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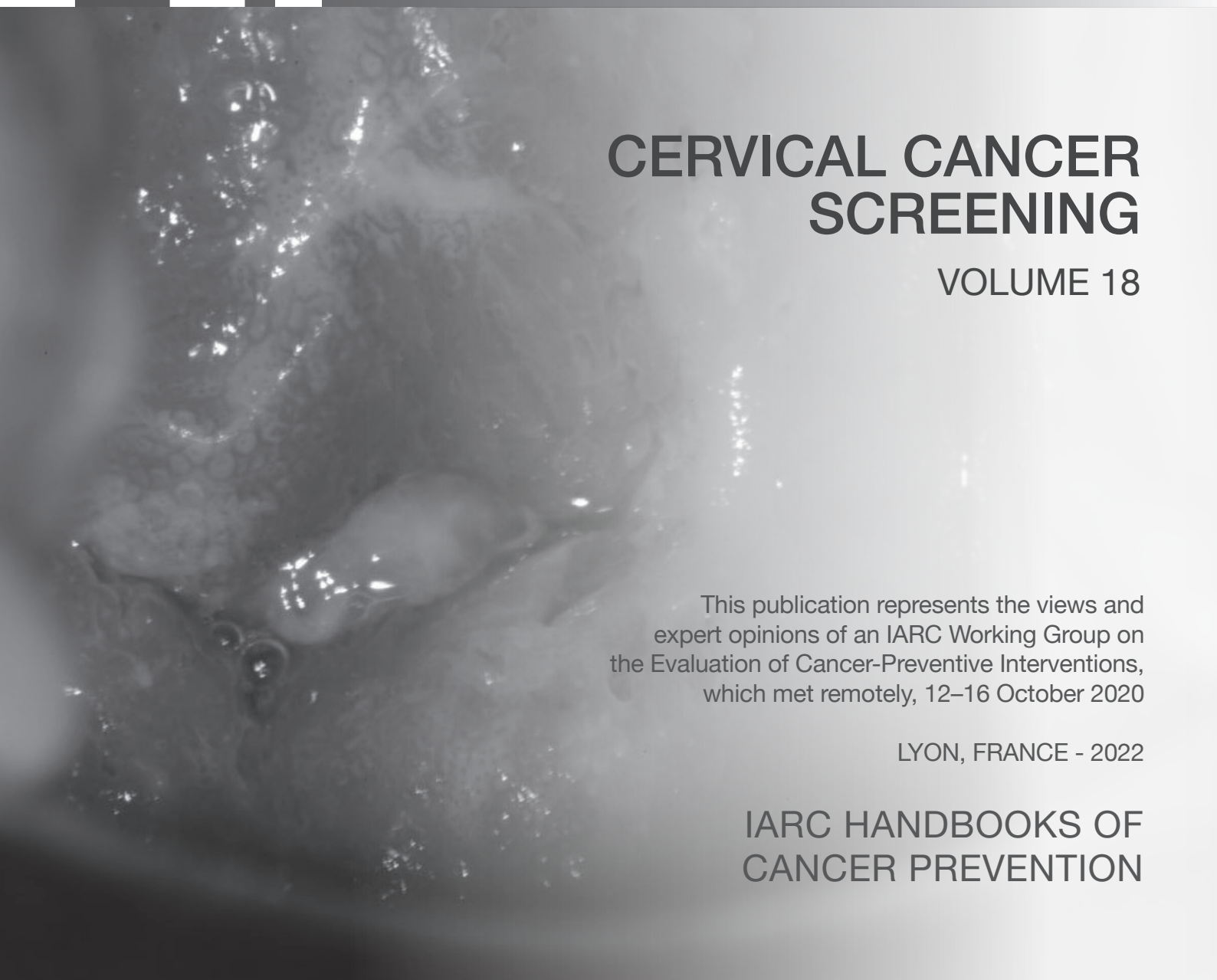

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4.5 Colposcopy

A colposcope is a low-magnification, light-illuminated, stereoscopic, binocular field microscope. It is used for visual examination of the lower genital tract, including the cervix. Colposcopic examination facilitates the identification of the TZ (see Fig. 1.18 in Section 1.2.5), which is where most cervical cancers originate, and the characterization and localization of intraepithelial lesions in the lower genital tract to guide biopsies, where necessary, for confirmation of disease status.

In the 20th century, colposcopy was used in many countries as part of a standard gynaecological examination (van Niekerk et al., 1998). It is still used as a primary screening tool, together with cytology, by some clinicians in a few countries in Europe and Latin America. The rationale for this combined testing approach is that the use of the colposcope to guide cytology sample collection may decrease the false-negative and false-positive rates associated with blind sampling, and may also reduce the need for women to be recalled for repeat cytology (van Niekerk et al., 1998). However, there is no agreement about whether colposcopic impression improves the quality of cytology testing (Hilgarth & Menton, 1996; Schulmeyer et al., 2020). Moreover, it has been shown that colposcopy does not perform well for primary screening (Leeson et al., 2014; AEPCC, 2018). In contrast, there is wide consensus that colposcopy is the cornerstone of management of women with a positive Pap test result or symptomatic women. Table 4.33 shows the indications for performing colposcopy.

