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Practice guidelines for the early detection of cervical cancer in Korea: Korean Society of Gynecologic Oncology and the Korean Society for Cytopathology 2012 edition

Jae Kwan Lee[1], Jin Hwa Hong[1], Sokbom Kang[2], Dae-Yeon Kim[3], Byoung-Gie Kim[4], Sung-Hoon Kim[5], Yong-Man Kim[3], Jae-Weon Kim[6], Jae-Hoon Kim[7], Tae-Jin Kim[8], Hyun Jung Kim[9], Hye Sun Kim[10], Hee-Sug Ryu[11], Jae Yun Song[12], Hyeong Sik Ahn[9], Chong Woo Yoo[13], Hye-Kyoung Yoon[14], Keun-Ho Lee[15], Ahwon Lee[16], Yonghee Lee[17], In Ho Lee[8], Jeong-Won Lee[4], Taek Sang Lee[18], Myong Cheol Lim[2], Suk-Joon Chang[11], Hyun Hoon Chung[6], Woong Ju[19], Hee Jae Joo[17], Soo-Young Hur[15], Sung-Ran Hong[10], Joo-Hyun Nam[3]

[1]Department of Obstetrics and Gynecology, Guro Hospital, Korea University College of Medicine, Seoul; [2]Center for Uterine Cancer, Research Institute and Hospital, National Cancer Center, Goyang; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul; [4]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [5]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul; [6]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul; [7]Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul; [8]Department of Obstetrics and Gynecology, Cheil General Hospital and Women's Healthcare Center, Kwandong University College of Medicine, Seoul; [9]Institute for Evidence-Based Medicine, The Korean Branch of Australasian Cochrane Center, Department of Preventive Medicine, Korea University College of Medicine, Seoul; [10]Department of Pathology, Cheil General Hospital and Women's Healthcare Center, Kwandong University College of Medicine, Seoul; [11]Department of Obstetrics and Gynecology, Ajou University Hospital, Ajou University School of Medicine, Suwon; [12]Department of Obstetrics and Gynecology, Korea University Anam Hospital, Korea University College of Medicine, Seoul; [13]Department of Pathology, Center for Uterine Cancer, Research Institute and Hospital, National Cancer Center, Goyang; [14]Department of Pathology, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan; Departments of [15]Obstetrics and Gynecology and [16]Pathology, The Catholic University of Korea College of Medicine, Seoul; [17]Department of Pathology, Ajou University Hospital, Ajou University School of Medicine, Suwon; [18]Department of Obstetrics and Gynecology, Seoul National University Boramae Hospital, Seoul; [19]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ewha Womans University School of Medicine, Seoul, Korea

The consensus guideline development committee of Korean Society of Gynecologic Oncology was reconvened in March 2012. The committee consisted of 36 experts representing 12 university hospitals and professional organizations. The objective of this committee was to develop standardized guidelines for cervical cancer screening tests for Korean women and to distribute these guidelines to every clinician, eventually improving the quality of medical care. Since the establishment of the consensus guideline development committee, evidence-based guidelines have either been developed *de novo* considering specific Korean situations or by adaptation of preexisting consensus guidelines from other countries. Recommendations for cervical cancer screening tests, management of atypical squamous and glandular cells, and management of low-grade and high-grade squamous intraepithelial lesions were developed. Additionally, recommendations for human papillomavirus DNA testing and recommendations for adolescent and pregnant women with abnormal cervical screening test results were also included.

Keywords: Atypical glandular cells, Atypical squamous cells, Cervical cancer, Human papillomavirus, Screening, Squamous intraepithelial lesion

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Correspondence to Joo-Hyun Nam
Department of Obstetrics and Gynecology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea. Tel: +82-2-3010-3633, Fax: +82-2-476-7331, E-mail: jhnam@amc.seoul.kr

Correspondence to Sung-Ran Hong
Department of Pathology, Cheil General Hospital and Women's Healthcare Center, College of Medicine, Kwandong University, 17 Seoae-ro 1-gil, Jung-gu, Seoul 100-380, Korea. Tel: +82-2-2000-7661, Fax: +82-2-2000-7779, E-mail: srh7661@naver.com

INTRODUCTION

Unlike other gynecological cancers, cervical cancer has some distinct characteristics. First, sexual activity is strongly related to the development of this cancer. Second, cervical cancer is almost always preceded by precancerous lesions, namely, cervical intraepithelial neoplasias (CIN). Third, the precancerous stage is quite long and ranges from 7 to 20 years, which enables early diagnosis at this stage [1]. Fourth, as compared with other organs, the cervix can be easily exposed using a speculum, which makes clinical procedures more feasible.

Various screening guidelines for abnormal cervical cytology have been developed for the early diagnosis and treatment of precancerous lesions, and these guidelines are used worldwide [2-5]. However, most of the current guidelines were developed in the United States; thus, these guidelines may not be useful for Koreans. For example, the incidence of cervical cancer in Korea is much higher than that in Western countries, although it has been decreasing gradually over the past decade [6,7]. Moreover, the costs associated with the Papanicolaou (Pap) test, human papillomavirus (HPV) DNA test, and colposcopy are lower in Korea than that in the United States. Consequently, the development of Korean-specific guidelines for cervical cancer screening is necessary.

GUIDELINE DEVELOPMENT PROCESS

Since the reconvening of the consensus guideline development committee in March 2012, numerous workshops and conferences have been held. Many experts, including gynecologic oncologists representing the Korean Society of Gynecologic Oncology, pathologists representing the Korean Society for Cytopathology, and statisticians working in preventive medicine, were involved in this committee. The committee was further divided into the 5 subcommittees for the following themes: 1) cervical cancer screening tests, 2) atypical squamous cells (ASC) and atypical glandular cells (AGC), 3) low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL), 4) HPV DNA tests, and 5) special situations including those involving adolescent and pregnant women. Each subcommittee consisted of 1 chairperson, 1 secretary, and 4–5 members.

The guidelines were developed based on preexisting guidelines developed by the American Society for Colposcopy and Cervical Pathology [2], the National Comprehensive Cancer Network [3], the United States Preventive Services Task Force [4], and the Institute for Clinical Systems Improvement [5]. Some guidelines were created *de novo*, whereas some were adaptations of the aforementioned guidelines. In either case, every effort was made to reflect specific situations in Korea, for example, the high incidence of cervical cancer, low medical costs, and distinct characteristics of the medical service systems.

Each subcommittee created several key questions and performed a literature review to provide supporting evidence. Recommendations were then developed, revised, and approved through vigorous discussions among members at multiple workshops, small group meetings, and public hearings as well as through a web-based survey. Each recommendation was rated as "H (high)," "M (moderate)," "L (low)," "VL (very low)," or "E (expert consensus or lack of evidence)" according to the level of evidence [8,9]. Each recommendation was also rated as "S (strong)" or "W (weak)" following discussions among members of each subcommittee. In this paper, the ratings for each recommendation are provided as VLS, MS, etc. within parenthesis, where VLS stands for very low and strong, MS for moderate and strong, and so on.

The terminology used for this guideline adhered to the 2001 Bethesda system. Abnormal morphology that may represent preinvasive squamous disease fell into 4 descriptive categories: ASC, AGC, LSIL, and HSIL. Clinical judgment should be used first when applying a guideline to an individual patient because the guideline may not reflect all situations.

CONSENSUS GUIDELINES

1. General screening guidelines

All women ≥20 years of age who have commenced sexual activities should undergo cervical cancer screening tests (VLS) [10-15]. In contrast, routine cervical cancer screening tests are not recommended for women under 20 years of age because despite the high incidence of HPV infection, spontaneous regression occurs frequently, and there is a very low incidence of invasive cervical cancer. Screening tests can however be performed when cervical cancer or preinvasive disease is suspected. Cervical cancer screening tests can be discontinued in women ≥70 years old after 3 consecutive negative Pap tests within 10 years (ES). However, a woman should continue undergoing screening tests regardless of age if she has a history of CIN grade 2 or greater or if she does not know her previous Pap test results. Considering the relatively high incidence of cervical cancer in Korea, easy access to the screening test, and relatively low medical cost, annual screening using the Pap test alone is recommended for 20-year-old to 70-year-old women. However, a 3-year interval is recommended in Western countries (ES).

According to the previous literature, liquid-based cytology

did not show improved sensitivity or specificity when compared with conventional cytology [16-20]. However, the use of liquid-based cytology decreases the number of inadequate specimens. Considering the situation in Korea, either test can be chosen as a screening test (MS). A combination of cervical cytology and cervicography is not generally recommended due to increased false-positive results and low cost-effectiveness; however, this combination might be beneficial in terms of sensitivity (LW) [21-23].

Most newly acquired HPV infections regress spontaneously, and HPV DNA positivity decreases with age following a peak in adolescents and in women in their 20s [24]. Therefore, the HPV DNA test in combination with a cervical cytology test is recommended for women ≥30 years old (HS) [25-43]. When both tests are negative, the screening interval can be extended to 2 years (HS). Although the prevalence of invasive cervical cancer and preinvasive diseases is expected to decrease due to vaccination, a change in the screening interval should be considered after more clinical data have accumulated (EW). A woman who has undergone hysterectomy should continue with screening tests if she has a history of CIN grade 2 or greater or if she does not know her previous cytology results (ES).

