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Comparison of immediate colposcopy, repeat conventional cytology and high-risk human papillomavirus testing for the clinical management of atypical squamous cells of undetermined significance cytology in routine health services of Medellin, Colombia: The ASCUS-COL trial

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Abstract

In the context of opportunistic cervical cancer screening settings of low-and-middle-income countries, little is known about the benefits of high-risk human papillomavirus (hrHPV) testing on high-grade cervical abnormality detection among women with

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia grade 2 or more severe diagnoses; CIN3+, cervical intraepithelial neoplasia grade 3 or more severe diagnoses; HMO, healthcare management organization; HPI, healthcare provider institution; HPV, human papillomavirus triage arm; hrHPV, high-risk human papillomavirus; IC, immediate colposcopy arm; LLETZ, large loop excision of the transformation zone; LP, HPIs' local pathologists; MAM, metropolitan area of Medellin; QC, quality-control external review; RC, repeat cytology at 6 and/or 12 months arm; RP, relative proportion.

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atypical squamous cells of undetermined significance (ASC-US) cytology in routine clinical practice. We compared the effectiveness of immediate colposcopy (IC), conventional cytology at 6 and 12 months (colposcopy if ≥ASC-US) (RC) and hrHPV testing (colposcopy if hrHPV-positive) (HPV) to detect cervical intraepithelial neoplasia grade 2 or more severe diagnoses (CIN2+) among women aged 20 to 69 years with ASC-US in routine care. Participants (n = 2661) were evenly randomized into three arms (n = 882 IC, n = 890 RC, n = 889 HPV) to receive services by routine healthcare providers and invited to an exit visit 24 months after recruitment. Histopathology was blindly reviewed by a quality-control external panel (QC). The primary endpoint was the first QC-diagnosed CIN2+ or CIN3+ detected during three periods: enrolment (≤6 months for IC and HPV, ≤12 months for RC), follow-up (between enrolment and exit visit) and exit visit. The trial is completed. Colposcopy was done on 88%, 42% and 52% of participants in IC, RC and HPV. Overall, 212 CIN2+ and 52 CIN3+ cases were diagnosed. No differences were observed for CIN2+ detection (P = .821). However, compared to IC, only HPV significantly reduced CIN3+ cases that providers were unable to detect during the 2-year routine follow-up (relative proportion 0.35, 95% CI 0.09-0.87). In this context, hrHPV testing was the most effective and efficient management strategy for women with ASC-US cytology.

KEYWORDS

ASC-US cytology, cervical cancer screening, Colombia, human papillomavirus implementation science

1 | INTRODUCTION

In 2018, worldwide, there were an estimated 311 000 cervical cancer deaths, mostly in less developed regions worldwide.[1] Cervical cancer mortality has steadily decreased in Colombia,[2] particularly in regions with higher human development indexes,[3] reflecting positive effects of cytology-based screening, healthcare system improvements and decreasing birth rates.[4]

Colombia introduced guidelines for high-risk HPV (hrHPV) testing implementation for cervical screening of 30 to 65 years old women in 2014.[5] However, hrHPV testing has not yet being implemented in Colombia, and opportunistic, cytology-based screening continues to be most common in routine practice.[6] Additionally, since all activities for cervical cancer early detection are conducted through Healthcare Management Organizations (HMOs)-contracted Healthcare Provider Institutions (HPIs) offering services independently of each other and women could switch between HPIs without linkage between them, there are limitations in the follow-up of screen-positives and timely treatment of women with cervical intraepithelial neoplasia grade 2 (CIN2) or more severe diagnoses (CIN2+).[7,8] Furthermore, quality assurance is only implemented for cytology and limited or absent for colposcopy or pathology.[9]

Controlled clinical trials or studies within organized programs have conclusively demonstrated that hrHPV testing is effective for triaging women with atypical squamous cells of undetermined significance (ASC-US).[10-17] However, evidence for its effectiveness in opportunistic settings, such as in the Latin American context, is lacking. Despite the cost-effectiveness and efficacy of hrHPV testing for the management of women with ASC-US,[5,18-22] healthcare providers in Colombia primarily use immediate colposcopy or repeat cytology.

This gap in evidence highlights the need to evaluate the best strategy for managing women with ASC-US cytology within the relevant healthcare

What's new?

Guidelines for high-risk human papillomavirus (hrHPV) testing in cervical cancer screening were introduced in Colombia in 2014 but have yet to be adopted in clinical practice. Moreover, follow-up for screen-positive women, including those with atypical squamous cells of undetermined significance (ASC-US) cytology is limited. Here, hrHPV testing for follow-up of women with ASC-US cytology was compared with two approaches currently available in Colombia, immediate colposcopy and repeat cytology at two-year routine follow-up. Compared to immediate colposcopy, hrHPV testing reduced the burden of high-grade cervical abnormalities by 65 percent and colposcopy referral by 41 percent.

context and compare it with current practices, using outcomes meaningful for treatment referral and considering the use of resources. Ideally, pragmatic trials measure all outcomes important to patients and decision-makers, such as disease status, and healthcare cost and utilization.

We, therefore, conducted a randomized pragmatic trial that compared the effectiveness of immediate routine colposcopy (IC), repeat routine conventional cytology at 6 and 12 months (RC) and triage with hrHPV testing (HPV) to identify CIN2+ during 2 years follow-up of women with ASC-US cytology, under routine conditions of opportunistic screening settings and gynecological care providers, serving women insured by three Colombian HMOs. Although findings are relevant for healthcare services for women with ASC-US cytology living in Colombia, our study contributes to knowledge on best practices for the management of women with ASC-US cytology in similar settings.

2 | METHODS

2.1 | Trial design

The ASCUS-COL was a pragmatic three-arm parallel-group trial. The trial was considered pragmatic because all procedures, except hrHPV testing, were delivered by the HMOs and HPIs under routine clinical conditions, and results are relevant to participants, healthcare providers and funders.[23-25] The trial design is presented in Figure 1 and described in detail below. Our study is registered with ClinicalTrials.gov (NCT02067468).

2.2 | Eligibility criteria

We included women 20 to 69 years old with first time ASC-US cytology reported within 3 months of recruitment. Women were identified from routine screening services of three HMOs of the metropolitan area of Medellin (MAM), Colombia. Women were excluded if they had abnormal cytology within the last year (suggesting that the index cytology was a follow-up rather than screening test) or large loop excision of the transformation zone (LLETZ), and/or hysterectomy. Additionally, women were excluded if not mentally able to provide informed consent, pregnant, HIV positive or with other immunosuppression conditions or planning to move out of the study area.

2.3 | Settings and locations for data collection

The primary study site was based at the Group Infection and Cancer, School of Medicine, University of Antioquia. Supporting Information Figure S1 shows the healthcare system structure and secondary institutions where the study was conducted under routine care. The study was conducted using the HPIs offering services to women insured by three HMOs that jointly covered 54.1% of the total MAM population as of 2010. Two of the HMOs insure 43% and the other 97% of the individuals enrolled in the two national health insurance schemes, the contributory (employed and with income above poverty threshold) and subsidized regime (unemployed with income below the poverty threshold), respectively.

