from cervical pathology services. Total valid samples included in the study were 382 paired samples (382/385; 99.22 %). One sample pair was excluded because they were not properly identified, and two self-sample group (2/385; 0.52 %) were excluded due to invalid internal control (beta-globin not amplified).

3.2. Comparison of hrHPV positivity between clinician collected and self-collected samples

The positivity for hrHPV was higher (n = 117; 30.6 %) on self-collected samples vs clinician collected samples (n = 93; 24.3 %). This difference was statistically significant (McNemar (P) < 0.0001). A high agreement was obtained for the detection of the different genotypes (16, 18, other hrHPV) and overall, for any hrHPV, between both sample types (98.4 %, 99.5 %, 92.4 % and 92.1 %, respectively) (Table 1). The kappa value was from substantial (0.747 for HPV 18; 0.786 for other hrHPV; 0.804 for hrHPV overall) to almost perfect for HPV16 (0.867).

The samples for this study were collected from two different settings: primary care centers and cervical pathology services. The main target population for self-sampling are the women participating on an organized population-based screening. In this sense, the WHO has recommended the use of self-sampling as an additional approach to sampling in cervical cancer screening (World Health Organization, 2020b). However, this study also included a group of women from cervical pathology services with a previous history of cervical lesions or HPV infection, with the main objective of enriching the HPV positivity.

When analyzing the hrHPV results grouped by the origin of the samples, the overall agreement for hrHPV detection between both types of samples on the primary care cohort (n = 185) was substantial, with a kappa value of 0.795 (Table 2). For the detection of the HPV16 genotype, HPV18 genotype and the pool of hrHPV genotypes the agreement was also substantial (κ value of 0.755 for hrHPVs) or almost perfect (1 for HPV18; 0.85 for HPV16).

On this population, overall hrHPV positivity was higher (n = 26; 14.1 %) on Vitroveil® self-collected samples vs clinician collected samples (n = 18; 9.7 %). This difference was statistically significant (McNemar (P) = 0.0078).

On the cohort of samples from cervical pathology services (n = 197) the overall agreement for hrHPV detection was substantial, with a kappa value of 0.773 (Table 3). For the detection of HPV16 and 18 genotypes

Table 1
hrHPV positivity agreement between self-collected sample (ss) and clinician collected sample(cc) for the overall samples of the study.

Total population N = 382	HPV type	cc/ss[a] +/+	cc/ss +/-	cc/ss -/+	cc/ss-/-	Agreement (%)	Kappa (95 % CI)
	16	21	1[b]	5[c]	355	98.4	**0.867 (0.767;0.967)**
	18	3	1	1[d]	377	99.5	**0.747 (0.647;0.847)**
	Other hrHPV	73	3	26[e]	280	92.4	**0.786 (0.687;0.885)**
	Overall hrHPV	90	3	27	262	92.1	**0.804 (0.705;0.903)**

[a] +/+ positive on clinician collected sample and self-collected sample; +/- positive only on clinician collected sample; -/+ positive only on self-collected sample; -/- Negative on both sample types. CI= Confidence interval.bThis patient had a previous HSIL/CIN3 (high-grade intra-epithelial lesion/ cervical intraepithelial neoplasia 3) biopsy.
[c] Only one sample had an abnormal cytology (ASCH (atypical Squamous Cells, suspicious for High-grade intra-epithelial lesion)), and two women had a previous HPV16 result.
[d] This patient had a previous HPV18 result.
[e] Thirteen out of those 26 women had a previous hrHPV positive result. Ten women had a persistent genotype and two had a previous HPV16 positive result.

Table 2
hrHPV positivity agreement between self-collected samples and clinician collected samples for the cohort of samples collected on primary care centers.

Total population N = 185	HPV type	cc/ss[a] +/+	cc/ss +/-	cc/ss -/+	cc/ss -/-	Agreement (%)	Kappa (95 % CI)
	16	3	0	1	181	99.5	**0.85 (0.712; 0.996)**
	18	1	0	0	184	100	**1 (0.856; 1.144)**
	Other hrHPV	14	0	8	163	92.4	**0.755 (0.615; 0.895)**
	Overall hrHPV	18	0	8	159	95.7	**0.795 (0.654;0.936)**

[a] +/+ positive on clinician collected sample and self-collected sample; +/- positive only on clinician collected sample; -/+ positive only on self-collected sample; -/- Negative on both sample types. CI = Confidence interval.