2. Atypical squamous cells

ASC is further divided into ASC-undetermined significance (ASC-US) and ASC-cannot exclude a high grade squamous intraepithelial lesion (ASC-H). The risks of high-grade CIN and invasive cervical cancer are low in women with ASC-US versus those with ASC-H [44]. Excision or ablative therapies are not recommended for these patients in order to avoid potential overtreatment. Because of the high prevalence of CIN grades 2 and 3 among women with ASC-H, the management of these patients is almost the same as that of patients with HSIL.

1) Recommended management of women with ASC-US

Repeat cytological tests, a high-risk HPV DNA test, and an immediate colposcopy are all acceptable management strategies for ≥20-year-old women with ASC-US (HS) [45-48]. When repeat cytology with a 6-month interval is chosen, colposcopy should be performed if the result of repeat cytology is ASC-US or greater [2]. After 2 consecutive "negative for intraepithelial lesion or malignancy" cytology results, the patient can return to routine screening. When an HPV DNA test is chosen for follow-up, a colposcopy should be performed if high-risk HPV is detected [2]. If immediate colposcopy is required and the colposcopy is satisfactory, the recommended management of women with CIN grade 1 or less is either an HPV DNA test at 12 months or repeat cytological tests at 6 and 12 months (MS) [49,50]. Women can return to routine screening after 2 consecutive "negative for intraepithelial lesion or malignancy" cytology results 6 months apart or a negative HPV DNA test result at 12 months (ES). However, if CIN grade 2 or 3 is identified, a diagnostic excisional procedure should be performed.

2) Recommended management of women with ASC-H

The recommended management of women with ASC-H is referral for a colposcopic examination [2]. A review of cytological, histological, and colposcopic findings can be performed if a colposcopy-directed biopsy did not indicate CIN grade 2 or greater (EW). Cervical cytology and colposcopy can be performed at 6-month intervals if a colposcopy-directed biopsy did not indicate CIN grade 2 or greater (ES). These women can return to routine screening if 2 consecutive cytology and colposcopy results obtained 6 months apart are negative (ES). If CIN grade 2 or 3 is identified after colposcopy-directed biopsy, a diagnostic excisional procedure should be performed.

3. Atypical glandular cells

Although AGC frequently arise due to benign conditions such as reactive cellular changes or polyps, they are associated with a clinically significant lesion (including CIN, cervical adenocarcinoma *in situ* [AIS], cervical cancer, and endometrial, ovarian, and fallopian tube cancers) in 45% of patients [2,51]. Previous studies have noted that 9%–38% of women with AGC have a clinically significant neoplasia such as CIN grade 2 or 3, AIS, or cancer [2]. Gynecologic cancer is less common in women ≤35 years of age compared to women above 35 years of age [2]. No single test has sufficient sensitivity to be utilized as an initial triage for women with AGC [52]. Therefore, multiple testing modalities should be used during the initial evaluation.

1) Recommended management of women with AGC

For women with cytological AGC, an HPV DNA test, colposcopy, and endocervical curettage (ECC) are recommended (VLS) [44,53-56]. An endometrial biopsy is also recommended for women ≥35 years of age (VLS) [44,55,56]. However, it is only recommended for women <35 years of age if they have risk factors for endometrial cancer such as obesity, infertility, anovulation, or polycystic ovarian syndrome; if they have undergone tamoxifen therapy; or if they have abnormal vaginal bleeding or atypical endometrial cells; or if they have family history of colorectal or endometrial cancer [3]. If colposcopy-directed biopsy and ECC identify CIN grades 1–3 or AIS, a diagnostic excisional procedure should be performed. However, women with satisfactory colposcopy results revealing CIN grade 1 and

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negative ECC may be managed conservatively either with repeat cervical cytology every 6 months or with an HPV DNA test at 12 months. Colposcopy is recommended for women with a follow-up cytology indicating ASC-US or greater [3].

4. Low-grade squamous intraepithelial lesion

An LSIL is closely associated with a high risk of HPV infection. A recent meta-analysis showed that the overall HPV prevalence and the estimated HPV 16/18-positive fractions were 72.9% and 26.7%, respectively, in women with LSIL [57]. Based on colposcopy-directed biopsy, the rate of CIN grade 2, CIN grade 3, or cancer in women with LSIL was reported to be 11%–14% [58,59].

1) Recommended management of women with LSIL

Colposcopy is recommended for women with LSIL (MS) [60]. The management of those with LSIL depends on whether the full transformation zone can be visualized by colposcopic examination, i.e., whether a satisfactory colposcopy can be achieved. ECC should be considered for patients in whom no lesions are identified and for those with an unsatisfactory colposcopy (with the exception of pregnant women) [2,3]. When CIN grade 2 or 3 is identified by ECC, excisional procedures should be performed. Repeat cervical cytology at 6 and 12 months or an HPV DNA test at 12 months is recommended as follow-up management for patients in whom CIN grade 2 or 3 is not detected by colposcopy-directed biopsy or in whom biopsy is not performed (ES). Excision or ablation is not recommended for these women. A return to routine screening is recommended if 2 consecutive cervical cytological tests are negative for intraepithelial lesions or malignancies or if an HPV DNA test is negative during follow-up. Referral for colposcopy is recommended if ASC-US or greater is identified by follow-up cytology or if an HPV DNA test is positive. If CIN grade 2 or 3 is detected following colposcopy-directed biopsy, a diagnostic excisional procedure is recommended [2,3].

5. High-grade squamous intraepithelial lesion

Cytological HSIL is accompanied by a significant risk of high-grade cervical disease or cancer. Histological CIN grade 2 or greater can be identified in 60%–70% of women with HSIL by colposcopy-directed biopsy, and CIN 2 or greater is diagnosed in 84%–97% of women who underwent a loop electrosurgical excision procedure [2,61]. Up to 18.8% of women with HSIL have invasive cervical cancer [62]. Therefore, follow-up of women with HSIL with an HPV DNA test or cervical cytology is inappropriate. Because colposcopy can miss a significant number of high-grade lesions, a majority of women will eventually undergo diagnostic excisional procedures [2].

1) Recommended management of women with HSIL

In cases of HSIL (with the exception of adolescent women), immediate diagnostic excisional procedures, including loop electrosurgical excision or conization, can be performed without colposcopic examination [63-65] (VLS). If colposcopic examination is elected, management of women with HSIL depends on whether the colposcopic examination was satisfactory or unsatisfactory. For those with a satisfactory colposcopy, management depends on whether the lesion was observable or not. When lesions cannot be visualized by colposcopy, ECC should be performed in women with no lesions or in those who have not undergone biopsy [3]. If ECC is negative, cytology and colposcopy should be repeated every 6 months until 2 consecutive negative results can be confirmed. If ECC is positive for CIN, diagnostic excisional procedures should be performed. When lesions are observable, 3 management options can be chosen if CIN grade 2 or greater is not identified following colposcopy-directed biopsy: diagnostic excisional procedures (VLS), review of cytological and histological specimens (ES), or observation with colposcopy and cytology at 6-month intervals for 1 year (ES). After 1 year of observation, women with 2 consecutive "negative for intraepithelial lesion or malignancy" cytological tests or negative colposcopy results can return to a routine screening program (ES). However, a diagnostic excisional procedure should be performed if the follow-up cytology shows HSIL. If CIN grade 2 or 3 is detected by colposcopy-directed biopsy at initial presentation, treatment with an excisional procedure should be performed [66]. When the presence of residual disease at the resection margin after an excisional procedure cannot be determined, cervical cytology can be performed at 6 months or an HPV DNA test can be performed at 12 months (ES).

6. HPV DNA test

Although cervical cytology has contributed to the early detection of CIN and cervical cancer, its shortcomings as a screening test (e.g., high false-negativity) are not negligible [67]. Moreover, because infection with high-risk HPV is now considered a necessary cause of cervical cancer, tests for high-risk HPV have been proposed as adjuncts to cervical cytology tests. Evidence from previous literature indicates that the HPV DNA test has superior sensitivity for the detection of CIN grade 2 or greater as compared with cervical cytology [17,68-73]. A Canadian randomized study comparing cervical cytology with the HPV DNA test in 9,667 women aged 30–69 years demonstrated that the sensitivities of cervical cytology, the HPV DNA test, and both tests combined for the detection of CIN grade 2 or greater were 56.4%, 97.4%, and 100%, respectively [70], while their specificities were 97.3%, 94.3%, and 92.5%,

respectively. Women who are negative for both cytology and the HPV DNA test have a less than 1 in 1,000 risk of having CIN grade 2 or greater, and the risk of developing CIN grade 3 is very low [74,75].