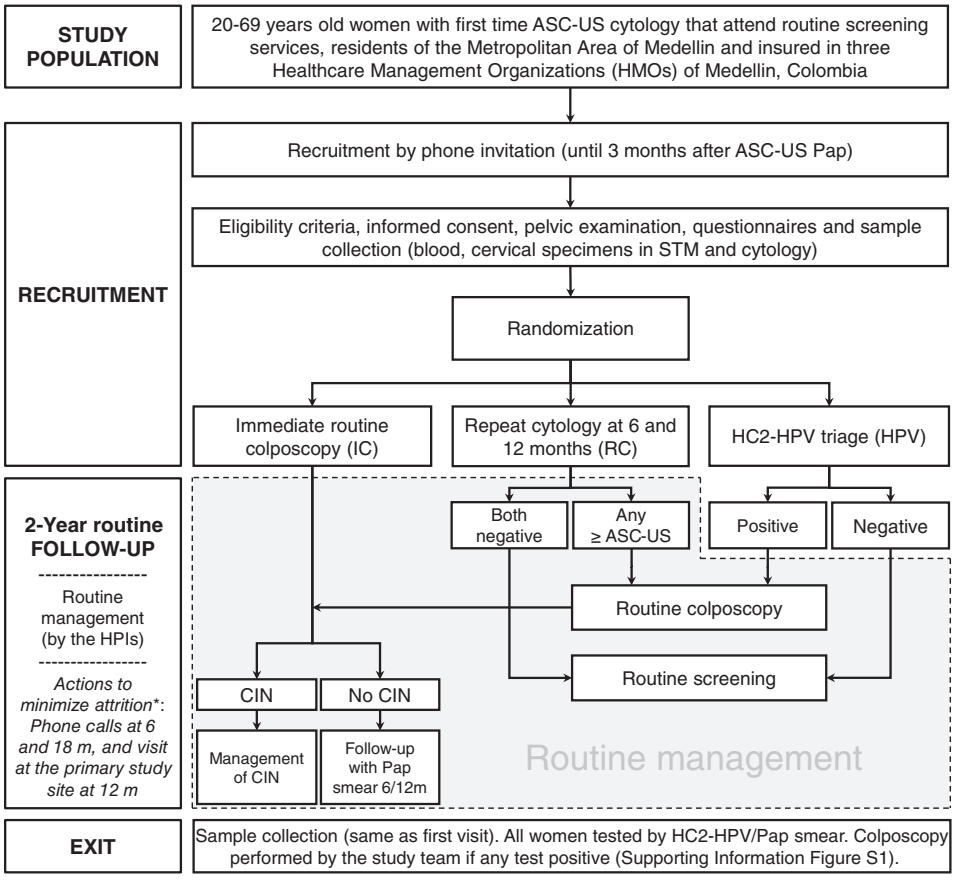

FIGURE 1 Study design. Routine management was provided by HMOs-contracted Healthcare Provider Institutions (HPIs) according to the national guidelines for the clinical management of women with ASC-US cytology. As issued in the technical standard for early detection of cervical cancer (resolution 412 of the Colombian Ministry of Health), women with CIN1 must be followed with Pap smear at 6 and 12 months and colposcopy if any ≥ASC-US. Women with CIN2 or CIN3 must be treated with cryotherapy or large loop excision of the transformation zone (LLETZ). Women with very advance lesions must receive hysterectomy, radiation, brachytherapy, and/or chemotherapy. *Done by the study team

2.4 | Recruitment

HMOs reported weekly to researchers, listings of women with a routine conventional cytology abnormality. From these lists, we identified all 20 to 69 years old women with ASC-US cytology and whose HPI was located in the MAM. Potential participants were contacted by telephone within 3 months of the date of the index ASC-US cytology by trained health staff to present the study. Women interested in participating were invited to the primary study site where eligibility was assessed in person and informed consent signed.

2.5 | Randomization and concealment

Arm allocation was done using central randomization before starting the study. Permuted-block randomization with block random sizes among 6, 9, 12 and 15 and an allocation ratio of 1:1:1 was generated by a researcher (AB), not participating in clinical care. The allocation was delivered concealed in sealed envelopes during the recruitment visit in the order of arrival and revealed after performing all procedures.

2.6 | Interventions

After recruitment, women received written instructions to request the corresponding procedures at their HPIs according to arm allocation (see below). Additionally, names, IDs and allocation were securely forwarded to their corresponding HMOs with indication to deliver either a routine colposcopy (IC arm, and hrHPV positives in HPV arm) or repeat routine conventional cytology at 6 and 12 months after the ASC-US index cytology followed by routine colposcopy for any follow-up ≥ASC-US result (RC arm). Women in the HPV arm were scheduled by phone to receive the hrHPV test result at the study site within 2 months. hrHPV negatives were advised to get routine screening at the recommended interval. Before starting the study, researchers signed agreements with the HMOs and the HPIs, establishing the conditions of confidentiality and a commitment to provide cytology, colposcopy, histopathological diagnoses and treatments to study participants according to the national guidelines,[26] including treatment of all CIN2+ cases routinely diagnosed by HPIs pathologists during the 2-year routine follow-up. The study protocol was communicated to administrative and healthcare personnel of cervical screening services in HMOs and HPIs. All procedures, except hrHPV testing, were performed under routine conditions by HMOs-contracted HPIs. No efforts were made to standardize the interventions and their delivery was allowed to vary between participants, practitioners and HPIs as they do in real-world practice.

2.7 | Study site examination procedures

There were three study visits: recruitment, 12-month follow-up (conceived to minimize attrition) and exit (24 months after recruitment). Each study visit included pelvic examination and conventional cytology (read at the Pathology Laboratory, University of Antioquia) and collection of samples (blood and exfoliated cervical specimen placed in the Digene specimen transport medium [Qiagen, Germantown, Maryland]), and sociodemographic and risk factors information. Participants with high-grade cytology (ASC-H, HSIL, SCC, AGC and AIS) at recruitment or 12-month follow-up visits were immediately referred to routine colposcopy. Only samples from women of the HPV arm at the recruitment visit and from women of all arms during the exit visit were HPV tested. Hybrid Capture 2 HPV DNA test (HC2; Qiagen) was performed according to the manufacturer's instructions at the laboratory of Infection and Cancer, University of Antioquia.

2.8 | Management of follow-up and minimization of attrition

Participants were contacted by telephone at 6 and 18 months after recruitment and invited to a 12-month follow-up visit to update personal data, inquire about adherence to protocol and advice regarding clinical management and/or on health insurance issues. All 2661 women, including the 20 (7, 8 and 5 in the IC, RC and HPV arms, respectively, chi-square $P = .703$) who had high-grade cervical abnormalities (9 ASC-H, 7 HSIL and 4 AIS) on recruitment cytology and even those attending visits after withdrawal were included in the follow-up.