4.5.1 Technical description of a colposcopic examination

In 1925, Hinselmann (Hinselmann, 1925; Jordan, 1985) designed the colposcope and described how to enhance the colposcopic view of the cervical epithelium to recognize cervical cancer and precancer by staining the cervix with acetic acid (Soutter, 1993). In 1929, Schiller introduced the use of iodine and showed that areas of the cervix harbouring early cervical cancer did not stain with iodine, in contrast to the dark staining of normal squamous epithelium of the ectocervix (Schiller, 1933; Colgan & Lickrish, 1990; Bappa & Yakasai, 2013). Initially colposcopy was used for primary screening, but during the 1960s studies showed that colposcopy enabled the more accurate localization of suspected lesions after cytology testing, which made it possible to more accurately select biopsy sites and reduced the need for diagnostic conization (Beller & Khatamee, 1966; Ruiz Moreno, 2010). These studies established the basis for the current use of colposcopy within the cytology–colposcopy–histology sequence.

When colposcopy is performed in a competent and quality-assured service, it is a comprehensive examination and provides information that is crucial for optimal clinical management. Colposcopy has important advantages, particularly for women with endocervical or glandular disease, very large lesions, or suspicion of invasion or microinvasive disease, and for lesions that are present during pregnancy or for residual or recurrent disease after treatment.

A colposcopic examination aims to:

- determine the adequacy of the examination;
- determine the site, size, and type of the TZ;
- recognize intraepithelial abnormality where present;
- identify the most accurate biopsy site for sampling; and
- facilitate precise treatment.

Table 4.33 Indications for performing colposcopy

Abnormal results in screening tests (cytology or HPV test) suggesting an increased risk of cervical intraepithelial neoplasia
Follow-up of patients with an intraepithelial lesion before or after treatment
Excisional treatment of premalignant lesions of the cervix, as an auxiliary method to guide the procedure
Presence of clinically apparent leukoplakia or any suspicious-looking or abnormal-looking cervix in the gynaecological examination
Presence of symptoms suggesting cervical cancer (unusual bleeding, abnormal vaginal discharge, etc.)

HPV, human papillomavirus.
Compiled by the Working Group.

(a) The colposcope

A colposcope has the following features (for more details, see Prendiville & Sankaranarayanan, 2017):

- A support for the colposcope head, which is the working part. This support can be either a simple vertical stand that is positioned between the operator's legs or an adjustable horizontal arm connected to a weighted stand that is positioned lateral to the patient and the operator and is attached to the colposcope head by a universal joint.
- Binocular view, so that depth of field may be appreciated. (Improving image-capture systems may reduce the disadvantages of monocular devices.) Depth of field is crucial for accurate assessment of the TZ or when performing excision of the TZ.
- Variable magnification, either stepwise or using a zoom facility.
- White light from a halogen light or, preferably, a light-emitting diode (LED) lamp.
- A green or blue filter, or green or blue light.
- Image capture.
- Facility to adjust the eyepieces to the operator's interpupillary distance.
- Fine focus adjustment.

(b) Performing a colposcopic examination

For a colposcopic examination to be performed competently, the following are required: a well-trained colposcopist, a well-equipped examination room (see Prendiville & Sankaranarayanan, 2017), and a skilled attendant.

The examiner inserts a speculum to expose the cervix and position it in a plane perpendicular to the colposcopic line of vision. The colposcope enables the examination of the whole lower genital tract, including the cervix, vagina, and vulva. The examiner first assesses whether the examination can be performed adequately (Bornstein et al., 2012). If so, the next step is to examine the cervix at low-power magnification and gently cleanse it with saline. The hormonal status and degree of inflammation are assessed. Once adequacy has been confirmed, the TZ is examined at low-power magnification, perhaps with a green filter, before 3% to 5% acetic acid is applied. Use of an endocervical forceps (preferably the Desjardins or Kurihara forceps) is often needed to achieve full visualization of the upper limit of the TZ, particularly in postmenopausal women. Examination of the TZ is performed at both low-power and high-power magnification. Documentation of the examination findings completes the colposcopy, and a management plan may be discussed with the patient.