An HPV DNA test can be performed as an adjunct test to cervical cytology in women aged 30 years and older to reduce the high false-negativity of cytology (HS) [68-73]. In addition to the Hybrid Capture 2 (HC2; Qiagen, Gaithersburg, MD, USA) test approved by the United States Food and Drug Administration, other HPV DNA detection methods including HPV DNA chip tests and polymerase chain reaction (PCR)-based HPV detection kits are commonly used in Korea. These tests were comparable to the HC2 test with respect to their sensitivity and specificity for the detection of CIN grade 2 or greater and their concordance with HPV positivity [62,76-78]. Considering the specific situation in Korea and evidence from previous validation studies, HPV DNA chip tests and various PCR-based HPV detection kits can be used for the detection of HPV infection (LW) [76-79].

Many women in the screened populations who are positive for HPV infection show negative cervical cytology. The overall prevalence of HPV positivity was 6.5%, and 58% of HPV-positive women had negative cytology [80]. Moreover, the risk of missing the diagnosis of CIN grade 2 or greater during routine screening is quite low (2.4%–5.1%) in women who are cytology-negative and HPV-positive [81,82]. It is important to determine which of these women are more likely to develop high-grade CIN or cancer. During a 10-year follow-up of cytology-negative, HPV-positive women ≥30 years of age, CIN grade 3 was detected in 21% and 18% of those carrying HPV 16 and 18, respectively [75]. In contrast, the risk of CIN grade 3 in women with other high-risk HPVs was only 1.5%. Based on these results, which indicate a differential risk of developing high-grade CIN depending on HPV genotype, an HPV genotyping test is recommended for cytology-negative, HPV-positive women (LS) [74,75,83,84]. If HPV 16 or 18 is detected, referral to a gynecologic oncologist and a colposcopic examination are recommended (LS). In women who are positive for HPVs other than HPV 16 or 18, an HPV DNA test and HPV genotyping test can be performed 1 year later (LS).

7. Special situations

1) Management of adolescent women

The management of cervical abnormalities requires special consideration in adolescents and women younger than 20 years of age. Previous studies indicate that the majority of young women will be infected with HPV within several years of commencement of sexual activities [69,85,86]. Because of the high prevalence of HPV and frequent regression in these women, routine HPV DNA testing is not recommended for those with cytological ASC-US or LSIL (LS) [86-88]. Instead, a regular follow-up with annual cytology is recommended. If cytology results at 12 months indicate HSIL or greater, the patient should be referred for colposcopy [2,3]. If cytology results at 24 months indicate ASC-US or greater, referral for colposcopy is also recommended [2,3].

Colposcopy is recommended if the initial cytology reveals ASC-H because of the increased risk of CIN grade 2 or greater [3]. When colposcopy is satisfactory, repeat cytology at 6 months is recommended if CIN grade 2 or 3 is not identified. The patient can return to routine screening after 2 consecutive negative cytology tests. However, colposcopy should be performed if cytology at 6 months reveals ASC-US or greater. When CIN grade 2 or 3 is identified, there are 2 management options: 1) excision or ablation, or 2) observation with cytology and colposcopy every 6 months. Patients with unsatisfactory colposcopy results should undergo ECC and cervical biopsy [3].

In adolescents with HSIL, colposcopy is recommended [2,3], although immediate excisional procedures are not. If histological CIN grade 2 or 3 is not identified, follow-up with cytology and colposcopy at 6-month intervals for up to 2 years is preferred. During follow-up, if a high-grade colposcopic lesion is identified or if HSIL persists for 1 year, biopsy should be performed. When HSIL persists for 24 months without identifiable CIN grade 2 or 3, excisional procedures should be performed. After 2 consecutive negative cytology results and no evidence of high-grade colposcopic abnormalities, adolescents can return to routine screening. When CIN grade 2 or 3 is histologically confirmed, either excision/ablation or cytology and colposcopy every 6 months up to 24 months can be selected. Patients with unsatisfactory colposcopy results should undergo ECC and cervical biopsy [3].

2) Management of pregnant women

The management of nonadolescent pregnant women with ASC-US or LSIL is identical to that of nonpregnant women with ASC-US or LSIL. ECC is not permitted in pregnant women. Deferring the initial colposcopy until at least 6 weeks postpartum is a safe and acceptable management option for pregnant women with either ASC-US or LSIL (LS) [89,90]. Colposcopy is recommended for pregnant women with HSIL, and biopsy should be performed if high-grade CIN or cancer is suspected [2,3]. Among 78 women with histologically proven CIN grade 2 or 3, 48 (62%) showed disease regression during postpartum assessment [91]. No cases of invasive cancer were identified during follow-up. According to another prospective study on pregnant women with CIN grade 2 or 3 who were

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followed-up with colposcopy and/or cytology, nearly half of the enrolled women showed regression of the initial disease, and none showed progression to invasive cancer [92]. If CIN grade 2 or 3 (but not invasive cancer) is identified histologically, diagnostic excisional procedures can be deferred until postpartum (LS).

8. Follow-up after treatment of CIN with excisional procedures or ablation

When ablative treatments such as laser therapy or cryotherapy are performed, the surgical margins cannot be assessed. In these cases, follow-up with cervical cytology at 6 months or an HPV DNA test at 12 months is recommended [93]. Treatment of women initially managed with excisional procedures, such as the loop electrosurgical excisional procedure or conization, depends on the status of the resection margins. Cervical cytology at 6 months or an HPV DNA test at 12 months is recommended for women with CIN grade 2 or 3 with negative margins and for all women with CIN grade 1 [3]. For women with CIN grade 2 or 3 with positive margins, 3 options are available: 1) cervical cytology at 6 months, 2) ECC, or 3) re-excision if invasion is suspected or hysterectomy after a consultation with a specialist. If cervical cytology at 6 months indicates ASC-US or greater, management should be performed as per the guidelines previously mentioned. For women with negative cytology results or a negative HPV DNA test, routine screening can be resumed. If an HPV DNA test is positive at 12 months, the patient should be referred for colposcopy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Schiffman M, Castle PE. The promise of global cervical-cancer prevention. N Engl J Med 2005;353:2101-4.
2. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 Consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol 2007;197:340-5.
3. Partridge EE, Abu-Rustum NR, Campos SM, Fahey PJ, Farmer M, Garcia RL, et al. Cervical cancer screening. J Natl Compr Canc Netw 2010;8:1358-86.
4. Moyer VA; U.S. Preventive Services Task Force. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;156:880-91.
5. Institute for Clinical System Improvement. Initial management of abnormal cervical cytology (Pap test) and HPV test in adult and adolescent females. Bloomington, MN: Institute for Clinical System Improvement; 2013 [cited 2013 Mar 19]. Available from: https://www.icsi.org/_asset/hks01y/AbPap-Interact0910.pdf.
6. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
7. Lee YH, Choi KS, Lee HY, Jun JK. Current status of the National Cancer Screening Program for cervical cancer in Korea, 2009. J Gynecol Oncol 2012;23:16-21.
8. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995-8.
9. Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336:1106-10.
10. Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical caner screening: a population-based study. Am J Obstet Gynecol 2004;191:105-13.
11. Sigurdsson K. Cervical cancer: cytological cervical screening in Iceland and implications of HPV vaccines. Cytopathology 2010;21:213-22.
12. Sigurdsson K, Sigvaldason H. Is it rational to start population-based cervical cancer screening at or soon after age 20? Analysis of time trends in preinvasive and invasive diseases. Eur J Cancer 2007;43:769-74.
13. Peto J, Gilham C, Deacon J, Taylor C, Evans C, Binns W, et al. Cervical HPV infection and neoplasia in a large population-based prospective study: the Manchester cohort. Br J Cancer 2004;91:942-53.
14. Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet 2001;357:1831-6.
15. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. BMJ 2009;339:b2968.