2.9 | Management at exit

To maximize the detection of disease at the exit, all women underwent hrHPV testing and conventional cytology at the exit visit. Women hrHPV-negative and negative for intraepithelial lesion or malignancy (NILM) were considered safe to exit the study. Those who tested hrHPV+ or/and had ≥ASC-US cytology were invited to a research colposcopy conducted by a certified colposcopist using a standardized protocol, in which after acetic acid application, one or two biopsies from observed "acetowhite" cervical abnormalities and one at random were taken (Supporting Information Figure S2). To improve disease ascertainment, two random biopsies were taken when no acetowhite abnormalities were observed. Endocervical cytology was collected using a cytobrush when colposcopy was unsatisfactory. Women with CIN2+ biopsy or high-grade endocervical cytology were referred to treatment by the HMOs. A telephone survey was then conducted to verify treatment and exit from the study. Women with low-grade cervical abnormalities (<CIN2) were referred to HMOs for routine management.

2.10 | Endpoints

We recovered all the histologic records and their corresponding histology slides by tracking clinical records from local pathology laboratories and HMO/HPI databases. We ascertained records and slides read by local pathologists (LPs) from the enrolment, follow-up and exit periods

and until an average date of up to 30 months after recruitment. Overall, 1407 participants had at least one histological (n = 1327) or endocervical (n = 80) diagnosis record of which 26 (1.8%) were unsatisfactory. The primary study endpoint was the first CIN2+ or CIN3+ diagnosed by a quality-control external review (QC) panel. The QC panel, formed by two expert pathologists (MS and MR), independently and blindly reviewed the slides in all unsatisfactory, 90% of CIN1+, 20% of randomly selected negative diagnoses during the 2-year follow-up, and 96% of all exit visit diagnoses. Upgraded local pathologists' (LP) slides were blindly reviewed again by MS. When slides were not reviewed by the QC panel (10% CIN1+, 80% of follow-up negative diagnoses and 4% exit diagnoses), the LP diagnosis was used as final. LP-diagnosed CIN2+ (without discriminating for more severe disease) was established as a secondary study endpoint. We used this threshold because it is the clinical basis to refer to treatment in routine care. Finally, women without biopsy (n = 1254) were considered free of disease.

2.11 | Sample size

The sample size was computed to compare the proportion of CIN3+ that was missed during the 2-year follow-up (ie, at exit). Following the ALTS,[17] we assumed that around 19% of CIN3+ cases in the HPV arm are detected at exit, and at least 40% in other arms. Thus, to detect differences of 21% in a two-tailed test with 80% power and 0.05 type I error, we needed approximately 219 CIN3+ cases. Assuming that the cumulative detection of CIN3+ at 24 months of women with ASC-US cytology was 8.8%,[17,27] we estimated that at least 2489 women with ASC-US should have been recruited.

2.12 | Analytical approach

We described the baseline characteristics as well as the cumulative QC-diagnosed CIN2+ and CIN3+ cases per arm to assess the balance of randomization, using Pearson's chi-square tests and/or relative proportions, RP, (IC arm as reference) with their corresponding 95% binomial confidence intervals (95% CI) for significant differences. The 2 years of follow-up were divided into three time periods: enrolment, follow-up and exit. The enrolment corresponded to the period when the strategies should have been delivered (≤6 months after recruitment for IC and HPV, and ≤12 months for RC arm), the follow-up corresponded to the period between the enrolment period and the exit visit (or 24 months if exit visit was not attended), and the exit period to the exit visit (or ≥24 months if that visit was not attended). Then, the cumulative QC-diagnosed CIN2+ and CIN3+ were compared between arms according to time period to identify the strategy able to detect more high-grade cervical abnormalities early, that is, at enrolment, and therefore to reduce the burden of disease at the exit visit. Because some cases at enrolment were not necessarily detected at that period in routine care, we also performed an additional analysis using the LP-diagnosed CIN2+ secondary endpoint, pursuing the same previous purpose. We assume that QC-diagnosed CIN2+ or CIN3+ cases that were missed ("under calling") because the strategies failed (ie, women were not biopsied correctly or did not receive biopsy ever, during the follow-up or not diagnosed as CIN2+ by LPs in routine care) within each arm, are more realistically attributed to the failure of the corresponding management strategy. QC-diagnosed CIN2+ or CIN3+ cases that were missed during the 2-years routine follow-up (enrolment and follow-up periods) were compared according to arm to determine the strategy that least missed our best cancer risk surrogates (QC-diagnosed CIN2+ and CIN3+). Differences between arms were tested using Pearson's or likelihood-ratio chi-square tests and RPs (IC arm as reference). The intention-to-treat (ITT) principle was used to represent better how these management strategies would perform in routine practice. A *P*-value <.05 was considered statistically significant. All analyses were performed in R.[28]

3 | RESULTS

3.1 | Participants

HMOs reported 7866 women with ASC-US cytology between January 2011 and January 2014 (Figure 2), of which 3357 were ineligible because of age (n = 856), residence outside the study area (n = 513) or ASC-US index cytology more than 3 months old (n = 1988). We checked the eligibility of 4509 women by phone and of 3693 during the recruitment visit and excluded 816 and 1032, respectively. Seven hundred and two (9%) of the 7866 identified with ASC-US cytology declined participation. We allocated 2661 women (882 to IC arm, 890 to RC arm and 889 to HPV arm). The average time from the ASC-US index cytology to recruitment was 23 days (interquartile range 12-28 days) and the median follow-up was 22.9 months (interquartile range 21.8-24.8 months).

The positivity of hrHPV in the HPV arm was 41%. We ascertained from HMOs and/or HPIs during the 2-year routine follow-up at least one cytology record for 67% (591/882), 80% (712/890) and 61% (539/889) of women allocated in IC, RC and HPV arms. Twenty-two (8 of IC, 10 of RC and 4 of HPV arms) were inadequately reported. Of those with adequately reported cytology, 22% (128/583), 31% (217/702) and 23% (125/535) in IC, RC and HPV arms, had at least one abnormal cytology (≥ASC-US) during the 2-year routine follow-up (Figure 2).