Table 4.34 Modifications in colposcopic terminology over time

Terminology (name, year)	Normal findings	Abnormal findings	Other terms	Reference
Hinselmann, 1933	Thick leukoplakia	Mosaic leukoplakia	Cervico-uterine ectopy	ASCCP guidelines, Mayeaux & Cox (2013)
Coppleson, 1960	Grade I: not suspicious, white semi-transparent epithelium, flat, with indistinct borders	Grade II: suspicious white epithelium Grade III: opaque epithelium with very suspicious defined borders	Transformation zone	Reid & Campion (1989)
IFCPC Graz, 1975	Normal colposcopy	Atypical transformation zone	Colposcopy not satisfactory Miscellaneous	Stafl (1976)
Reid score, 1985	Category 1: benign, minor dysplasia	Category 2: intermediate Category 3: suspicious	Four criteria: border, colour, vessels, iodine uptake	Reid & Campion (1989)
IFCPC Rome, 1990	Normal colposcopy Cylindrical epithelium: ectopy	Abnormal colposcopy within or outside the transformation zone Fine or coarse mosaic or punctation	Miscellaneous not acetowhite	Stafl & Wilbanks (1991)
IFCPC Barcelona, 2002	Type 1, 2, 3 transformation zone	Minor or major changes Suggestive of low-grade or high-grade lesion	Colposcopy suggestive of invasive cancer	Walker et al. (2003)
IFCPC Rio de Janeiro, 2011	Includes metaplasia and deciduosis	Grade 1 or grade 2 changes Location of lesion, number of cervical quadrants the lesion covers New signs: inner border sign and ridge sign	Includes description of vaginal lesions Incorporates types of excision	Bornstein et al. (2012)

ASCCP, American Society for Colposcopy and Cervical Pathology; IFCPC, International Federation of Cervical Pathology and Colposcopy.

(c) Colposcopic terminology and correlation with histological diagnosis

Different classifications have been used throughout the 90-year history of colposcopy (AEPCC, 2018). Table 4.34 shows the most relevant and clinically used global colposcopic classifications and the modifications that have been introduced over time. Currently, the classification that is most commonly used in health-care practice worldwide is that adopted unanimously by the International Federation of Cervical Pathology and Colposcopy (IFCPC). The most recent IFCPC terminology, prepared in 2011 (Bornstein et al., 2012), is summarized in Table 4.35. However, in this section, results from scientific publications are presented according to the terminology as reported originally, wherever possible.

Substantial information is available on the correlation between the categorization of lesions using the IFCPC classification and the histological diagnosis. Some studies have reported a good correlation between the colposcopic impression and the final diagnosis (Ferris & Litaker, 2005). Some particular findings (such as coarse punctation, coarse mosaic or dense acetowhitening, inner border sign, and ridge sign) have been shown to have a good predictive accuracy for HSIL+/CIN2+ (Vercellino et al., 2013; Beyer et al., 2017; Li et al., 2017), although the sensitivity of colposcopic impression for detection of HSIL+/CIN2+ ranged from 20% to 100%

Table 4.35 2011 IFCPC colposcopic terminology of the cervix

Section	Pattern	
General assessment	Adequate or inadequate; if inadequate, for what reason (e.g. cervix obscured by inflammation, bleeding, scar) Squamocolumnar junction visibility: completely visible, partially visible, not visible Transformation zone types 1, 2, 3	
Normal colposcopic findings	Original squamous epithelium: mature, atrophic Columnar epithelium; ectopy or ectropion Metaplastic squamous epithelium; nabothian cysts; crypt (gland) openings Deciduosis in pregnancy	
Abnormal colposcopic findings	*General principles* Location of the lesion: • Inside or outside the transformation zone • By the "clock position" *Grade 1 (minor)* • Fine mosaic; fine punctation • Thin acetowhite epithelium • Irregular, geographical border	Size of the lesion: • Number of cervical quadrants the lesion covers • Size of the lesion as a percentage of the cervix *Grade 2 (major)* • Sharp border; inner border sign; ridge sign • Dense acetowhite epithelium • Coarse mosaic; coarse punctation • Rapid appearance of acetowhitening • Cuffed crypt (gland) openings
	Non-specific • Leukoplakia (keratosis, hyperkeratosis); erosion • Lugol's staining (Schiller test): stained or non-stained	
Suspicious for invasion	Atypical vessels Additional signs: • Fragile vessels • Irregular surface • Exophytic lesion • Necrosis • Ulceration (necrotic) • Tumour or gross neoplasm	
Miscellaneous findings	Congenital transformation zone Condyloma Polyp (ectocervical or endocervical) Inflammation	Stenosis Congenital anomaly Post-treatment consequence Endometriosis
Excision treatment types	Excision types 1, 2, 3	
Excision specimen dimensions	Length: the distance from the distal or external margin to the proximal or internal margin Thickness: the distance from the stromal margin to the surface of the excised specimen Circumference (optional): the perimeter of the excised specimen	

IFCPC, International Federation of Cervical Pathology and Colposcopy.
From Bornstein et al. (2012).

and the specificity from 96% to 99%. However, some authors have suggested that the degree of concordance depends mainly on the training and the experience or expertise of the colposcopist (Mayeaux & Cox, 2013; American Society for Colposcopy and Cervical Pathology [ASCCP] guidelines, Perkins et al, 2020). High-quality training and quality assurance programmes are essential for the competent practice of colposcopy.