16. Taylor S, Kuhn L, Dupree W, Denny L, De Souza M, Wright TC Jr. Direct comparison of liquid-based and conventional cytology in a South African screening trial. Int J Cancer 2006;118:957-62.
17. Coste J, Cochand-Priollet B, Cremoux P, Le Gales C, Cartier I, Molinie V, et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ 2003;326:733.
18. Cochand-priollet B, Le Gales C, de Cremoux P, Molinie V, Sastre-Garau X, Vacher-Lavenu MC, et al. Cost-effectiveness of monolayers and human papillomavirus testing compared to that of conventional Papanicolaou smears for cervical cancer screening: protocol of the study of the French Society of Clinical Cytology. Diagn Cytopathol 2001;24:412-20.
19. Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomized controlled trial. BMJ 2007;335:28.
20. Siebers AG, Klinkhamer PJ, Grefte JM, Massuger LF, Vedder JE, Beijers-Broos A, et al. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. JAMA 2009;302:1757-64.
21. Baldauf JJ, Dreyfus M, Lehmann M, Ritter J, Philippe E. Cervical cancer screening with cervicography and cytology. Eur J Obstet Gynecol Reprod Biol 1995;58:33-9.
22. Autier P, Coibion M, De Sutter P, Wayemberg M. Cytology alone versus cytology and cervicography for cervical and cervicography for cervical cancer screening: a randomized study. European Society for Oncological Research. Obstet Gynecol 1999;93:353-8.
23. Kim YT, Kim JW, Kim SH, Kim YR, Kim JH, Yoon BS, et al. Clinical usefulness of cervicogram as a primary screening test for cervical neoplasia. Yonsei Med J 2005;46:213-20.
24. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Updating the natural history of HPV and anogenital cancer. Chapter 5. Vaccine 2006;24(Suppl 3):S42-51.
25. Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst 2006;98:765-74.
26. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol 2010;11:249-57.
27. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst 2008;100:492-501.
28. Ronco G, Cuzick J, Segnan N, Brezzi S, Carozzi F, Folicaldi S, et al. HPV triage for low grade (L-SIL) cytology is appropriate for women over 35 in mass cervical cancer screening using liquid based cytology. European Journal of Cancer 2007;43:476-80.
29. Ronco G, Brezzi S, Carozzi F, Dalla Palma P, Giorgi-Rossi P, Minucci D, et al. The New Technologies for Cervical Cancer Screening randomised controlled trial: an overview of results during the first phase of recruitment. Gynecol Oncol 2007;107:S230-2.
30. Kotaniemi-Talonen L, Anttila A, Malila N, Tarkkanen J, Laurila P, Hakama M, et al. Screening with a primary human papillomavirus test does not increase detection of cervical cancer and intraepithelial neoplasia 3. Eur J Cancer 2008;44:565-71.
31. Leinonen M, Nieminen P, Kotaniemi-Talonen L, Malila N, Tarkkanen J, Laurila P, et al. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. J Natl Cancer Inst 2009;101:1612-23.
32. Anttila A, Kotaniemi-Talonen L, Leinonen M, Hakama M, Laurila P, Tarkkanen J, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. BMJ 2010;340:c1804.
33. Anttila A, Hakama M, Kotaniemi-Talonen L, Nieminen P. Alternative technologies in cervical cancer screening: a randomised evaluation trial. BMC Public Health 2006;6:252.
34. Kotaniemi-Talonen L, Nieminen P, Anttila A, Hakama M. Routine cervical screening with primary HPV testing and cytology triage protocol in a randomised setting. Br J Cancer 2005;93:862-7.
35. Bulkmans NW, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. Lancet 2007;370:1764-72.
36. Bulkmans NW, Rozendaal L, Snijders PJ, Voorhorst FJ, Boeke AJ, Zandwijken GR, et al. POBASCAM, a population-

 http://dx.doi.org/10.3802/jgo.2013.24.2.186

based randomized controlled trial for implementation of high-risk HPV testing in cervical screening: design, methods and baseline data of 44,102 women. Int J Cancer 2004;110:94-101.
37. Naucler P, Ryd W, Tornberg S, Strand A, Wadell G, Elfgren K, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med 2007;357:1589-97.
38. Naucler P, Ryd W, Tornberg S, Strand A, Wadell G, Elfgren K, et al. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. J Natl Cancer Inst 2009;101:88-99.
39. Elfgren K, Rylander E, Radberg T, Strander B, Strand A, Paajanen K, et al. Colposcopic and histopathologic evaluation of women participating in population-based screening for human papillomavirus deoxyribonucleic acid persistence. Am J Obstet Gynecol 2005;193:650-7.
40. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol 2009;10:672-82.
41. Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, et al. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. Health Technol Assess 2009;13:1-150, iii-iv.
42. Kitchener HC, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A, et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. Br J Cancer 2006;95:56-61.
43. Sargent A, Bailey A, Almonte M, Turner A, Thomson C, Peto J, et al. Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial. Br J Cancer 2008;98:1704-9.
44. Jones BA, Novis DA. Follow-up of abnormal gynecologic cytology: a college of American pathologists Q-probes study of 16132 cases from 306 laboratories. Arch Pathol Lab Med 2000;124:665-71.
45. ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 2003;188:1383-92.
46. Ferris DG, Wright TC Jr, Litaker MS, Richart RM, Lorincz AT, Sun XW, et al. Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy? J Fam Pract 1998;46:125-34.
47. Manos MM, Kinney WK, Hurley LB, Sherman ME, Shieh-Ngai J, Kurman RJ, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. JAMA 1999;281:1605-10.
48. Lonky NM, Felix JC, Naidu YM, Wolde-Tsadik G. Triage of atypical squamous cells of undetermined significance with hybrid capture II: colposcopy and histologic human papillomavirus correlation. Obstet Gynecol 2003;101:481-9.
49. Jeronimo J, Khan MJ, Schiffman M, Solomon D. Does the interval between papanicolaou tests influence the quality of cytology? Cancer 2005;105:133-8.
50. Guido R, Schiffman M, Solomon D, Burke L. Postcolposcopy management strategies for women referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous cells of undetermined significance: a two-year prospective study. Am J Obstet Gynecol 2003;188:1401-5.
51. Veljovich DS, Stoler MH, Anderson WA, Covell JL, Rice LW. Atypical glandular cells of undetermined significance: a five-year retrospective histopathologic study. Am J Obstet Gynecol 1998;179:382-390.
52. Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Soroski JI. Dysplasia associated with atypical glandular cells on cervical cytology. Obstet Gynecol 2005;105:494-500.
53. Derchain SF, Rabelo-Santos SH, Sarian LO, Zeferino LC, de Oliveira Zambeli ER, do Amaral Westin MC, et al. Human papillomavirus DNA detection and histological findings in women referred for atypical glandular cells or adenocarcinoma in situ in their Pap smears. Gynecol Oncol 2004;95:618-23.
54. Mulhem E, Amin M, Copeland J, Sharma J, Hunter S. Type-specific human papillomavirus DNA detected in atypical glandular cell Pap tests. Acta Cytol 2012;56:155-9.
55. Ronnett BM, Manos MM, Ransley JE, Fetterman BJ, Kinney WK, Hurley LB, et al. Atypical glandular cells of undetermined significance (AGUS): cytopathologic features, histopathologic results, and human papillomavirus DNA detection. Hum Pathol 1999;30:816-25.
56. Chhieng DC, Elgert P, Cohen JM, Cangiarella JF. Clinical significance of atypical glandular cells of undetermined significance in postmenopausal women. Cancer 2001;93:1-7.
57. Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Sorosky JI. Lack of adherence to practice guidelines for women with atypical glandular cells on cervical cytology. Obstet Gynecol 2005;105:501-6.
58. Bao YP, Smith JS, Qiao YL; ACCPAB members. Human papillomavirus type distribution in women from Asia: a meta-analysis. Int J Gynecol Cancer 2008;18:71-9.
59. Alvarez RD, Wright TC; Optical Detection Group. Effective

cervical neoplasia detection with a novel optical detection system: a randomized trial. Gynecol Oncol 2007;104:281-9.
60. ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. Am J Obstet Gynecol 2003;188:1393-400.
61. Chute DJ, Covell J, Pambuccian SE, Stelow EB. Cytologic-histologic correlation of screening and diagnostic Papanicolaou tests. Diagn Cytopathol 2006;34:503-6.
62. Lee JK, Kim MK, Song SH, Hong JH, Min KJ, Kim JH, et al. Comparison of human papillomavirus detection and typing by hybrid capture 2, linear array, DNA chip, and cycle sequencing in cervical swab samples. Int J Gynecol Cancer 2009;19:266-72.
63. Numnum TM, Kirby TO, Leath CA III, Huh WK, Alvarez RD, Straughn JM Jr. A prospective evaluation of "see and treat" in women with HSIL Pap smear results: is this an appropriate strategy? J Low Genit Tract Dis 2005;9:2-6.
64. Holschneider CH, Ghosh K, Montz FJ. See-and-treat in the management of high-grade squamous intraepithelial lesions of the cervix: a resource utilization analysis. Obstet Gynecol 1999;94:377-85.
65. Dunn TS, Burke M, Shwayder J. A "see and treat" management for high-grade squamous intraepithelial lesion pap smears. J Low Genit Tract Dis 2003;7:104-6.
66. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 Consensus guidelines for the management of women with cervical intraepithelial neoplasia and adenocarcinoma in situ. Am J Obstet Gynecol 2007;197:340-5.
67. International Agency for Research on Cancer (IARC). IARC handbooks of cancer: cervix cancer screening. Vol 10. Lyon: IARC; 2005.
68. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. Br J Cancer 2005;93:575-81.
69. Kulasingam SL, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. JAMA 2002;288:1749-57.
70. Mayrand MH, Duarte-Franco E, Coutlee F, Rodrigues I, Walter SD, Ratnam S, et al. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). Int J Cancer 2006;119:615-23.
71. Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med 2007;357:1579-88.
72. Cardenas-Turanzas M, Nogueras-Gonzalez GM, Scheurer ME, Adler-Storthz K, Benedet JL, Beck JR, et al. The performance of human papillomavirus high-risk DNA testing in the screening and diagnostic settings. Cancer Epidemiol Biomarkers Prev 2008;17:2865-71.
73. Petry KU, Menton S, Menton M, de Carvalho Gomes H, Holz B, Schopp B, et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. Br J Cancer 2003;88:1570-7.
74. Kjaer S, Hogdall E, Frederiksen K, Munk C, van den Brule A, Svare E, et al. The absolute risk of cervical abnormalities in high-risk human papillomavirus-positive, cytologically normal women over a 10-year period. Cancer Res 2006;66:10630-6.
75. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst 2005;97:1072-9.
76. Cho EJ, Do JH, Kim YS, Bae S, Ahn WS. Evaluation of a liquid bead array system for high-risk human papillomavirus detection and genotyping in comparison with Hybrid Capture II, DNA chip and sequencing methods. J Med Microbiol 2011;60:162-71.
77. Hong JH, Song SH, Kim JK, Han JH, Lee JK. Comparison of the novel human papillomavirus 4 auto-capillary electrophoresis test with the hybrid capture 2 assay and with the PCR HPV typing set test in the detection of high-risk HPV including HPV 16 and 18 genotypes in cervical specimens. J Korean Med Sci 2009;24:579-84.
78. Song SH, Hong JH, Kwak SH, Lee JK, Kim MK. Clinical performance assessment of five human papillomavirus DNA tests using liquid-based cytology samples. J Obstet Gynaecol Res 2012;38:408-14.
79. Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol 2011;12:880-90.
80. Fetterman B, Shaber R, Pawlick G, Kinney WK. Human papillomavirus DNA testing in routine clinical practice for