At least one routine record of colposcopy was ascertained during the 2-year routine follow-up for 88% (772/882), 42% (372/890) and 52% (462/889) of women allocated in IC, RC and HPV arms. These percentages were 84% (183/217) or 25% (119/485) in women of the RC arm with ≥ASC-US or NILM cytology, and 93% (335/361) or 24% (127/526) in hrHPV-positive or hrHPV-negative women of the HPV arm. Among women with colposcopy, we ascertained at least one histology record for 64% (492/772) of women in IC arm, 73% (271/372) in RC arm and 68% (313/462) in HPV arm. The percentages of histology records ascertained for women of the RC arm with at least one colposcopy and ≥ASC-US or NILM cytology during the 2-year routine follow-up were 82% (150/183) or 63% (75/119), and for women of the HPV arm with at

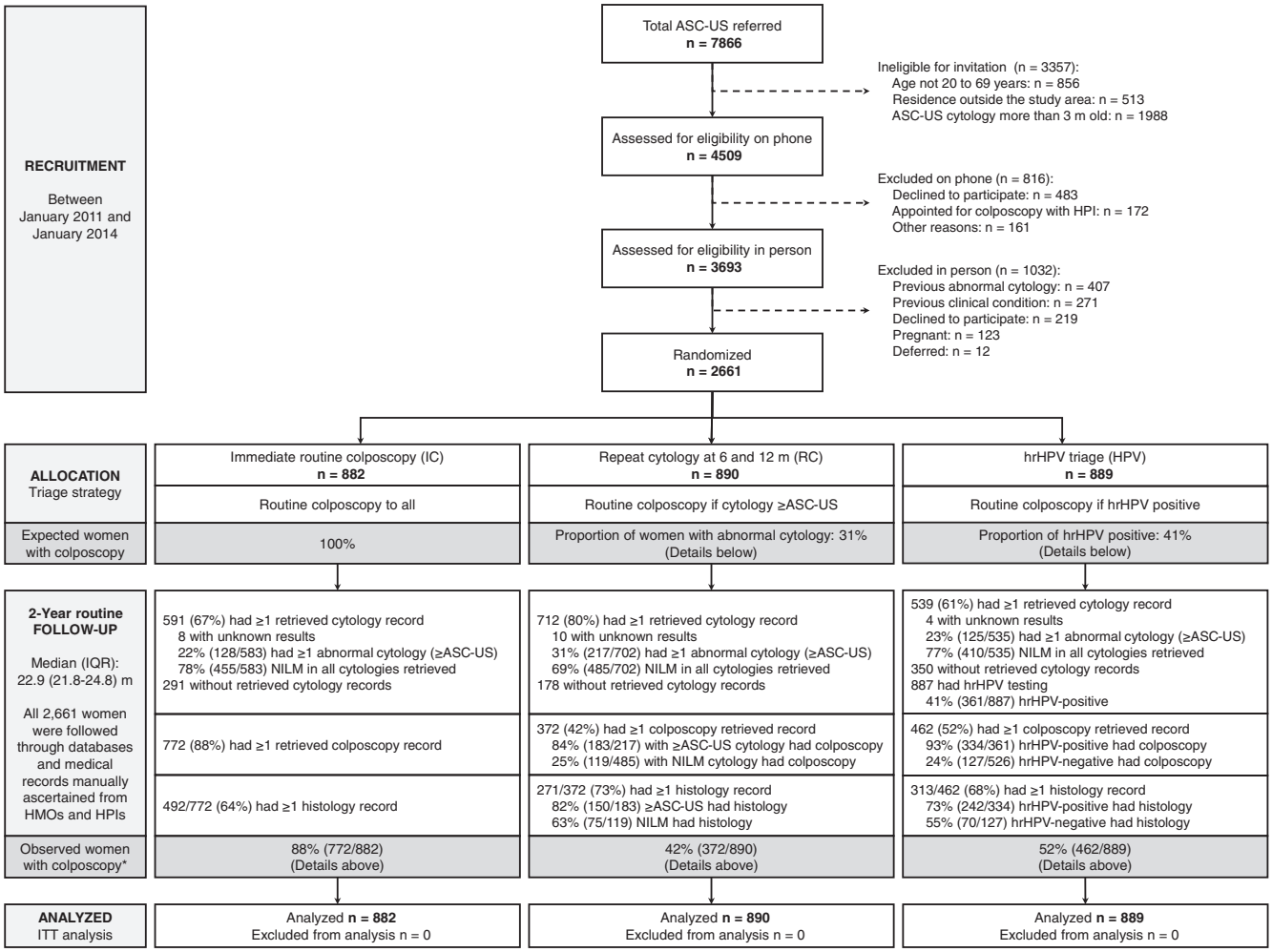

FIGURE 2 CONSORT Flowchart. The number of women recruited and allocated in each arm and triage strategy for colposcopy referral are shown. Reports of cytology, colposcopy, and histology were ascertained manually for all women from medical records or databases in the corresponding HMOs and HPIs. Numbers and percentages of women with at least one record of cytology, colposcopy, and histology found during the 2-year routine follow-up are shown. All women who attended exit visit (n = 2117, 687 in IC, 707 in RC, and 723 in HPV) received hrHPV testing and Pap smear regardless of allocation, and 527 of them (162 in IC, 199 in RC, and 166 in HPV) were referred to exit colposcopy. The outcomes of women who did not attend the exit visit (n = 544, 195 in IC, 183 in RC, and 166 in HPV) were determined using the histologic diagnoses closest to the 24 months of follow-up (n = 216) or assumed free-disease if not available (n = 328) in order to be included in the analysis under the intention-to-treat (ITT) principle. *The cumulative number of colposcopies during the 2-year routine follow-up per arm

least one colposcopy and hrHPV-positive or hrHPV-negative were 73% (242/334) or 55% (70/127) (Figure 2).

Baseline characteristics were distributed evenly by arm (Table 1). Most women were over 31 years (mean 37, SD 11), half were insured by HMO2, 49% were married/cohabiting, around 10% were professionals and 62% earned up to 1 Colombian monthly minimum wage (about USD330). Around half started regular sex between 16 and 19 years old, 60% had 3 or more lifetime sexual partners, 55% had 1 to 2 children and a third had used hormonal contraceptives >5 years. The majority of women had no history of cigarette smoking and had at least one cytology in the last 3 or 5 years.

Eighty percent (2129/2661) of enrolled women attended the exit visit (693 IC, 712 RC, 724 HPV), of which 25% (n = 539) were hrHPV-positive and/or ≥ASC-US (168 IC, 204 RC, 167 HPV) and 98% (n = 520) of this set of women had full compliance with clinical management according to protocol (Supporting Information Figure S2). Supporting Information Table S1 shows that women not attending (n = 532) and not complying (n = 12) with the exit visit (n = 544, 195 of IC, 183 of RC and 166 of HPV) were younger (Mean ± SD 35.5 ± 11.6 vs 37.7 ± 10.8), started sexual activity at a younger age (Mean ± SD 17.3 ± 3.6 vs 18 ± 3.8) and were more often insured in the HMO2. Attenders and nonattenders to the exit visit were comparable in the remaining sociodemographic variables and risk factors.