Some attempts have been made to quantify qualitative descriptions into scoring systems, such as the Reid Colposcopic Index (RCI) (Reid & Scalzi, 1985) and the Swede score (Strander et al., 2005). It has been suggested that colposcopic

findings are best assessed formally using a scoring system (Prendiville & Sankaranarayanan, 2017; Ranga et al., 2017; Alan et al., 2020; Schulmeyer et al., 2020). However, some studies report better correlation of histology with colposcopic impression than with colposcopy-based quantitative scores. Li et al. (2017) compared the performance of the IFCPC colposcopic terminology, the RCI, and the Swede score for the identification of HSIL+ in 525 women in Shanghai, China, referred for colposcopy with suspicious-looking cervixes (including cervixes with abnormal bleeding or obvious contact bleeding, abnormal vaginal discharge, recurrent erosion, cervical polyp, leukoplakia, condyloma, gross neoplasm, irregular surface, or cervical canal stenosis, or barrel-like cervixes), abnormal cervical cytology (ASC-US+), or positive hrHPV test results. The results showed that the colposcopic accuracy was lower with the RCI and the Swede score than with the IFCPC classification; the sensitivity of the RCI for identification of HSIL+ was 38% and the specificity was 95%, and the sensitivity of the Swede score for identification of HSIL+ was 13% and the specificity was 99%; these scores are currently not widely used. For the IFCPC classification, the sensitivity for identification of HSIL+ was estimated to be 64% and the specificity 96%. However, no unique classification has yet been adopted in clinical practice worldwide.

(d) Colposcopy training

Expertise in performing colposcopic examinations is attained and maintained by comprehensive training and experience with an adequate caseload. However, colposcopy training and assessment is neither uniform nor quality-assured worldwide. Even within the same country, there is considerable variation among colposcopists in training and experience (Wright, 2017).

Scientific colposcopy societies recognize the need to develop colposcopy standards for quality, and some have recently published training programmes (Public Health England, 2016; Mayeaux et al., 2017; Prendiville & Sankaranarayanan, 2017; AEPCC, 2018). Different societies propose different requirements, and few societies provide committees or infrastructures to support and oversee the training programmes (Moss et al., 2015). Nonetheless, most experts agree that training should involve supervised and unsupervised colposcopic assessment as well as attendance at clinical, histopathological, and cytopathological sessions (Public Health England, 2016; Prendiville, 2022).

Once a colposcopist is trained, performing a sufficient number of colposcopies per year is necessary to ensure continuing competence. The number differs between national colposcopy societies (Moss et al., 2013; Société Française de Colposcopie et de Pathologie Cervico-Vaginale, 2014; Public Health England, 2016; IFCPC, 2021), and some scientific groups do not specify the number of colposcopic evaluations needed per year to maintain competence (Mayeaux et al., 2017; Prendiville & Sankaranarayanan, 2017; AEPCC, 2018).

The systematic review by Mayeaux et al. (2017) of the different international guidelines for colposcopy quality described the wide variation between colposcopy societies in both colposcopy guidance and quality indicators, and emphasized the need for the standardization of guidance.

4.5.2 Accuracy of colposcopy in cytology-based screening

Despite the central role of colposcopy and colposcopy-directed biopsy in detecting cervical HSIL (Darragh et al., 2012), most of the available studies have evaluated colposcopy to assess the risk of underlying precancer or cancer. A limited number of studies have presented specific data for HSIL/CIN3+. However, recent studies evaluating colposcopy have shown that risk estimates for HSIL/CIN3+ were much less heterogeneous than results for HSIL/CIN2+; this probably reflects

the known variability and lack of reproducibility of CIN2/CIN3 diagnoses (Carreon et al., 2007; Herbert et al., 2008).

Four systematic reviews or meta-analyses have been performed on the accuracy of diagnostic colposcopy applied to women referred with abnormal cytology (Mitchell et al., 1998; Olaniyan, 2002; Mustafa et al., 2016; Brown & Tidy, 2019) (Table 4.36; web only; available from https://publications.iarc.fr/604). The most recent meta-analysis (Brown & Tidy, 2019), which included 10 973 women referred for colposcopy after abnormal cytology, reported a weighted mean sensitivity for histologically verified CIN2+ at a threshold of "any colposcopic abnormality" of 96% (range, 83–100%) and a weighted mean specificity of 34% (range, 5–67%). At a threshold of "high-grade colposcopic impression", the pooled sensitivity was 68% (range, 30–95%) and the pooled specificity was 76% (range, 48–97%). [The methods used for the calculation of diagnostic accuracy in clinical colposcopy trials are subject to several types of bias. The use of punch biopsies as the reference standard has been questioned in comparison with the results from excisional treatment after punch biopsy. It is important to consider that in many clinics biopsy is performed only when there is suspicion of disease. As a result, verification by biopsy is performed only when the outcome of colposcopy is positive and not when the outcome is negative. This form of bias results in overestimation of the sensitivity and underestimation of the specificity (Walter, 1999).]