Table 3
hrHPV positivity agreement between self-collected sample and clinician collected sample for the cohort of samples collected on cervical pathology services.

Total population N = 197	HPV type	cc/ss +/+	cc/ss +/-	cc/ss -/+	cc/ss -/-	Agreement (%)	Kappa (95 % CI)
	16	18	1	5	173	97	**0.84 (0701; 0.979)**
	18	2	1	1	193	99	**0.662 (0.522; 0.802)**
	Other hrHPV	59	3	18	117	89.3	**0.768 (0.63; 0.906)**
	Overall hrHPV	72	3	19	103	88.8	**0.773 (0.635; 0.911)**

+/+ positive on clinician collected sample and self-collected sample; +/- positive only on clinician collected sample; -/+ positive only on self-collected sample; -/- Negative on both sample types. CI = Confidence interval.

and the rest of hrHPV genotypes the agreement was substantial (κ value of 0.768 for hrHPV and 0.662 for HPV18) or almost perfect (0.84 for HPV16).

On this population, overall hrHPV positivity was much higher than on the primary care cohort and higher (n = 91; 46.2 %) on Vitroveil® self-collected samples vs clinician collected samples (n = 75; 38.1 %). This difference was statistically significant (McNemar (P) = 0.0009).

3.3. Cytological and histopathological findings of the population

Most of the women (n = 342; 89.52 %) had a negative Pap result at the time of the study. Eighteen cytological samples were not valuable according to the pathologists for different reasons (insufficient material or presence of artifacts). Of the ones presenting cytological alterations (22/382; 6.28 %) atypical squamous cells of undetermined significance (ASCUS) was the alteration most frequently detected (9 women); followed by low-grade intraepithelial lesion (LSIL) (8 women). Atypical squamous cells - cannot exclude high grade squamous intraepithelial lesion (ASC-H) were found in 4 women, and finally, 1 woman presented a high-grade squamous intraepithelial lesion (HSIL) (Table 4).

When we analyzed the hrHPV positivity of the samples according to the cytological alterations, the main difference between the two types of samples were among the group with normal cytology where 70 samples were positive for the clinician collected sample (70/342; 20.46 %) versus 92 that were hrHPV positive on the self-collected sample (26.9 %).Of the 382 participants with valid samples (those that gave a Beta-globin positive signal on both types of samples), 21 women (21/382; 5.49 %) underwent biopsy. Six of them were already scheduled for this procedure on the same day as the samples for this study were taken; the rest of the biopsies were performed following routinary protocol for risk management after the findings on the clinician collected sample analyzed on the study. One of these biopsies was not valuable due to

Table 4
hrHPV positivity according to cytological characteristics of the population.

Cytology	N Total (%) 382 (100 %)	N (% over the total) hrHPV positive clinician collected sample (cc)	self-collected sample (ss)
Normal	342 (89.52 %)	70 (20.46 %)	92 (26.90 %)
ASCUS	9 (2.35 %)	5 (55.55 %)	6 (66.66 %)
ASCH	4 (1.04 %)	4 (100 %)	4 (100 %)
LSIL	8 (2.09 %)	7 (87.5 %)	7 (87.5 %)
HSIL	1 (0.26 %)	1 (100 %)	1 (100 %)
Not valuable*	18 (4.71)	6 (33.33 %)	7 (38.88 %)

*Not able to classify the samples due to insufficient material or artifacts. N = number.

insufficient material. The histological results showed 8 women with less than cervical intraepithelial neoplasia grade 1 (<CIN1), 8 with CIN1, and 4 with cervical intraepithelial neoplasia grade 2 or worse (≥CIN2). All the samples that had cervical intraepithelial neoplasia (CIN1-3) were positive for hrHPV with the self-collected sample, and 1 among the 8 samples with CIN1 had a negative hrHPV result on the clinician collected sample.