3.2 | Cumulative CIN2+ and CIN3+ by pathology QC panel according to arm

Table 2 presents the cumulative number and risk of QC-diagnosed CIN2+ and CIN3+ over the 2-year routine follow-up and exit visit. There

TABLE 1 Distribution of baseline sociodemographic characteristics and risk factors of women with ASC-US cytology according to arm

	IC (N = 882)		RC (N = 890)		HPV (N = 889)		Total (N = 2661)		
Characteristic	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	***P*[a]**
Age, y									
[Mean/SD]	[37.3/11.0]		[37.0/11.0]		[37.4/10.9]		[37.3/11.0]		
20-30	290	(32.9)	305	(34.3)	289	(32.5)	884	(33.2)	.684
31-40	240	(27.2)	248	(27.9)	233	(26.2)	721	(27.1)	
41-50	239	(27.1)	225	(25.3)	261	(29.4)	725	(27.2)	
51-69	113	(12.8)	112	(12.6)	106	(11.9)	331	(12.4)	
HMO									
1	196	(22.2)	233	(26.2)	207	(23.3)	636	(23.9)	.390
2	461	(52.3)	442	(49.7)	461	(51.9)	1364	(51.3)	
3	225	(25.5)	215	(24.2)	221	(24.9)	661	(24.8)	
Marital status									
Married/cohabiting	420	(47.6)	440	(49.4)	446	(50.2)	1306	(49.1)	.535
Divorced/separated	70	(7.9)	83	(9.3)	83	(9.3)	236	(8.9)	
Widowed	31	(3.5)	34	(3.8)	25	(2.8)	90	(3.4)	
Single	361	(40.9)	333	(37.4)	335	(37.7)	1029	(38.7)	
Education									
Complete/some elementary school	220	(24.9)	236	(26.5)	246	(27.7)	702	(26.4)	.898
Complete/some secondary school	426	(48.3)	430	(48.3)	418	(47.0)	1274	(47.9)	
Technician	150	(17.0)	147	(16.5)	144	(16.2)	441	(16.6)	
Professional or higher	86	(9.8)	77	(8.7)	81	(9.1)	244	(9.2)	
Income (Colombian minimum wage)									
Up to 1	539	(61.1)	563	(63.3)	543	(61.1)	1645	(61.8)	.582
More than 1 and up to 4	305	(34.6)	295	(33.1)	306	(34.4)	906	(34.0)	
More than 4	24	(2.7)	24	(2.7)	22	(2.5)	70	(2.6)	
Do not know/no answer	14	(1.6)	8	(0.9)	18	(2.0)	40	(1.5)	
Age at first intercourse, y									
[Mean/SD]	[17.9/3.6]		[17.8/3.9]		[17.9/3.9]		[17.9/3.8]		
≥20	215	(24.4)	205	(23.0)	226	(25.4)	646	(24.3)	.783
16–19	438	(49.7)	449	(50.4)	426	(47.9)	1313	(49.3)	
≤15	229	(26.0)	236	(26.5)	237	(26.7)	702	(26.4)	
Lifetime sexual partners									
[Median/range]	[3.0/1-100]		[3.0/1-200]		[3.0/1-98]		[3.0/1-200]		
1–2	355	(40.2)	360	(40.4)	369	(41.5)	1084	(40.7)	.934
3-4	282	(32.0)	279	(31.3)	285	(32.1)	846	(31.8)	
≥5	245	(27.8)	251	(28.2)	235	(26.4)	731	(27.5)	
Parity									
[Median/range]	[2.0/0–18]		[2.0/0–12]		[2.0/0-10]		[2.0/0-18]		
0	154	(17.5)	134	(15.1)	159	(17.9)	447	(16.8)	.593
1-2	493	(55.9)	493	(55.4)	488	(54.9)	1474	(55.4)	
3-4	182	(20.6)	209	(23.5)	186	(20.9)	577	(21.7)	
≥5	53	(6.0)	54	(6.1)	56	(6.3)	163	(6.1)	
Years of contraceptive use									
[Median/range]	[2.0/0–39]		[2.5/0-34]		[2.0/0–30]		[2.0/0–39]		
0	195	(22.1)	164	(18.4)	202	(22.7)	561	(21.1)	.081
<5	418	(47.4)	419	(47.1)	423	(47.6)	1260	(47.4)	
≥5	269	(30.5)	307	(34.5)	264	(29.7)	840	(31.6)	

TABLE 1 (Continued)

Characteristic	IC (N = 882)		RC (N = 890)		HPV (N = 889)		Total (N = 2661)		P^a
	n	(%)	n	(%)	n	(%)	n	(%)	
Cigarette use									
Never	692	(78.5)	667	(74.9)	691	(77.7)	2050	(77.0)	.094
In the past	84	(9.5)	81	(9.1)	90	(10.1)	255	(9.6)	
Currently	106	(12.0)	142	(16.0)	108	(12.1)	356	(13.4)	
Frequency of cytology use									
Once or more than once every year	608	(68.9)	593	(66.6)	590	(66.4)	1791	(67.3)	.826
Once every 2–3 y	174	(19.7)	181	(20.3)	176	(19.8)	531	(20.0)	
Once every 4–5 y	54	(6.1)	59	(6.6)	64	(7.2)	177	(6.7)	
Once every 6-10 y	24	(2.7)	25	(2.8)	22	(2.5)	71	(2.7)	
Less than once every 10 y	6	(0.7)	6	(0.7)	9	(1.0)	21	(0.8)	
Do not know/no answer	16	(1.8)	26	(2.9)	28	(3.1)	70	(2.6)	

Abbreviations: HPV, HC2-hrHPV triage; IC, immediate colposcopy; RC, repeat cytology at 6/12 m; %, column percentage..
[a]Pearson's chi-square test.

were 212 women diagnosed with CIN2+ (69 in IC arm, 81 in RC arm and 62 in HPV arm) and 52 of them were CIN3+ (18 in IC arm, 20 in RC arm and 14 in HPV arm). There were no significant differences in 2-year cumulative risk of QC-diagnosed CIN2+ by study arm, 7.8% for IC, 9.0% for RC and 7.0% for HPV (P = .249, RPs = 1), and QC-diagnosed CIN3+, 2.0% for IC, 2.2% for RC and 1.6% for HPV (P = .577, RPs = 1).

The highest cumulative risks of CIN2+ and CIN3+ were observed in women with ≥ASC-US cytology in the RC arm (19.8% for CIN2+, 4.1% for CIN3+) or hrHPV+ in the HPV arm (15.8% for CIN2+, 3.6% for CIN3+). Importantly, cumulative risks of CIN2+ and CIN3+ were lower among HPV-negative women in the HPV arm than cytology-negative (NILM cytology) women in the RC arm (5.8% vs 1.0%, respectively, for CIN2+, P < .001; 1.9% vs 0.2%, respectively, for CIN3+, P = .019).

3.3 | Cumulative QC-diagnosed CIN2+ and CIN3+ according to time period and study arm

The distribution of cumulative QC-diagnosed CIN2+ and CIN3+ within each period and relative proportions of cases detected at enrolment are presented in Table 3. The distribution of CIN2+ was similar according to period and arm (P = .821) and the proportion of cases detected at enrolment was similar between the arms ranging from 47.8% to 53.2% (RPs = 1). Although not significant, we observed marginal differences for the distribution of CIN3+ according to period and arm (P = .099). Compared to IC arm, the relative proportion of CIN3+ detected at enrolment was 1.50 (95% CI 0.70-3.66) for RC arm and 2.14 (95% CI 1.08-5.04) for HPV arm. Although not significant, the percentage of CIN2+ and CIN3+ detected at exit tended to be lower for the HPV arm (33.9% and 21.4%, respectively) than for the IC arm (37.7% and 38.9%, respectively) and the RC arm (42.0% and 45.0%, respectively).

