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AEPCC



Guidelines

COLPOSCOPY GUIDELINES. STANDARDS OF QUALITY



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1. RATIONALE AND OBJECTIVES

The principal objective of the Spanish Association of Cervical Pathology and Colposcopy (AEPCCC) is to “**promote knowledge and investigation of the lower genital tract in women**”. The “**AEPCCC-Guidelines**” were developed to fulfill this objective and to respond to the demand of professionals devoted to disease of the lower genital tract and colposcopy.

The **AEPCCC-Guidelines** cover specific areas of knowledge of disease of the lower genital tract which are characterized by their relevance and important repercussion in clinical practice. The **AEPCCC-Guidelines** are scientific evidence-based documents which have been systematically developed and aim to help professionals achieve consensus in decision making in clinical practice regarding the most adequate diagnostic and therapeutic options for a determined health problem.

The specific objectives pursued by the AEPCCC-Guidelines are:

- To promote standardized lines of action based on the current scientific evidence and reliable consensus information.
- Guarantee patient equality when attended, independently of their location of residence, promoting good praxis.
- Improve the effectiveness of interventions and the quality of health care.
- Favor the implementation of indicators of quality control or of clinical efficacy.
- Facilitate decision making within the administrative setting for managers or health care resources planners.

Lastly, the methodological rigor established for the preparation of the **AEPCCC-guidelines** is aimed at the development of documents of outstanding scientific quality which will allow better clinical practice and greater knowledge of lower genital tract diseases.

2. METHODOLOGY

The specific methodology followed for the elaboration of the AEPCCC-Guidelines includes the following aspects:

- The AEPCCC Steering Committee appoints a Coordinator who is responsible for the elaboration of the **AEPCCC-Guidelines**. In accordance with the Steering Committee, the Coordinator appoints the Writing Committee consisting of him/herself, a Secretary and the participants. The members are professional experts who are members of the AEPCCC or other scientific societies with recognized prestige in this topic.
- Consensual development of the index.
- Critical review of the available literature and assignment of levels of evidence.
- Discussion and consensus among the members of the Committee for assigning the grade of recommendation.
- Elaboration of the document.
- Final analysis of the document on behalf of the Review and Editing Committee.
- Printed and online format of the final version.
- Diffusion of the **AEPCCC-Guidelines** in congresses, courses and seminars organized by the AEPCCC.
- Elaboration of online Courses of Continuing Education on the content of the **AEPCCC-Guidelines** to provide in depth knowledge of the guidelines and facilitate their application in daily clinical practice (training credits).
- Translation of the **AEPCCC-Guidelines** to English (online edition).
- Update of the **AEPCCC-Guidelines**.

3. EVALUATION OF THE SCIENTIFIC EVIDENCE. CRITERIA FOR ESTABLISHING STANDARDS OF QUALITY

The “Guidelines of Clinical Practice” consist of recommendations aimed at health professionals to help them with patient care related to a determined clinical condition. They are based on the most important bibliographic evidence of a determined subject (systematic reviews of the medical literature and identification of studies with the greatest scientific evidence available) and on clinical practice. In general, the highest level of classification is given to prospective studies to which patients are randomly assigned, and the minimum levels are given to data related to expert opinion. In this way it is possible to assess the quality of evidence associated with the results obtained by a determined strategy. For the elaboration of the **AEPCG-Guidelines** all the recommendations made have considered the quality of the current scientific documents. The strength of the recommendations is agreed upon by the Committee of the AEPCG-Guidelines based on the quality of the studies available.