Some analyses have attempted to eliminate this risk of bias. Underwood et al. (2012), in their systematic review, compared 7873 cases of colposcopy-directed cervical punch biopsy with their paired definitive histology from an excisional cervical biopsy or hysterectomy. At a threshold of "any colposcopic abnormality", the pooled sensitivity for a punch biopsy performed to diagnose a CIN2+ present in the surgical specimen was 91% (95% CI, 85–95%) and the pooled specificity was 25% (95% CI, 16–36%). At a threshold of "high-grade colposcopic impression", the pooled sensitivity was 80% (95% CI, 73–86%) and the pooled specificity was 63% (95% CI, 51–77%). Three subsequent retrospective studies (Kahramanoglu et al., 2019; Stuebs et al., 2019; Kim et al., 2020) evaluated the accuracy of colposcopy-directed biopsies with a paired specimen from an excisional treatment (including hysterectomy) and reported a sensitivity of punch biopsy for HSIL+/CIN2+ of 88–90% (92% in women with the entire TZ visible) and variable specificity of 37–59%. [None of these three studies specified whether the biopsies were performed for any colposcopy abnormality or only if a high-grade lesion was suspected.]

4.5.3 Colposcopy in HPV-based screening

When a transition is made from cytology-based strategies to strategies based on HPV testing, the central diagnostic role of colposcopy is maintained but the clinical characteristics of the patients and the number of women referred for colposcopy change profoundly. A major concern with switching from cytology to primary HPV screening is the management of HPV-positive women.

A study in 8369 women in the Guanacaste cohort study in Costa Rica (Porras et al., 2012) compared colposcopy characteristics and performance in women referred for colposcopy based on conventional cytology-based screening (ASC-US+) versus women with positive results in HPV-based screening (HPV typing using type-specific probes). The absolute risks of histological CIN2+ in women with abnormal colposcopy (or PPV) after cytology-based or HPV-based screening were similar (47.8% vs 41.5%, respectively; $P = 0.15$ for women aged 30 years or older). Similarly, there was no difference when ruling out histological CIN2+ in women with normal colposcopy (or NPV) in a cytology-based compared with an HPV-based

screening programme (87.2% vs 87.0%; $P = 0.92$ in women aged 30 years or older).

Colposcopy referrals for HPV-based screening compared with cytology-based screening were discussed in Section 4.4.2. To avoid overburdening the health-care system and overtreating women who are at low risk, a risk-based approach is needed to manage women with a positive HPV screening test result. A triage strategy enables the identification of HPV-positive women who are at higher risk of HSIL+ and who would most benefit from colposcopic examination. The different triage strategies were analysed in Section 4.4.7.

4.5.4 Random biopsies for diagnosis of CIN2+

In cervical cancer screening, it is especially important to rule out HSIL/CIN3+ in women with normal colposcopy, because most of these women do not undergo biopsy but are followed up.

In the Shanxi Province Cervical Cancer Screening Study I (SPOCCS I), Pretorius et al. (2004) evaluated colposcopies of 364 women in Shanxi Province, China, who were referred for colposcopy after an abnormal screening test with an entirely visible TZ in which all colposcopically abnormal areas were biopsied. If the colposcopic examination showed no lesion in a quadrant, a non-directed (random) biopsy was obtained within the TZ in that quadrant. In addition, endocervical curettage was performed after the cervical biopsies. The diagnosis of CIN2+ was made on a colposcopy-directed biopsy in 57% of women, a random biopsy in 37% of women, and an endocervical curettage in 6% of women.

Bekkers et al. (2008) evaluated the accuracy of colposcopy for the identification of HSIL in 6020 women in Melbourne, Australia, for whom the colposcopic impression was correlated with the histopathology result. In this study, colposcopy had a sensitivity of 60% and a PPV of 60% for the identification of HSIL, and the colposcopy-directed biopsies missed 39% of the HSIL. The sensitivity of colposcopy for the identification of HSIL was significantly higher ($P < 0.001$) with junior colposcopists (66.7%) than with senior colposcopists (57.5%), but the PPV was significantly lower ($P < 0.001$) with junior colposcopists (56%) than with senior colposcopists (64%).

In the analysis of the two studies in Shanxi Province, China (SPOCCS I and II), which evaluated 1383 women with abnormal cytology who were referred for colposcopy (Pretorius et al., 2011), 25% of the 222 CIN3+ and 10% of the 31 cervical cancers were diagnosed in a random biopsy. [The sensitivity of colposcopy for diagnosis of CIN3+ varied significantly among the seven physicians performing colposcopy, from 29% to 93% ($P < 0.001$).]