3.4. Extended hrHPV genotyping analysis

All the samples that had a positive result for the hrHPV pool with the Vitro HPV Screening assay were further analyzed with the HPV Direct Flow CHIP assay to identify the genotypes present on the sample. Data comparing hrHPV genotype positivity (other than 16 and 18) by sample type (clinician collected versus self-sample) is reported in Table 5.

The most prevalent genotype on the samples analyzed was HPV52 (22 samples) followed by HPV31 (20 samples). Thirty-one clinician collected samples presented coinfections of different hrHPV genotypes vs 45 coinfections that were found on the self-collected samples.

3.5. Questionnaire results

We received 380 questionnaires. Twenty-eight questionnaires were received with some missing information and only the completed files were analyzed (352 questionnaires) (Table 6).

The mean responses for questions 1, 2, 4, 5 and 7 are closer to 4, meaning totally agree with the statement, whereas questions 3 and 6 are closer to 1, meaning totally disagree with the statement. Overall, results represent positive experiences with the device and/or preference for self-testing (Table 6).

The women were divided in three age groups in order to analyze if there was any difference among the responses based on age: from 23 to 40 years (40.52 %; 154 women), from 41 to 55 years (42.10 %; 160 women) and from 56 to 73 years (16.9 %; 65 women). Overall, there was not an effect of age on the total score ($P = 0.4170$) but analyzing the different questions individually there is a significant difference among the three age groups on question 1 ($P = 0.0354$) observing a lower score as the age increases.

4. Discussion

The aim of this study was to compare the analytical performance for hrHPV detection between self-collected samples with Vitroveil® device and clinician collected samples, tested using the Vitro HPV screening assay.

Table 5
hrHPV genotypes positivity (other than 16 and 18) by sample type. A total of 102 samples were genotyped using the hpv direct flow chip assay. The table shows the results of hrhpv genotypes detected by sample type (medium risk and low risk genotypes).

HPV genotype	cc/ss[a] +/+	cc/ss	cc/ss +/-	cc/ss -/-	Total
31	9	3	8	82	20
33	9	0	0	93	9
35	4	0	1	87	5
39	6	1	2	93	9
45	3	0	3	96	6
51	11	1	7	83	19
52	18	1	3	80	22
56	8	2	4	88	14
58	8	1	2	91	11
59	2	0	2	98	4
66	5	0	5	92	10
68	9	1	7	85	17

[a] +/+ positive on clinician collected sample and self-collected sample; +/- positive only on clinician collected sample; -/+ positive only on self-collected sample; -/- Negative on both sample types.

Table 6
Mean results from the questionnaire provided to the participants of the study.

Q#	Questions	MEAN	SD	N
Q1	Are the instructions to use Vitroveil® clear?	3.78	0.60	380
Q2	Do you prefer a self-sampling device rather than a sample taken by a gynecologist or specialist?	3.22	1.10	377
Q3	Has the application of Vitroveil® caused you any discomfort?	1.81	1.20	373
Q4	Did you find Vitroveil® easy to use?	3.80	0.60	377
Q5	Was it easy for you to remove Vitroveil® from the vaginal cavity?	3.85	0.55	369
Q6	Do you prefer to take the sample at the medical center?	1.81	1.19	375
Q7	Do you prefer to take the sample at home and then bring it to the medical center?	3.39	1.11	377

Overall concordance for hrHPV detection was substantial (κ 0.804) on the whole population as well as in the two cohorts analyzed (primary care: κ 0.795; and cervical pathology services: κ 0.773). These results agree with previous results obtained with other self-sampling devices (Saidu et al., 2020; Katanga et al., 2021; Gupta et al., 2018), confirming that self-sampling could be a reliable procedure to improve screening coverage. In addition to the agreement on the results, the women of the study preferred self-collection as the collection method and found the instructions of the self-sampling device easy to understand and the collection using Vitroveil® easy and convenient to perform. This preference for self-sampling is in line with other studies assessing acceptance of self-sampling (Ibáñez et al., 2023; Morgan et al., 2019).