COLPOSCOPY GUIDELINES STANDARDS OF QUALITY

INDEX

1. INTRODUCTION.....	8		
2. SAMPLE COLLECTION FOR SCREENING OF CERVICAL CANCER.....	9		
2.1 Cytology smears collection.....	10		
2.1.1 Material and methods.....	11		
2.1.2 Reports.....	11		
2.2 Sample collection for HPV testing.....	11		
2.2.1 Material and methods.....	11		
2.2.2 Reports.....	11		
2.3 Sample collection in special clinical situations.....	12		
2.3.1 Cervical stenosis.....	12		
2.3.2 Cervicitis, leukorrhea, contaminants.....	12		
2.3.3 Severe atrophy.....	12		
2.3.4 Previous hysterectomy.....	13		
2.3.5 Previous radiotherapy.....	13		
2.3.6 Absence of endocervical cells or cells from the transformation zone.....	13		
2.3.7 Repeated inflammatory or hemorrhagic cytology results.....	13		
3. GUIDELINES FOR REFERRING A PATIENT TO COLPOSCOPY. STANDARDS OF QUALITY.....	14		
3.1 Waiting time to perform colposcopy in asymptomatic patients with abnormal screening study results.....	14		
3.1.1 Cytology showing atypical squamous cells of undetermined significance (ASCUS).....	14		
3.1.2 Cytology showing low grade squamous intraepithelial lesion (LSIL).....	14		
3.1.3 Cytology showing high grade squamous intraepithelial lesion (HSIL).....	15		
3.1.4 Cytology showing atypical squamous cells which cannot rule out a high grade lesion (ASC-H).....	15		
3.1.5 Atypical glandular cells (AGC) which cannot rule out high grade lesion (AGC-H).....	15		
3.1.6 Cytology of adenocarcinoma in situ (AIS) or carcinoma.....	16		
3.1.7 Positive HPV test and negative cytology.....	16		
3.2 Waiting time to perform colposcopy in patient with symptoms or with suspicious findings on routine gynecological examination.....	16		
3.2.1 Women with symptoms suggestive of cervical cancer (CC).....	16		
3.2.2 Macroscopically abnormal cervix at the moment of screening test sampling.....	17		
3.3 Waiting time between confirmed histological diagnosis by colposcopy and treatment.....	17		
4. COLPOSCOPY INSTRUMENTS AND MATERIAL.....	18		
4.1 Colposcope.....	18		
4.1.1 Elements making up a colposcope.....	19		
4.1.2 Colposcope accessories.....	19		
4.2 Instruments or colposcopy consultation.....	19		
4.2.1 Instruments for colposcopy access and viewing.....	19		
4.2.2 Fungible material.....	20		
4.2.3 Instruments for the collection of histological samples.....	20		
4.2.4 Other materials.....	20		
4.3 Acetic acid.....	20		
4.4 Lugol solution.....	21		
4.5 Hemostatic solutions.....	21		
4.6 Maintenance of colposcopy material.....	22		
5. NOMENCLATURE AND DESCRIPTION OF COLPOSCOPIC FINDINGS.....	23		
5.1 Terminology.....	23		
5.2 Accuracy of colposcopic diagnosis.....	23		
5.3 Benefits of colposcopy.....	26		
5.4 Potential harmful effects of colposcopy.....	27		
6. STANDARDS OF QUALITY IN COLPOSCOPIC DIAGNOSIS.....	29		
6.1 Registry of the clinical history of patients referred to colposcopy.....	29		
6.1.1 Anamnesis (pathological, gynecological and obstetric history).....	29		
6.1.2 Indication for performing colposcopy.....	29		
6.1.3 Verbal information and informed consent.....	29		