Other studies did not report a benefit from random biopsies. In the Evaluating the Visual Appearance of Cervical Lesions in Relation to its Histological Diagnosis, Human Papillomavirus Genotype and Other Viral Parameters (EVAH) study in the Netherlands and Spain, van der Marel et al. (2014) evaluated the benefit of random biopsies performed in 610 women referred for colposcopy after an abnormal cytology result. Multiple directed biopsies were collected from lesions, and a non-directed biopsy of normal-appearing tissue was added if fewer than four biopsies were collected. In women with at least two lesion-directed biopsies, the yield for CIN2+ increased from 51.7% (95% CI, 45.7–57.7%) for one directed biopsy to 60.4% (95% CI, 54.4–66.2%; $P < 0.001$) for two biopsies. An additional 5% of CIN2+ were detected in biopsies from women who had been underdiagnosed by colposcopy.

In the Biopsy Study of the University of Oklahoma Health Sciences Center and the United States National Cancer Institute (Wentzensen et al., 2015), only 2% of all HSIL diagnosed in the 690 participants were detected by random biopsies performed on a normal-appearing TZ.

A retrospective follow-up study in the setting of the National Health Service (NHS) Cervical Screening Programme in England within the HPV or LBC pilot studies (Kelly et al., 2012) evaluated the risk of incident CIN2+ in 1063 HPV-positive women with low-grade cytological abnormalities (ASC-US or LSIL) who had a normal colposcopy with a completely visible TZ. In these women, the cumulative rate of CIN2+ at 3 years of follow-up was 4.4% (95% CI, 4–7%), independent of the age of the woman.

In the TOMBOLA trial, 884 women aged 20–59 years, with the same inclusion criteria as in the study of Kelly et al. (2012), were evaluated to determine the rate of CIN2+ over 3 years of cervical cytology follow-up including an exit colposcopic examination (Cruickshank et al., 2015). CIN2+ was detected in 5% of the women at the end of the study.

Munmany et al. (2018) evaluated the accuracy of colposcopic evaluation at the time of large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excision procedure (LEEP), to identify women with a previous biopsy diagnosis of HSIL/CIN2/3 with a low probability of dysplasia at the time of treatment. Of 162 women included in the study, 34 (21%) had a normal colposcopy with a completely visible TZ, and the absence of LSIL (CIN1) or HSIL/CIN2/3 in the excised specimen was confirmed in 28 (82%) of the 34 women.

Overall, these studies indicate that in countries in which colposcopy is part of a properly constructed, quality-assured programme, a normal colposcopy is associated with a very high NPV.

4.5.5 Risk-based colposcopy practice

Women referred for colposcopy after an abnormal screening result have a wide range of risk of harbouring a cervical lesion. Recently, it has been suggested that the risk of underlying histological HSIL can be estimated before colposcopic evaluation by assessing the information provided by the screening test (cytology and/or molecular test results). In this strategy, the practice of colposcopy and biopsy can be modified depending on the risk of precancer (Wentzensen et al., 2017; AEPCC, 2018; Perkins, et al., 2020). The risk of cervical precancer can be based on the results of the screening and follow-up tests (Dillner et al., 2008; Schiffman et al., 2015; Castle et al., 2016; Wentzensen et al., 2017; AEPCC, 2018; de Sanjosé et al., 2018; Egemen et al., 2020; Perkins, et al., 2020), as summarized in Table 4.37 (web only; available from https://publications.iarc.fr/604).

Moreover, information provided by the colposcopic impression may modify the need to perform multiple biopsies, including random biopsies (Wentzensen & Clarke, 2017; AEPCC, 2018; Silver et al., 2018; Egemen et al., 2020). A recent meta-analysis evaluated the risk strata based on combinations of cytology, HPV16 and/or HPV18 genotyping, and colposcopic impression (Silver et al., 2018). Eligible studies reported colposcopic impression and either cytology results or HPV16/18 partial genotyping results as well as a histological biopsy diagnosis from adult women. Women with < HSIL cytology who were HPV16/18-negative and had a normal colposcopic impression had the lowest risk of prevalent precancer and cancer (< 0.5% for HSIL/CIN3+). Women with at least two of the three high-risk results (i.e. HSIL cytology, HPV16- and/or HPV18-positive, and grade 2 changes at colposcopy) were at high risk (29–53% for HSIL/CIN3+), and women with all three of these high-risk results had the highest risk (> 70% for HSIL/CIN3+). Table 4.38 shows the levels (low, intermediate, and high) of risk of histological HSIL on the basis of cytology, HPV testing, and colposcopic findings.