The prevalence of any hrHPV infection was higher in self-collected samples (30.6 %) than in clinician-collected samples (24.3 %). These results have also been observed with other self-sampling devices (Arbyn et al., 2022). The difference could be due to the total volume used for sample resuspension: clinician collected samples were resuspended in 20 mL PreservCyt media whereas self-collected samples were resuspended in 6.5 mL of Vitroveil®́s transport medium. The reduction in volume of collection medium may improve HPV detection (Giubbi et al., 2022). This could be explained due to a more concentrated sample but also due to the characteristics of the collection medium. As Vitroveil®́s transport medium is not an alcohol based medium, it doesńt fix the cells and the extraction of both the viral and human genomic DNAs can be performed more efficiently. We have seen that the average Ct value obtained for the internal control (β Globin) on the self-collected samples is lower than the one for the clinician collected samples in this study (results not shown). Self-collection device can collect a larger quantity of cells as it covers the whole vaginal cavity, this could also explain the lower ct value obtained with these samples vs clinician collected cervical samples.

HPV16, HPV52 and HPV31 were the most prevalent hrHPV types overall, as also previously reported in other European populations (Baasland et al., 2019). Even though extended HPV genotyping is not suggested by most primary cervical screening guidelines, it is useful to verify the persistence of a specific hrHPV type. Persistent infection with the same hrHPV genotype is associated with higher risk of CIN2 and CIN3 (Bonde et al., 2021). Furthermore, extended hrHPV genotyping could serve as a molecular triage strategy since different genotypes have different associated risk of progression to High-Grade Cervical Neoplasia (CIN) and cancer (Adcock et al., 2019). This approach is supported by several articles that show that other hrHPV types such as HPV31, 33, 52 or 58 pose a higher risk than other hrHPV genotypes (Cuzick et al., 2014; Bonde et al., 2019).

In this study it has been observed that most of the genotypes detected with the self-sampling device but not with the clinician collected sample, were the same genotypes that were previously present in each woman, demonstrating the persistence of hrHPV infection and highlighting the importance of genotyping on the follow up of a persistent infection.

Self-collection provides an opportunity to improve population- based

screening programs (Di Gennaro, G., et al. 2022), in addition to reducing costs, time and barriers to screening. Self-collection gives women a sense of empowerment by actively participating on taking care of their own health and protecting their intimacy.

The WHO has recommended the use of self-sampling for HPV screening (World Health Organization, 2022). Self-sampling has already been implemented in several countries to increase participation in cervical cancer screening (Madzima et al., 2017). Seventeen (12 %) of the total number of countries that have screening programs in place, recommend the use of self-sampling, nine of them as the primary collection method (Serrano et al., 2022). Even though this number is still low, and this type of sample was originally thought and recommended for non-responders, the results presented in this study may support the idea of generalizing the use of self-sampling for organized population-based screenings.

5. Conclusion

In summary, hrHPV testing may be safely and accurately performed on self-obtained vaginal samples with the help of Vitroveil® self-sampling device with equivalent results to clinician-obtained specimens.

Further studies will be required for the validation of the performance of Vitroveil® self-sampling device using clinical outcomes of histologically confirmed disease (cervical intraepithelial neoplasia grade two or higher (≥CIN2).

6. Limitations

The main limitation of this study lies in the relatively small cohort of women and in the lack of histological data from many of the patients included in the study. We could not compare all the HPV results to the histological diagnosis from biopsies so the relative clinical accuracy could not be assessed.

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CRediT authorship contribution statement

Rodrigo Lopez Castro: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Raquel Escudero Rivas:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **María Ángeles Calderón:** Methodology, Investigation. **Lucía Iglesias Linares:** Writing – review & editing, Writing – original draft, Conceptualization. **María Dolores Hurtado González:** Investigation, Methodology, Writing – review & editing. **Nadia Méndez Gómez:** Writing – review & editing, Supervision. **Beatriz de la Rosa Martos:** . **María Esther Hidalgo Carmona:** Writing – original draft, Validation, Writing – review & editing, Supervision. **Javier Luis López Hidalgo:** Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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