3.4 | QC-diagnosed CIN2+ and CIN3+ diagnosed as CIN2+ by LPs during the enrolment and follow-up periods

Table 4 presents the QC-diagnosed CIN2+ and CIN3+ that was missed in routine care during the enrolment and follow-up periods. Assuming that the cases diagnosed at the exit visit did not receive adequate diagnosis during the follow-up, in this analysis we excluded the diagnoses given by the LPs in the biopsy taken at the exit visit, even if this diagnosis was consistent with the diagnosis of QC pathologists. This table compares between arms the proportions of QC-diagnosed CIN2+ and CIN3+ that were missed. The proportion of QC-diagnosed CIN2+ cases that were missed by the strategies was high, ranging from 61.3% to 72.5%, and did not differ between arms (P = .326). Instead, the proportion of missed QC-diagnosed CIN3+ marginally varied between arms (P = .072), ranging from 21.4% (3 of 14) for HPV to 61.1% (11 of 18) for IC arm. The proportion of missed QC-diagnosed CIN3+ in the HPV arm was 65% lower compared to IC (RP: 0.35, 95% CI 0.09-0.87), and no difference was observed between RC and IC arms (RP: 0.74, 95% CI 0.38-1.36). Although not significant, it is worth noting that IC had the largest proportion of missed QC-diagnosed CIN2+ (50 of 69 in IC vs 51 of 81 in RC, and 38 of 62 in HPV, P = .333). This proportion was even more noticeable for CIN3+ (11 of 18 in IC vs 9 of 20 in RC, and 3 of 14 inHPV, P = .150).

4 | DISCUSSION

This randomized pragmatic trial compares three clinical management strategies for women with ASC-US cytology under real-world clinical conditions of Medellin, Colombia. The main aim of this trial was to determine the most effective and efficient triage strategy to reduce cervical cancer risk (by earlier detection of QC-diagnosed CIN2+ and

TABLE 2 Cumulative QC-diagnosed CIN2+ and CIN3+ during the 2-year routine follow-up and exit visit according to arm

	IC (N = 882)		RC (N = 890)								HPV (N = 889)						
	Total N = 882		≥ASC-US N = 217		NILM N = 485		Not found N = 178		Total N = 890[b]		Positive N = 361		Negative N = 526		Total N = 889[c]		
QC diagnosis	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	*P*[a]
Less than CIN2	813	(92.2)	174	(80.2)	457	(94.2)	168	(94.4)	809[b]	(90.9)	304	(84.2)	521	(99.0)	827[c]	(93.0)	
CIN2	51	(5.8)	34	(15.7)	19	(3.9)	8	(4.5)	61	(6.9)	44	(12.2)	4	(0.8)	48	(5.4)	.622
CIN3	16	(1.8)	7	(3.2)	9	(1.9)	2	(1.1)	18	(2.0)	13	(3.6)	1	(0.2)	14	(1.6)	
SCC/ADC	2	(0.2)	2	(0.9)	0	(0.0)	0	(0.0)	2	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	
CIN2+	69	(7.8)	43	(19.8)	28	(5.8)	10	(5.6)	81	(9.1)	57	(15.8)	5	(1.0)	62	(7.0)	.249
CIN3+	18	(2.0)	9	(4.1)	9	(1.9)	2	(1.1)	20	(2.2)	13	(3.6)	1	(0.2)	14	(1.6)	.577
RP (95% CI) of CIN2+	Reference								1.16 (0.86-1.58)						0.89 (0.64-1.24)		
RP (95% CI) of CIN3+	Reference								1.10 (0.59-2.09)						0.77 (0.38-1.54)		

Note: All women and cases diagnosed by the quality-control external review (QC) panel during the 2-year routine follow-up and exit visit (ie, enrolment, follow-up and exit periods) are included in the analysis.
Abbreviations: CI, confidence interval; HPV, HC2-hrHPV triage (stratified by women with positive or negative status at recruitment); IC, immediate colposcopy; RC, repeat cytology at 6/12 m (stratified by women with at least one abnormal cytology [≥ASC-US] or with NILM in all cytologies during the 2-year routine follow-up); RP, relative proportion; %, column percentage.

[a]Pearson's chi-square test for high-grade diagnosis distribution according to arm.

[b]Includes 10 women with unknown cytology result.

[c]Includes 2 hrHPV untested women.

TABLE 3 Cumulative QC-diagnosed CIN2+ and CIN3+ according to time period and arm

	IC (N = 882)		RC (N = 890)						HPV (N = 889)							
	Total		≥ASC-US		NILM		Not found		Total		Positive		Negative		Total		
Time periods	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	*P*
QC-diagnosed CIN2+																	
Enrolment period	33	(47.8)	28	(65.1)	8	(28.6)	3	(30.0)	39	(48.1)	32	(56.1)	1	(20.0)	33	(53.2)	.821[a]
Follow-up period	10	(14.5)	8	(18.6)	0	(0.0)	0	(0.0)	8	(9.9)	8	(14.0)	0	(0.0)	8	(12.9)	
Exit period	26	(37.7)	7	(16.3)	20	(71.4)	7	(70.0)	34	(42.0)	17	(29.8)	4	(80.0)	21	(33.9)	
Total No. of women	69	(100.0)	43	(100.0)	28	(100.0)	10	(100.0)	81	(100.0)	57	(100.0)	5	(100.0)	62	(100.0)	
RP (95% CI) of CIN2+ at enrolment	Reference								1.01 (0.72-1.42)						1.11 (0.79-1.57)		.786[b]
RP (95% CI) of CIN2+ at exit	Reference								1.11 (0.75-1.68)						0.90 (0.56-1.42)		.610[b]
QC-diagnosed CIN3+																	
Enrolment period	6	(33.3)	7	(77.8)	2	(22.2)	1	(50.0)	10	(50.0)	10	(76.9)	0	(0.0)	10	(71.4)	.099[a]
Follow-up period	5	(27.8)	1	(11.1)	0	(0.0)	0	(0.0)	1	(5.0)	1	(7.7)	0	(0.0)	1	(7.1)	
Exit period	7	(38.9)	1	(11.1)	7	(77.8)	1	(50.0)	9	(45.0)	2	(15.4)	1	(100.0)	3	(21.4)	
Total No. of women	18	(100.0)	9	(100.0)	9	(100.0)	2	(100.0)	20	(100.0)	13	(100.0)	1	(100.0)	14	(100.0)	
RP (95% CI) of CIN3+ at enrolment	Reference								1.50 (0.70–3.66)						2.14 (1.08-5.04)		.786[b]
RP (95% CI) of CIN3+ at exit	Reference								1.16 (0.54-2.64)						0.55 (0.14-1.61)		.096[b]

Note: Women with negative tests (NLIM or hrHPV–) and that received colposcopy did not compliance with the recommended management.