On the basis of the current evidence, scientific societies have issued new colposcopy standards and risk-based management guidelines for the low-risk and high-risk groups of women based on

Table 4.38 Levels of risk of histological HSIL on the basis of cytology, HPV testing, and colposcopic findings

Low risk	Intermediate risk	High risk
Fulfil the following 3 criteria: • Cytology < HSIL • No HPV16/18 • Normal colposcopy	Cases not included in the other 2 risk groups	Fulfil at least 2 of the following 3 criteria: • Cytology ≥ HSIL, AGC, or ASC-H • HPV16 and/or HPV18 • Colposcopy showing grade 2 changes (high-grade/HSIL)

AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude high-grade squamous epithelial lesions; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion.
Reproduced with permission from AEPCC (2018).

the available test results (cytology, HPV testing, and colposcopic impression) (Wentzensen et al., 2017; AEPCC, 2018; Perkins et al., 2020). Random biopsies should not be performed for women with < HSIL cytology who are HPV16/18-negative and have normal colposcopy. In contrast, in the case of abnormal colposcopy, even without any suspicion of cervical HSIL, cervical biopsy should be performed in women with HSIL cytology and/or HPV16- and/or HPV18-positive tests, particularly where adequate training and quality assurance are not in place. In women in the highest-risk group, the benefit of taking random biopsies from normal colposcopic areas within the TZ could also be considered. When multiple biopsies are taken and are negative, it is mandatory to provide close follow-up of the woman (i.e. every 6 months) (AEPCC, 2015), and if high-grade abnormalities (HSIL cytology and/or colposcopy showing grade 2 changes with negative biopsies) persist in the follow-up tests, type 3 excision (Bornstein et al., 2012) should be considered (Del Pino et al., 2010; AEPCC, 2015, 2018). In contrast, expedited excisional treatment (defined as excisional treatment without preceding colposcopy-directed biopsy demonstrating histological HSIL/CIN2+) is entirely appropriate in selected women at very high risk of harbouring HSIL/CIN3+, according to clinical guidelines (Wentzensen et al., 2017; Wright, 2017; Egemen et al., 2020; Perkins et al., 2020) (see also Section 1.2.5).

The main advantage of risk stratification is that the colposcopic examination and the biopsy strategy are adapted to the risk stratum. The colposcopist can either not perform a biopsy (in women at low risk) or perform expedited excisional treatment (in women at high risk). In women at intermediate risk, colposcopy-directed biopsies are appropriate. The potential benefit of biopsies in minimal acetowhite areas or when the colposcopy is normal (random biopsies) should be considered in each case (Waxman et al., 2017; Wentzensen et al., 2017; AEPCC, 2018).

4.5.6 Harmful effects of colposcopy

The harmful effects of colposcopy are (i) harms related to the procedure, (ii) harms linked with inadequate indication for colposcopy, and (iii) harms related to lack of experience or quality assurance.

(a) Harms related to the procedure

(i) Pain or discomfort

Although colposcopy is generally a well-tolerated examination, and therefore administration of analgesic drugs before the procedure is not recommended, some women may report discomfort due to the prolonged placing of the speculum or the application of acetic acid or iodine solution, or cramping or pain associated with the biopsy procedure (Khan et al., 2017;

AEPCC, 2018). In the TOMBOLA trial (Sharp et al., 2009), of the 401 women who underwent colposcopic examination (without biopsy or treatment), 18% (95% CI, 15–23%) reported some pain or physical discomfort when questioned at 6 weeks and 4 months after a colposcopy, and 5% (95% CI, 3–8%) reported that the discomfort was moderate to severe. O'Connor et al. (2017) reported that 59% of 248 women questioned at 4, 8, and 12 months after a colposcopy described pain (75% of the procedures included punch biopsies or conization). Pain during colposcopy is more closely related to the biopsy procedure or the treatment than to the colposcopy procedure itself. In addition, in the TOMBOLA trial (Sharp et al., 2009), of the women who underwent colposcopic examination (without biopsy or treatment), 18% (95% CI, 15–23%) reported pain; this proportion increased to 53% (95% CI, 44–61%) for those who underwent colposcopy and punch biopsy and to 67% (95% CI, 59–74%) for those who underwent colposcopy and excisional treatment (conization).

Pain and discomfort are generally experienced at the time of the procedure, but sometimes cramping can persist for a few hours. On the basis of two RCTs including 129 women, a Cochrane review concluded that there was no difference in pain relief between women undergoing colposcopy (without treatment) who received oral analgesics and those who received placebo or no treatment (mean difference, −3.51; 95% CI, −10.03 to 3.01 [low-quality evidence]) (Gajjar et al., 2016).

A prospective study conducted at Concord Women's Health Center in Israel including 101 women who underwent colposcopy reported a negative correlation between age and pain associated with the procedure (Pearson correlation coefficient, −0.220; $P < 0.05$) (Handelzalts et al., 2015).