 http://dx.doi.org/10.3802/jgo.2013.24.2.186

prediction of underlying cervical intraepithelial neoplasia 2/3+ at initial evaluation and in follow-up of women with atypical glandular cell Papanicolaou tests. J Low Genit Tract Dis 2006;10:178-9.
81. Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003;362:1871-6.
82. Clavel C, Masure M, Bory JP, Putaud I, Mangeonjean C, Lorenzato M, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: as study of 7932 women. Br J Cancer 2001;84:1616-23.
83. Wright TC Jr, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. Am J Obstet Gynecol 2012;206:46.e1-46.e11.
84. Kjaer SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J Natl Cancer Inst 2010;102:1478-88.
85. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol 2003;157:218-26.
86. Brown DR, Shew ML, Qadadri B, Neptune N, Vargas M, Tu W, et al. A longitudinal study of genital human papillomavirus infection in cohort of closely followed adolescent women. J Infect Dis 2005;191:182-92.
87. Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, et al. Incidence, clearance and predictors of human papillomavirus infection in women. CMAJ 2003;168:421-5.
88. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998;338:423-8.
89. Wetta LA, Matthews KS, Kemper ML, Whitworth JM, Fain ET, Huh WK, et al. The management of cervical intraepithelial neoplasia during pregnancy: is colposcopy necessary? J Low Genit Tract Dis 2009;13:182-5.
90. Fader AN, Alward EK, Niederhauser A, Chirico C, Lesnock JL, Zwiesler DJ, et al. Cervical dysplasia in pregnancy: a multi-institutional evaluation. Am J Obstet Gynecol 2010;203:113.e1-113.e6.
91. Vlahos G, Rodolakis A, Diakomanolis E, Stefanidis K, Haidopoulos D, Abela K, et al. Conservative management of cervical intraepithelial neoplasia (CIN(2-3)) in pregnant women. Gynecol Obstet Invest 2002;54:78-81.
92. Serati M, Uccella S, Laterza RM, Salvatore S, Beretta P, Riva C, et al. Natural history of cervical intraepithelial neoplasia during pregnancy. Acta Obstet Gynecol Scand 2008;87:1296-300.
93. Kreimer AR, Guido RS, Solomon D, Schiffman M, Wacholder S, Jeronimo J, et al. Human papillomavirus testing following loop electrosurgical excision procedure identifies women at risk for posttreatment cervical intraepithelial neoplasia grade 2 or 3 disease. Cancer Epidemiol Biomarkers Prev 2006;15:908-14.

<Appendix A> Summary of recommendations

***Full paper with evidence tables is available at ejgo.org.**

1. General screening guideline

Recommendation 1 – When to start screening (adaptation)

All women ≥20 years of age that have commenced sexual intercourse should undergo cervical cancer screening tests. This is not recommended for women below the age of 20 because despite the high incidence of HPV infection, there is a high rate of spontaneous regression and a very low incidence of invasive cervical cancer. However, the screening test can be performed when cervical cancer or preinvasive disease is suspected (Level of evidence: very low; Recommendation: strong).

Recommendation 2 – When to discontinue screening (expert consensus)

Cervical cancer screening tests can be discontinued in women ≥70 years old after 3 consecutive negative Pap tests within 10 years. However, a woman should continue undergoing screening tests continuously regardless of age if she has a history of CIN 2 or greater or she does not know her previous Pap test results (Level of evidence: very low; Recommendation: strong).

Recommendation 3 – Screening interval (expert consensus)

Although the screening guidelines of Western countries recommend a 3-year interval, in Korea, annual screening with cervical cytology is recommended for women aged 20 to 70 years due to the high incidence of cervical cancer, easy access to screening, and low medical costs (Level of evidence: very low; Recommendation: strong).

Recommendation 4 – Screening modality (conventional Pap versus liquid-based cytology) (adaptation)

Based on previous literature, liquid-based cytology is not superior to conventional cytology in terms of sensitivity and specificity; however, liquid-based cytology can reduce the number of inadequate specimens. Both liquid-based cytology and conventional cytology are usable in Korea (Level of evidence: moderate; Recommendation: strong).

Recommendation 5 – Cervicography as an adjunct to cytology (de novo)

The use of a combination of cervical cytology and cervicography as a screening test is not commonly recommended due to increased false positivity. However, this combination may be beneficial in terms of improving sensitivity (Level of evidence: low; Recommendation: weak).

Recommendation 6 – HPV DNA test (adaptation)

Due to the high false-positivity rate of the test and the frequent spontaneous clearance of HPV, the HPV DNA test is not recommended for women <30 years of age. The screening interval can be extended to 2 years in women ≥30 years old with both a negative cytology and negative HPV (Level of evidence: high; Recommendation: strong).

Recommendation 7 – Screening interval (expert consensus)

Although the prevalence of invasive cervical cancer and preinvasive diseases is expected to decrease due to vaccination, a change in the screening interval should be considered after more clinical data have been accumulated (Level of evidence: very low; Recommendation: weak).

Recommendation 8 – Hysterectomized women (adaptation/expert consensus)

Women who have undergone hysterectomy should continue with screening tests if they have a history of CIN grade 2 or greater or if they do not know their previous cytology results (Level of evidence: very low; Recommendation: strong).

2. ASC/AGC

(1) ASC-US

Recommendation 1 (adaptation)

Repeat cytology can be performed for women with ASC-US (Level of evidence: high; Recommendation: strong).

Recommendation 2 (adaptation)

An HPV DNA test can be performed for women with ASC-US (Level of evidence: high; Recommendation: strong).

Recommendation 3 (adaptation)

Immediate colposcopy can be performed for women with ASC-US (Level of evidence: high; Recommendation: strong).

Recommendation 4 (adaptation)

When CIN grade 1 or less is confirmed after satisfactory colposcopy, either cytology at 6-month intervals or an HPV DNA test at 12 months is recommended (Level of evidence: moderate; Recommendation: strong).

Recommendation 5 (expert consensus)

After 2 consecutive negative cytologies 6 months apart or

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a negative HPV DNA test at 12 months, women with ASC-US can return to routine screening (Level of evidence: very low; Recommendation: strong).

(2) ASC-H

Recommendation 1 (expert consensus)
When CIN grade 2 or greater is not confirmed by colposcopy-directed biopsy in women with ASC-H, a review of the cytological and histological specimens can be performed (Level of evidence: very low; Recommendation: weak).

Recommendation 2 (expert consensus)
When CIN grade 2 or greater is not confirmed by colposcopy-directed biopsy in women with ASC-H, 2 consecutive cytology tests at 6-month intervals and colposcopy can be performed (Level of evidence: very low; Recommendation: strong).

Recommendation 3 (expert consensus)
When CIN grade 2 or greater is not confirmed by colposcopy-directed biopsy in women with ASC-H, women can return to routine screening after 2 consecutive negative cytology tests at 6-month intervals and a negative colposcopy (Level of evidence: very low; Recommendation: strong).

(3) AGC

Recommendation 1 (adaptation)
An HPV DNA test is recommended for women with AGC (Level of evidence: very low; Recommendation: strong).

Recommendation 2 (adaptation)
Colposcopy, endocervical curettage, and endometrial biopsy should be performed in women with AGC (Level of evidence: very low; Recommendation: strong).

3. LSIL/HSIL

(1) LSIL

Recommendation 1 (adaptation)
Colposcopy is recommended for women with LSIL (Level of evidence: moderate; Recommendation: strong).

Recommendation 2 (expert consensus)
If 2 consecutive cytology tests 6 months apart are negative for intraepithelial neoplasia or if an HPV DNA test is negative at 12 months, women with LSIL can return to routine screening (Level of evidence: very low; Recommendation: strong).

(2) HSIL

Recommendation 1 (adaptation)
Immediate diagnostic excisional procedures, such as the loop electrosurgical excision procedure or conization, can be performed in women with HSIL without colposcopic examination (Level of evidence: very low; Recommendation: strong).