6.2 Colposcopic examination.....	30	7.5.1 Training and certification of colposcopists.....	45	
6.2.1 Cervical examination.....	30	7.5.2 Content of the training and evaluation.....	45	
6.2.2 Vaginal examination.....	31	7.5.3 Maintenance of clinical skills and continuing		
6.2.3 Vulva examination.....	31	medical education (CME).....	46	
6.3 Reporting and registry of colposcopic findings.....	31			
6.3.1 Description of colposcopic findings.....	31	8. INFECTIONS, CYTOLOGY AND COLPOSCOPY.....	47	
6.3.2 Registry of colposcopic data and images		8.1 Sample collection for the study of infection		
(diagrams, photos).....	32	in the colposcopy visit.....	47	
6.3.3 Reporting of colposcopic impression.....	33	8.2 Action towards infection found in the cytology.....	47	
6.4 Colposcopy-guided biopsy.....	33	8.2.1 Actinomyces.....	47	
6.4.1 Adequacy of the biopsies.....	33	8.2.2 Tricomias vaginalis.....	47	
6.4.2 Number of biopsies.....	34	8.2.3 Candida species.....	48	
6.4.3 Cervical biopsy sampling according to		8.2.4 Bacterial vaginosis.....	48	
level of risk.....	35	8.2.5 Chlamydia tracomatis.....	48	
6.4.4 Non-guided biopsies.....	36	8.2.6 Neisseria gonorrhoeae.....	49	
6.4.5 Endocervical study (biopsy with cytological		8.2.7 Herpes Simplex Virus (HSV).....	49	
curettage or smear).....	36	8.3 Informing patients of the results.....	49	
6.5 Reporting and registry of diagnosis after				
colposcopy and treatment.....	37	9. COLPOSCOPY STANDARDS IN SPECIAL	SITUATIONS.....	50
6.5.1 Localization, number of biopsies and		9.1 Pregnancy.....	50	
characteristics of the areas selected for biopsy.....	37	9.2 Menopause.....	51	
6.5.2 Endocervical study (biopsy with curettage		9.3 Use of contraceptives.....	51	
or cytological smear).....	38	9.4 Hysterectomy.....	51	
6.6 Informing the patient of the results and follow-up.....	38			
		10. COLPOSCOPIC PRACTICE ACCORDING	TO THE LEVEL OF RISK.....	53
7. COLPOSCOPY UNITS. STANDARDS OF QUALITY	AND RECOMMENDATIONS.....	10.1 Definition of risk of premalignant cervical lesion.....	53	
39		10.2 Colposcopic practice in women with low risk		
7.1 Standards of quality of Colposcopy Units.....	39	of premalignant lesion.....	55	
7.1.1 Coordination and management of		10.3 Colposcopic practice in women with high risk of		
the Colposcopy Unit.....	39	pre-malignant lesion.....	56	
7.1.2 Quality control of the Colposcopy Unit.....	39			
7.1.3 Information and communication with		11. TABLES SUMMARIZING RECOMMENDATIONS	AND STANDARDS OF QUALITY IN COLPOSCOPY.....	58
the patient.....	41			
7.1.4 Certification.....	42			
7.1.5 Coordination of screening programs.....	42	12. REFERENCES.....	70	
7.2 Personnel, installations and equipment				
in the Colposcopy Unit.....	42			
7.2.1 Staffing.....	42			
7.2.2 Installations and equipment.....	43			
7.3 Organization and administrative management.....	44			
7.3.1 Organization and meetings of the Colposcopy				
Unit and with multidisciplinary teams.....	44			
7.4 Clinical documentation.....	44			
7.4.1 Clinical history.....	44			
7.4.2 Data.....	44			
7.5 Colposcopy training, certification and				
continuing medical education.....	45			

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COLPOSCOPY GUIDELINES STANDARDS OF QUALITY

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1. Introduction

Colposcopy is an essential study in the secondary prevention of cervical cancer (CC) and for evaluation of the lower genital tract. It is the only procedure able to identify intraepithelial cervical lesions, determine their localization and characteristics and guide biopsy for diagnostic confirmation. Therefore, most patients with abnormal results in screening tests require colposcopic evaluation. Since 2014, the Spanish Association of Cervical Pathology and Colposcopy (AEPCC) has promoted and published the AEPCC-Guidelines on cervical cancer (CC) screening and the actions to be taken with abnormal screening test results. These guidelines clearly establish when a colposcopy should be performed or repeated in both the diagnosis and follow-up or treatment of precursor lesions of CC.

The central role that colposcopy plays in the prevention of CC advocates the importance of having a standardized procedure, the need for colposcopy procedures to be uniformly performed in clinical practice and the availability of indicators of quality for evaluation.