(ii) Anxiety

Anxiety, worry, and fear are the feelings most commonly described during colposcopy (Galaal et al., 2011; O'Connor et al., 2016). In a systematic review evaluating psychological outcomes after colposcopy and related procedures, which included 16 studies (O'Connor et al., 2016), 60% of women undergoing colposcopy for the first time experienced anxiety (defined as an STAI score > 35), and 18% reported high anxiety levels (defined as an STAI score > 44); also, one third of the women undergoing colposcopy for the first time experienced distress or worry. The results of the procedure had impacts on the course of the negative feelings. At 6 weeks after the procedure, 21% of the women with a normal TZ and 42% of the women with an abnormal TZ still had significant distress. Moreover, in women with a normal TZ, distress and worry were significantly increased in those who reported pain or discharge after the procedure (Sharp et al., 2011, 2013).

Many women also report worry or anxiety in the period between the time of being notified of an abnormal screening result and the colposcopy appointment (Khan et al., 2017; Young et al., 2018). although it is unclear whether the diagnosis of an abnormal screening test or the colposcopy itself contributes to negative feelings (Khan et al., 2017). In general, women are less concerned about the procedure itself and are more anxious about having an HPV infection or cancer (see Section 4.4.8). Waller et al. (2007) evaluated the psychosocial impact of having a second positive HPV test result in 30 women undergoing cervical cancer screening who were HPV-positive with normal cytology at the first visit, and who attended for a repeat HPV test 12 months later. The study found that women appeared to be more distressed by a second positive HPV test result than by the first one. They also expressed a clear preference for immediate colposcopy over continued surveillance,

indicating that the anxiety was associated mainly with the screening result but also with a desire for a speedy resolution and fears about progression to cancer.

Colposcopy may also have a negative influence on sexual function. Seven studies included in the systematic review by O'Connor et al. (2016) assessed some aspect of sexual or psychosexual functioning after colposcopy. Although one study reported that the mean total score in the Female Sexual Function Index (FSFI) after colposcopy was above the threshold for female sexual disorder, the other studies comparing pre- with post-colposcopy sexual or psychosexual functioning reported conflicting results, with no consistent pattern of impact. [This secondary effect may be more closely related to abnormal screening test results than to the colposcopy procedure itself.]

Different approaches have been evaluated to reduce anxiety in women undergoing colposcopy after an abnormal screening test. Effective information and communication have consistently been shown to reduce anxiety (Kola et al., 2013; Handelzalts et al., 2015). Women who have not been extensively informed and are unaware of the possibility of experiencing side-effects score significantly higher for distress and anxiety during follow-up (O'Connor et al., 2017). Video colposcopy, which enables women to observe their own anatomy and watch what the colposcopist is doing, has been reported to reduce anxiety, in some studies (Kola et al., 2013) but not in others (Hilal et al., 2017).

Music therapy has been used to reduce anxiety associated with various medical procedures; however, in a recent meta-analysis, music therapy had no positive effect on reducing anxiety or pain or increasing satisfaction levels during colposcopy (Abdelhakim et al., 2019).

Most studies on the psychological impact of colposcopy have been performed in women undergoing colposcopy for the first time. However, compared with women undergoing subsequent colposcopic examinations, those undergoing colposcopy for the first time typically experience increased anxiety both before and after colposcopy and display a tendency to seek information about the procedure (Handelzalts et al., 2015).

(iii) Anaphylactic reaction to iodine solution

Isolated examples of allergic reactions to iodine solution have been described. These include pruritus, vaginal oedema, hypotension, tachycardia, and breathing difficulties. The symptoms usually disappear upon withdrawal of the iodine solution (Indraccolo et al., 2009).

(b) Harms linked with inadequate indication for colposcopy

Although colposcopy was initially used as a tool for primary screening of cervical cancer and precancer, an increased understanding of the natural history of HPV infection and its progression to cervical neoplasia has recently reduced the indications for colposcopy. Strict adherence to indications for colposcopy (Table 4.33) minimizes the side-effects associated with inappropriate use of this procedure.

(c) Harms related to lack of experience or quality assurance

Colposcopy requires adequate training and experience to attain proficiency, assure quality, and maintain competence in performing the procedure. The proportion of false-negative results of colposcopy (women with HSIL/CIN2+ classified as being disease-free) correlates directly with the expertise of the colposcopist.

As mentioned above, one study showed significantly higher sensitivity for the identification of HSIL when performed by junior colposcopists (with 0–2 years of experience in colposcopy) compared with senior colposcopists (with > 3 years of experience) (66.7% vs 57.5%; $P < 0.001$), but a significantly lower PPV (56% vs 64%; $P < 0.001$) (Bekkers et al., 2008).

A retrospective analysis comparing the precision of diagnosis by colposcopy-directed biopsy with the final histological outcome of the surgical specimen in 641 women showed a risk of underdiagnosis of HSIL (false negativity) of 12% when the colposcopist had 0–5 years of experience and of 8% when the colposcopist had more than 10 years of experience (Stuebs et al., 2019).

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