Recommendation 2 (adaptation)
Diagnostic excisional procedures can be performed in women with HSIL if CIN grade 2 or 3 is not identified by colposcopy-directed biopsy (Level of evidence: very low; Recommendation: strong).

Recommendation 3 (expert consensus)
A review of cytological and histological specimens might be helpful in women with HSIL if CIN grade 2 or 3 is not identified by colposcopy-directed biopsy (Level of evidence: very low; Recommendation: strong).

Recommendation 4 (expert consensus)
When CIN grade 2 or 3 is not identified in women with HSIL by colposcopy-directed biopsy, follow-up with 2 cytology tests 6 months apart and colposcopy can be performed (Level of evidence: very low; Recommendation: strong).

Recommendation 5 (expert consensus)
When CIN 2 or 3 is not identified in women with HSIL by colposcopy-directed biopsy, they can return to routine screening if 2 consecutive cytology tests 6 months apart and colposcopy are negative (Level of evidence: very low; Recommendation: strong).

Recommendation 6 (expert consensus)
When the margin status is not known after excisional procedures, either cytology at 6 months or an HPV DNA test at 12 months can be performed (Level of evidence: very low; Recommendation: strong).

4. HPV DNA tests

Recommendation 1 (adaptation)
An HPV DNA test can be performed in women ≥30 years old along with cervical cytology in order to reduce the false negativity of cytology (Level of evidence: high; Recommendation: strong).

Recommendation 2 (de novo)

Use of the hybrid capture assay and HPV DNA genotyping test (HPV DNA chip, PCR test) is recommended because of their equivalent sensitivity and specificity for the detection of CIN grade 2 or greater as well as the concordance among various HPV DNA tests (Level of evidence: low; Recommendation: weak).

Recommendation 3 (adaptation)

Use of the HPV genotyping test is recommended in cytology-negative, HPV-positive women. If HPV 16 or 18 is detected, referral to gynecologic oncologists and colposcopic examination are recommended. In women who are positive for HPVs other than 16 or 18, an HPV DNA test and HPV genotyping test can be performed 1 year later (Level of evidence: low; Recommendation: strong).

5. Special situations (adolescent/pregnant women)

Recommendation 1 (adaptation)

An HPV DNA test should not be performed in adolescent women with ASC-US or LSIL (Level of evidence: low; Recommendation: strong).

Recommendation 2 (adaptation)

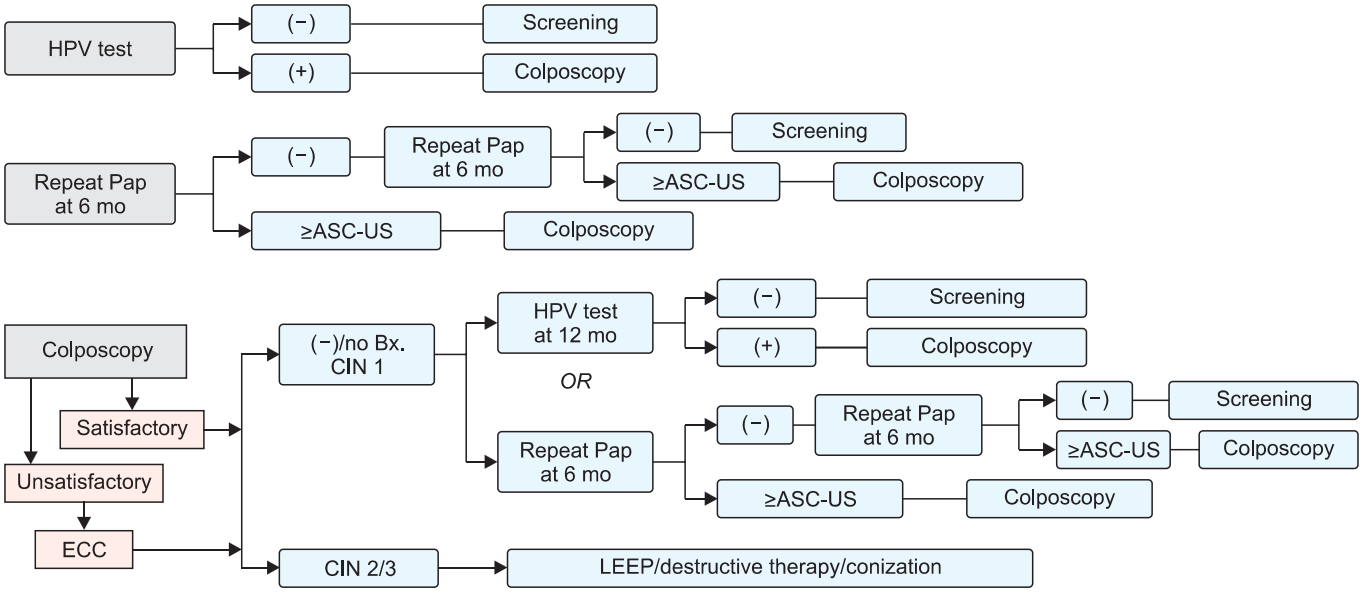
Postpartum colposcopy is safe for pregnant women with ASC-US or LSIL (Level of evidence: low; Recommendation: strong).

Recommendation 3 (adaptation)

Diagnostic excisional procedures can be deferred in pregnant women with histologically confirmed CIN grade 2 or greater (Level of evidence: low; Recommendation: strong).

<Appendix B> Flow charts of screening guidelines

1. Atypical glandular cells-undetermined significance



ASC-US, atypical squamous cells of undetermined significance; Bx, biopsy; CIN, cervical intraepithelial neoplasias; ECC, endocervical curettage; HPV, human papillomavirus, LEEP, loop electrosurgical excision procedure, Pap, Papanicolaou test.

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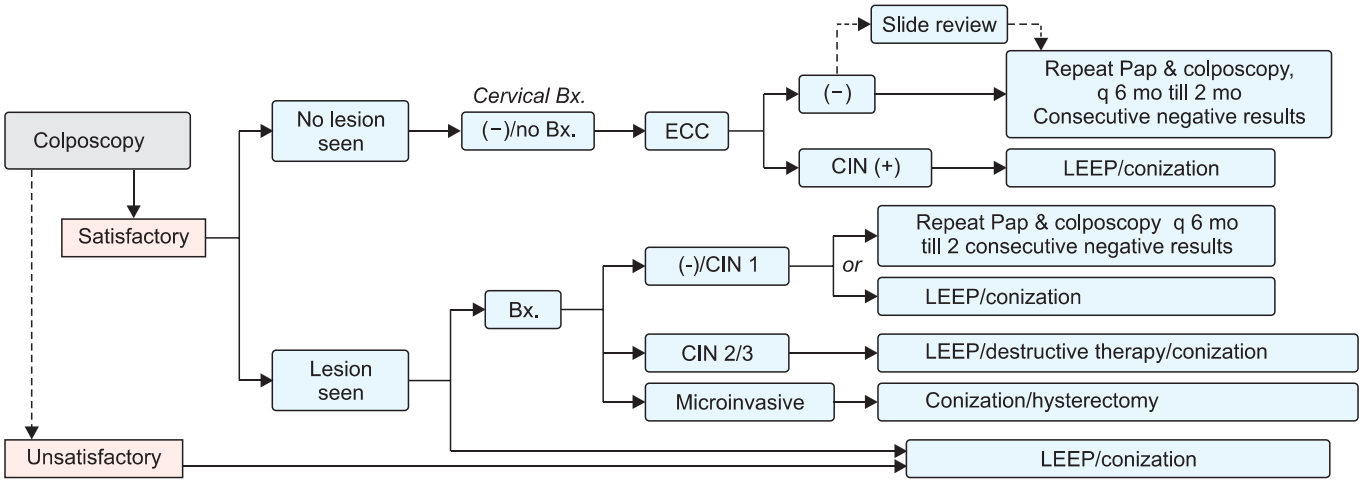
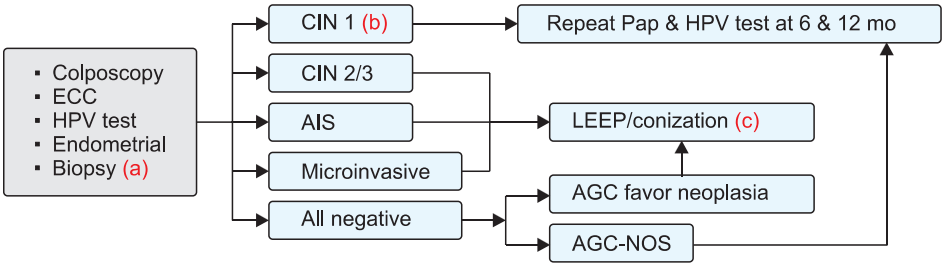
2. Atypical squamous cells-cannot exclude a high grade squamous intraepithelial lesion



Bx, biopsy; CIN, cervical intraepithelial neoplasias; ECC, endocervical curettage; LEEP, loop electrosurgical excision procedure; Pap, Papanicolaou test.