Abbreviations: CI, confidence interval; HPV, HC2-hrHPV triage (stratified by women with positive or negative status at recruitment); IC, immediate colposcopy; RC, repeat cytology at 6/12 m (stratified by women with at least one abnormal cytology [≥ASC-US] or with all NILM cytologies during the 2-year routine follow-up); RP, relative proportion of CIN2+ or CIN3+ cases by pathology QC panel at enrolment or exit; QC, quality-control external review; %, column percentage.

[a]Pearson's chi-square test for high-grade diagnosis distribution according to time period and arm.

[b]Likelihood-ratio chi-square test for high-grade diagnoses detected during the enrolment period (≤6 months for IC and HPV and ≤12 months for RC) or at exit.

TABLE 4 QC-diagnosed CIN2+ and CIN3+ routinely diagnosed as CIN2+ or CIN3+ by LPs according to arm

	QC-diagnosed CIN2 and CIN3+												
	IC (N = 882)				RC (N = 890)				HPV (N = 889)				
LP diagnosis	CIN3+	CIN2	<CIN2	Total	CIN3+	CIN2	<CIN2	Total	CIN3+	CIN2	<CIN2	Total	P^a
LP-diagnosed CIN3+	3	1	1	5	6	1	0	7	7	1	0	8	
LP-diagnosed CIN2	4	11	1	16	5	18	1	24	4	12	4	20	
LP-diagnosed <CIN2	11	39	811	861	9	42	808	859	3	35	823	861	
Total	18	51	813	882	20	61	809	890	14	48	827	889	
QC-diagnosed CIN2+ missed by LPs (%)	50/69 (72.5)				51/81 (63.0)				38/62 (61.3)				
QC-diagnosed CIN3+ missed by LPs (%)	11/18 (61.1)				9/20 (45.0)				3/14 (21.4)				
RP (95% CI) of missed QC-diagnosed CIN2+	Reference				0.87 (0.69-1.09)				0.85 (0.65-1.08)				.326
RP (95% CI) of missed QC-diagnosed CIN3+	Reference				0.74 (0.38–1.36)				0.35 (0.09–0.87)				.072

Abbreviations: CI, confidence interval; HPV, HC2-hrHPV triage (stratified by women with positive or negative status at recruitment); IC, immediate colposcopy; LP, HPIs' local pathologists; QC, quality-control external review; RC, repeat cytology at 6/12 m (stratified by women with at least one abnormal cytology [≥ASC-US] or with NILM in all cytologies during the 2-year routine follow-up); RP, relative proportion.

[a]Likelihood-ratio chi-square test to compare between arms the proportion of QC-diagnosed CIN2+ and CIN3+ that were not detected by HPIs' local pathologists (LP) during the 2-year routine follow-up (enrolment [≤6 months for IC and HPV and ≤12 months for RC] and follow-up [after enrolment period and before exit] periods).

CIN3+) and healthcare utilization in women with ASC-US cytology. Herein we present the study design and compare the effectiveness of the three strategies to detect QC-diagnosed CIN2+ and CIN3+ during 2 years of routine follow-up. Our study included an exit visit that aimed to identify high-grade cervical abnormalities that were not detected during the follow-up, providing a measure of sensitivity of these different strategies to find CIN2+ and CIN3+ earlier. This is important because in the Colombian healthcare system women can be lost to follow-up as they can switch between HMO/HPIs and there is no data linkage between systems. Although the histology was reviewed by an external panel (QC), all participants received diagnosis and treatment based solely on the results of the tests and histological diagnoses performed under routine care by the healthcare providers during the 2-year routine follow-up. Therefore, our results represent real-world conditions and true effectiveness of the different management strategies of ASC-US cytology of the healthcare services of Medellin, Colombia.

The most meaningful findings in our study were obtained for the primary endpoint QC-diagnosed CIN3+, our best proxy of cancer risk, rather than CIN2+. If the goal of a triage strategy for ASC-US cytology is to find high-grade cervical abnormalities early (most importantly QC-diagnosed CIN3+) to reduce the disease burden later, then HPV testing was the most effective strategy in this pragmatic trial. At enrolment period (Table 3), HPV testing detected a greater fraction of QC-diagnosed CIN3+ compared to IC (RP: 2.14, 95% CI 1.08-5.04) and the same number of cases than two rounds of cytology (RC arm ≤12 months) but earlier (HPV arm ≤6 months). This is important, since earlier identification of at-risk women is crucial to decrease the loss of follow-up particularly in LMICs. Although not significant, HPV testing reduced more QC-diagnosed CIN3+ at exit compared to IC (Table 3, RP: 0.55, 95% CI 0.14-1.61). However, the lack of significance of this reduction was because we defined the primary endpoint as the first QC-diagnosed high-grade cervical abnormality. Some participants showed this outcome both in the 2-year follow-up and at the exit visit, probably due to the undercalling of CIN2+ and CIN3+ diagnoses by LPs. Then, the high-grade cervical abnormalities at the exit were greater and the undercalled cases could have been distributed differently between the arms (due to knowledge of a positive triage test in the RC and HPV arms). Hence, we carried out the analysis presented in Table 4 finding that HPV significantly reduced the number of QC-diagnosed CIN3+ cases that were not detected by the strategies during the 2-year routine follow-up compared to IC (RP: 0.35, 95% CI 0.09-0.87). Therefore, this finding strengthens what we consider the most relevant observation of our study, which is that HPV detected a greater fraction of QC-diagnosed CIN3+ than IC arm and same fraction but earlier than RC arm. Importantly, HPV reduced the number of women undergoing colposcopy by 41% compared to immediate colposcopy (52% vs 88%, Figure 2, $P < .001$).

Additionally, we could indirectly observe that a substantial proportion of high-grade cervical abnormalities was not diagnosed by LPs in the routine care during the 2-year routine follow-up or until the exit visit despite colposcopy and biopsy collection, revealing a common problem related to a poor pathology performance in HPIs (Table 4).

Previous studies under controlled clinical conditions or in routine clinical practice of high-income settings have shown that IC and HPV strategies are equally safe and superior to RC.[11-13,16,17,29,30] Dillner et al. showed that in women over

35 years hrHPV testing and immediate colposcopy were equivalent to identify CIN2+ cases in routine care.[11] Since in our study the HPIs colposcopists were not blinded to the arm and/or they could have enquired women for their test results, we suggest that the previous knowledge of arm allocation or any positive result (eg, cytology and/or hrHPV) may have triggered a more careful colposcopic examination with increased likelihood of biopsy-taking. Also, LPs may have known previous cytologic and/or hrHPV results improving the chances of diagnosing high-grade cervical abnormalities. This was most likely among women in RC arm from one HMO, where cytology and histology are read by the same group of pathologists. Stratified analyses showed that CIN2+ detection in this HMO was 3-fold higher in RC than in the IC arm (data not shown). It was also observed that the proportion of CIN3+ at exit was lower for the HPV arm (Table 3). Further inquiry in the clinical management of women diagnosed with CIN2+ by local pathologists before the exit visit, revealed that 14 women (67%) of IC arm, 22 (71%) of RC arm and 25 (89%) of HPV arm received treatment (data not shown). This is consistent with the possibility of more cervical abnormalities detected and treated early (enrolment period) in the HPV arm.