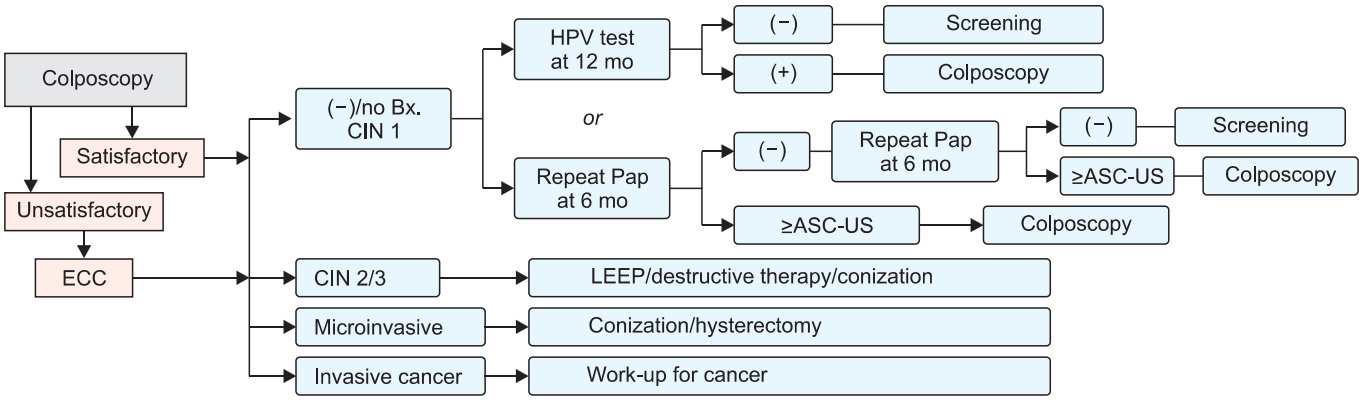
3. Atypical glandular cells



AIN, adenocarcinoma *in situ*; AGC, atypical glandular cells; NOS, not otherwise specified; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; Pap, Papanicolaou test.

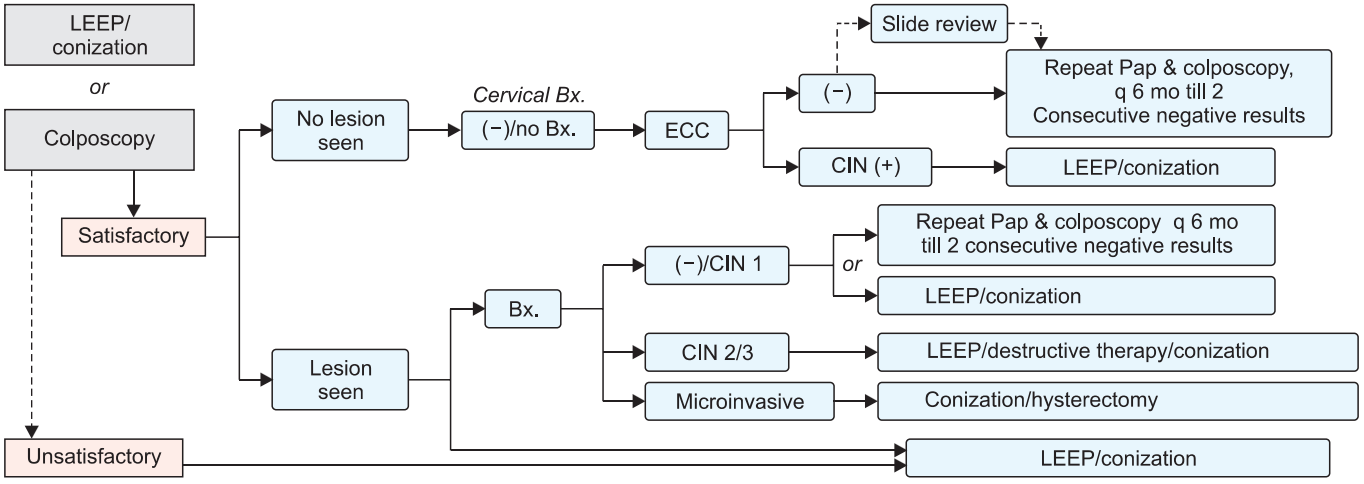
(a) Endometrial biopsy can be omitted if the patients meet the criteria described below:
(1) <35 years of age, (2) low risk for endometrial cancer (i.e., no obesity, polycystic ovarian syndrome, tamoxifen usage, infertility, anovulation, or family history of colorectal or endometrial cancer), (3) no abnormal uterine bleeding, and (4) no atypical endometrial cells.
(b) Patients with CIN grade 1 limited to the endocervix can be followed up with cytology and an HPV DNA test.
(c) Conization is recommended if the lesion is located in the endocervix (or additional resection is recommended if LEEP was performed initially).

4. Low-grade squamous intraepithelial lesions



ASC-US, atypical squamous cells of undetermined significance; Bx, biopsy; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; Pap, Papanicolaou test.

5. High-grade squamous intraepithelial lesions



Bx, biopsy; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; Pap, Papanicolaou test.

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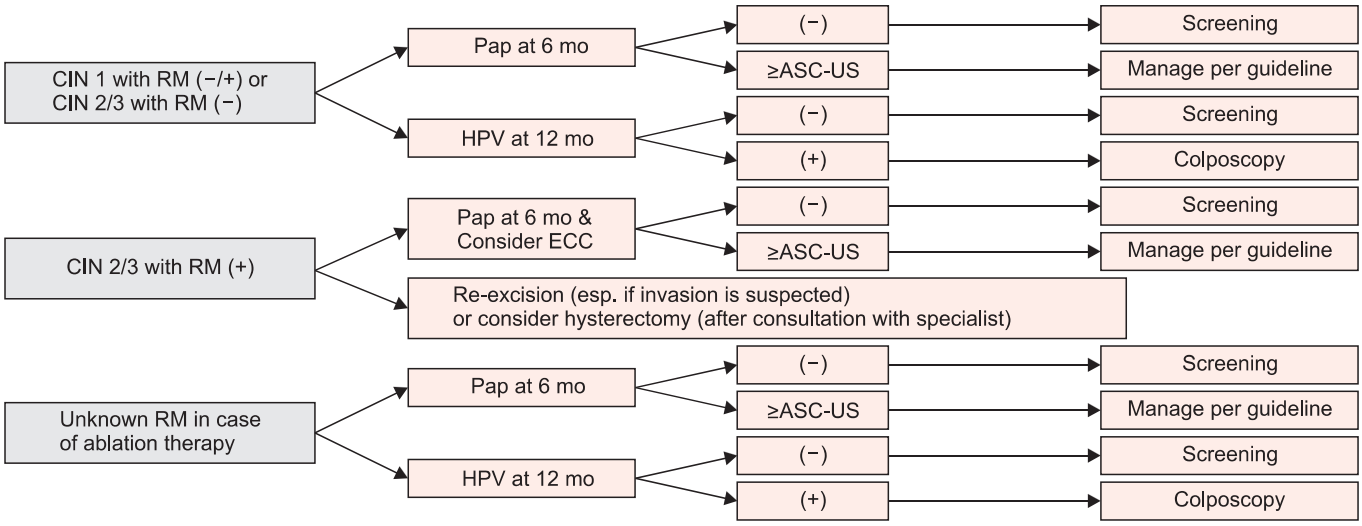
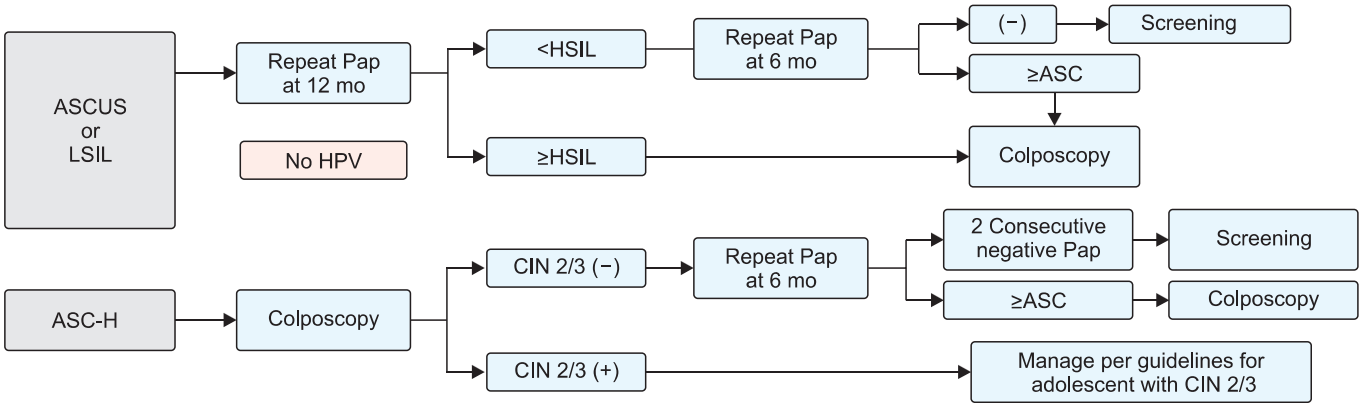
6. Follow-up after treatment of CIN with excisional procedures or ablation