Our 2-year cumulative LP-diagnosed CIN2+ [n = 131 CIN2+ (4.9%) cases in the three arms, data not shown] was lower than that observed in similar studies under real conditions.[11,29,30] Dillner et al.[11] estimated 20% of CIN2+ in 34 months, approximately 14% in 24 months. Likewise, in two major US cohorts including women with ASC-US cytology attending routine cervical screening services, the cumulative CIN2+ in 2 years was around 6%.[29,30] Because of the pragmatic nature of our study, we did not control the delivery or the quality of gynecological procedures. Indeed, high variability (15-89%) between colposcopists to perform a biopsy was observed in the three arms. Nevertheless, we observed that almost 90% of women in need of colposcopy received it (Figure 2). Therefore, variability in diagnostic practices among countries and laboratories[31] could explain the low rates of LP-diagnosed CIN2+ of our study.

The main strength of the ASCUS-COL trial is that most of the procedures were delivered by the healthcare system according to the arm allocation and with acceptable adherence. The percentage of women who needed colposcopy was as expected (88% for IC, 84% for ≥ASC-US in RC arm and 93% for hrHPV-positive in HPV arm) (Figure 2). Another strength was that the histology was reviewed by an external quality-control panel allowing us to obtain meaningful findings. Additionally, we highlight the well-achieved randomization. Although Hakama et al consider randomization by cluster important in real-conditions studies,[23] we opted for individual randomization because there were only three HMOs. Therefore, differences in practices and quality of healthcare services could have been better distributed using individual randomization. Given the important coverage of these three HMOs in the metropolitan area of Medellin (54.1%), our study could represent well the healthcare conditions for this urban area. However, because of the heterogeneity and absence of centralized quality assurance, we are not certain if it represents the clinical practice of other urban centers of Colombia.

Our study had also some limitations. It is well known that it is challenging to conduct purely pragmatic studies[24,32] and some features of explanatory trials were present. Because it was a novel study in Colombia, the ethics committee requested to obtain written informed consent, exclude women with previous cervical disease, and offer cytology to all women included in the study. Additionally, we made phone calls to recruit women less than 3 months after index ASC-US cytology, and for 6 and 18 months follow-up after recruitment, as well as a 12-month follow-up study visit. Because hrHPV testing has not been yet implemented in the Colombian healthcare system we offered it for free and controlled the delivery of the results. Also, we acknowledge that repeating cytology at enrolment does not reflect routine practice. Indeed, these interventions may have trigger more or shorter time for referral to colposcopy and hence, more detection of disease in the HPV arm. There were five CIN2+ cases (all of them came from the RC arm) diagnosed with high-grade lesions by LPs (3 CIN2, 1 CIN3 and 1 cancer) among the 20 women that had >HSIL cytology at enrolment. At enrolment period, 84%, 38% and 45% of women in IC, RC and HPV arms respectively had colposcopy. In an analysis restricted at time point of 5.8 months, the median time (months, 95% CI for the median), from entry to first colposcopy was 0.6 (95%CI 0.5-0.9) for IC arm, 1.6 (95% CI 1.1-5.8) for RC arm and 2.5 (95% CI 2.3-5.8) for HPV arm. Although we cannot rule out the possibility that women of the IC arm may have had a higher number of occult CIN2+ lesions at entry that were detected at exit visit, these interventions did not seem to have influenced more the HPV arm than the other arms. However, this confirms previous observations of the advantages of centralizing the hrHPV test service for proper use in the social security system.[33] Also, to reflect more closely the population and the expected benefit in practice, we included 544 (20%) women who did not attend (n = 532) or completed the exit visit (n = 12) in the ITT analysis.[34] Nevertheless, we indirectly enquired for the risk of CIN2+ in these women using the information available during the follow-up. In 216 of them, histological diagnosis closest (before or after) to the 24 months of follow-up was recovered from the healthcare system. The remaining women were considered free of disease because they had negative colposcopy impressions (n = 50) or were NILM in all cytologies during the study (n = 47). We further enquired about the hrHPV status at baseline in all participants and found that 188 (43 in IC, 61 in RC and 84 in HPV) who did not attend the exit visit were hrHPV negative and therefore expected to be at low risk of CIN2+.[30] The 43 remaining women (42 hrHPV+, 1 untested) (11 in IC, 24 in RC, 8 in HPV) were assumed disease-free despite the risk of CIN2+. Nevertheless, results and conclusions were identical when we conducted the analyses under per-protocol conditions (data not shown).

Another limitation was the low number of QC-diagnosed CIN3+ cases probably due to misclassification of QC-diagnosed CIN2.[35] Our cumulative QC-diagnosed CIN3+ was 1.95% (Table 3), lower than expected[17,27] but in line with recent studies.[29,30] If differences had been as expected,[17,27] this would have implied a 28% power.

However, the results of missed QC-diagnosed CIN3+ cases (Table 4), consequently to the pragmatic nature of our study, had larger differences (21.4% vs 61.1%) with an improved 70% power.

In conclusion, our results show that under routine conditions of healthcare services of an urban region in Colombia, a strategy that includes hrHPV testing detected more and earlier cases with high-grade cervical abnormalities, reducing both the use of colposcopy and disease burden after 2-year of routine follow-up since an ASC-US index cytology compared to immediate colposcopy. Our results do not support immediate colposcopy for the management of ASC-US cytology in this healthcare context.

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CONFLICT OF INTERESTS

Philip E. Castle has received HPV tests and assays for research at a reduced or no cost from Roche, Becton Dickinson, Arbor Vita Corporation and Cepheid. All the rest of the authors do not have conflict of interest to declare. The HC2-hrHPV DNA test was donated by QIAGEN.

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

DATA AVAILABILITY STATEMENT

Anonymized data and samples can be shared for future studies. The PI and those authorized by the PI can have access and right to analyze and publish data from the onset of the data collection. The data will also be made accessible by e-mail request to corresponding author.

ETHICS STATEMENT

Our study complied with Colombian Resolution 8430 of 1993 for studies in humans and followed CIOMS guidelines.[36] The ethics committees for human experimentation of Sede de Investigación Universitaria (SIU) (Resolution 08-036-171) and School of Medicine (Resolution 004/2008), University of Antioquia, as well as the HMOs review boards approved our study. All participants signed informed consent and authorization to use samples and data for future research. The risk of adverse effects (bleeding in cervical sampling) was not deemed greater than the exposure in clinical practice. All data collected and stored within the study were safeguarded by the PI, and confidentiality and anonymity were guaranteed to ensure data protection.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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