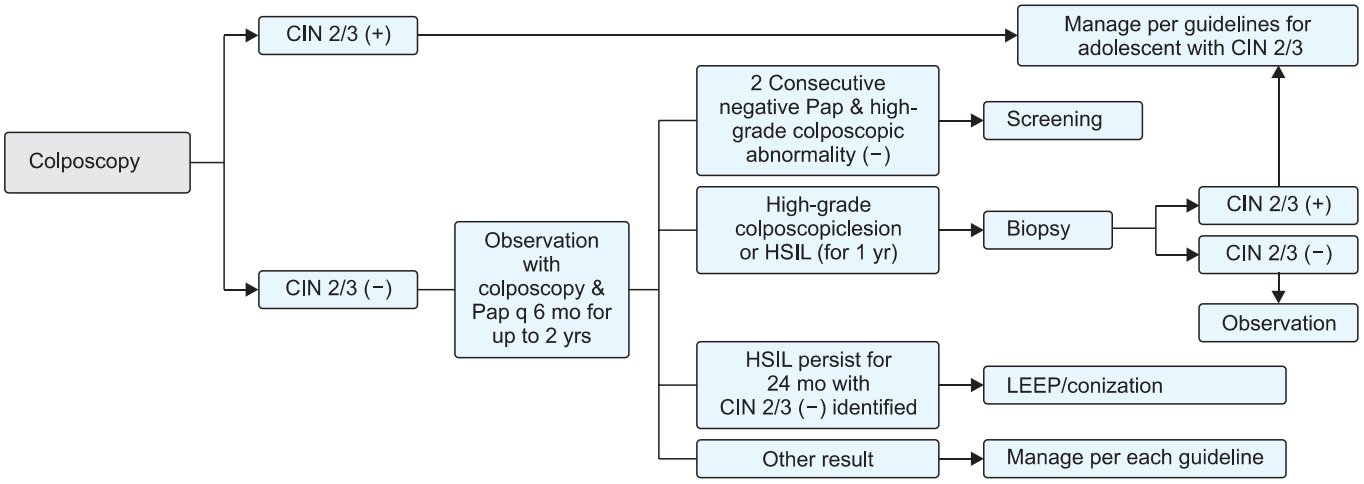
ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; HPV, human papillomavirus; Pap, Papanicolaou test; RM, resection margin.

7. Adolescents with ASC-US, LSIL, or ASC-H



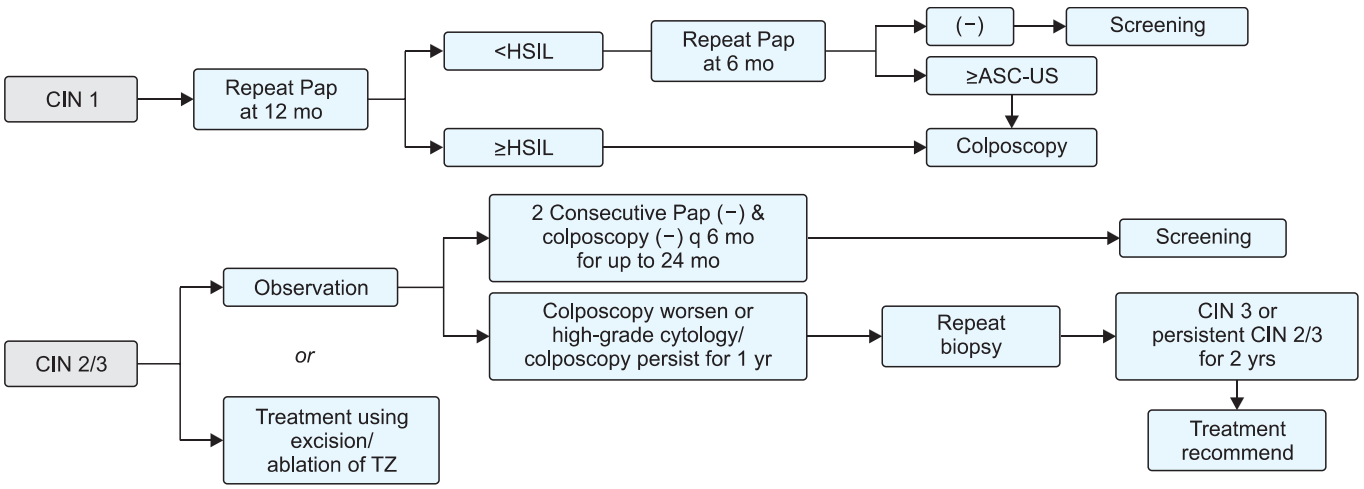
ASC-H, atypical squamous cells (cannot exclude a high-grade squamous intraepithelial lesion); ASC-US, atypical squamous cells of undetermined significance; Bx, biopsy; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolaou test.

8. Adolescents with HSIL



CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; Pap, Papanicolaou test.

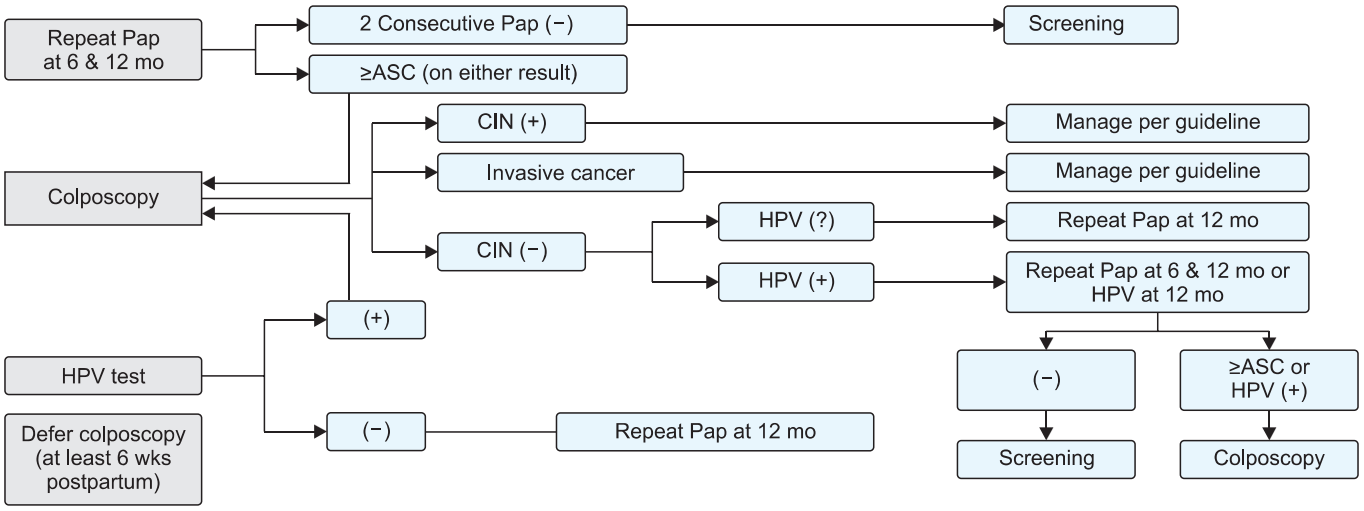
9. Adolescents with CIN 1-3



ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; Pap, Papanicolaou test; TZ, transformation zone.

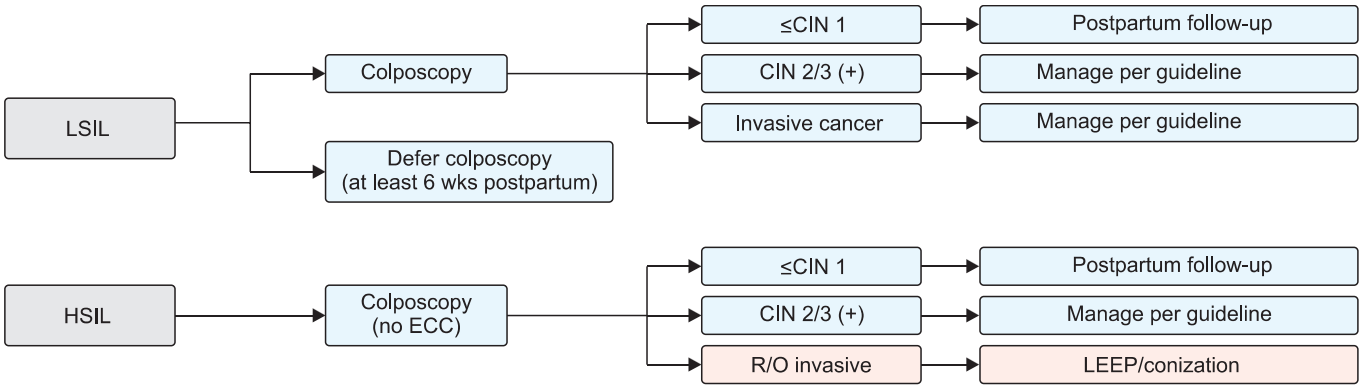
http://dx.doi.org/10.3802/jgo.2013.24.2.186

10. Pregnant women with ASC-US



ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; Pap, Papanicolaou test.

11. Pregnant women with LSIL or HSIL



CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion; R/O, rule out.