In Spain and in most countries with CC screening programs there is a great lack of uniformity in the performance of colposcopy. Hundreds or thousands of gynecologists in Spain carry out colposcopies in very diverse settings (primary care, county hospitals, regional hospitals, level 3 hospitals).

Some professionals do a type of basic colposcopy and very sporadically (very few times a month), while others perform advanced colposcopy (in well organized Colposcopic and Lower Genital Tract Disease Units) almost exclusively and with a large volume of examinations. Therefore, there is a great variability in the experience and training of different colposcopists. Some have received minimum training during medical residency, while others have attended basic courses or congresses and still others have participated in advanced courses and/or have obtained specific training.

Since 2007, the AEPCC provides “accreditation” which recognizes the experience (years of specific work in colposcopy), the curricular merits in this setting or the global knowledge in colposcopy and disease of the lower genital tract (accreditation exam). To date, 464 accreditations have

been granted. One registry of colposcopic activity estimated that in Spain 45% of Colposcopy and Lower Genital Tract Disease Units have one or two accredited professionals, and 20% have three or more accredited specialists.

One fundamental aspect of colposcopic practice is the need to use standardized terminology for understanding and evaluating colposcopy results. There are multiple classifications and descriptions of colposcopic findings but the terminology recognized as “official”, and which should thus, be systematically applied in all studies is the terminology described by the International Federation of Cervical Pathology and Colposcopy (IFCPC) [1].

On the other hand, colposcopies and the criteria for performing biopsies should not be uniform for all women presenting alterations in screening tests. For years, the algorithms of action in these patients follow the concept of “stratification of risk” so that the action varies based on the risk of the patient presenting a high grade squamous intraepithelial lesion (HSIL/CIN2-3). Performing the same colposcopic procedures in women with very different risks could lead to overdiagnosis/overtreatment in some cases or underdiagnosis/undertreatment in others.

Lastly, in addition to establishing how to carry out a colposcopy, indicators of quality of all the process should be established which clearly define not only the minimum requirements but also the optimal health care levels. Undoubtedly, it is crucial to have indicators of quality when evaluating colposcopy practice and to therefore continue improving our health care activity or to certify that both the specialists in Colposcopy Units and the units themselves achieve the desired level of excellence.

The present AEPCC-Guidelines on “Colposcopy and Standards of Quality” should embody an obligatory benchmark for both colposcopists and Colposcopy Units in Spain. These Guidelines describe most of the areas involved in the practice of colposcopy: instruments, material, sample collection, guidelines for patient referral, classification and terminology, colposcopy practice according to the level of risk, standards and indicators of quality in colposcopy diagnosis and in the organization of Colposcopy Units.

The AEPCC hopes that these Guidelines will decisively contribute to increasing the quality of health care in the practice of colposcopy and facilitate evaluation of this procedure at both an individual level as well as in Colposcopy Units. Any advance in this sense will undoubtedly contribute

to achieving the fundamental objective of the AEPCC which consists in improving the training of professionals and patient care within the setting of the prevention of cancer of the lower genital tract.

2. Sample collection for screening of cervical cancer

2.1. CYTOLOGY SMEARS COLLECTION

The objective of cytological cervical sample smears is to obtain cells from the transformation zone (TZ) which is where most premalignant lesions are found.

Before describing cytological smear collection in depth, it is important to note that if clinical signs suggestive of malignancy are observed when taking the smear, a biopsy sample should be taken or the woman should be referred to specialized gynecological consultation for closer study independently of the cytology results [2].

The days of the menstrual cycle should be taken into account when obtaining a cervical smear. The number of unsatisfactory cytologies significantly increases in smears obtained in the presence of bleeding, and therefore cytological smears should preferably be performed when the patient is not menstruating. However, it is important to consider that it is always better to perform the screening during menstruation than not to do the screening [3, 4].

Recommendation:

- Ideally the cytological smear should be done when the patient is not menstruating.
- On the presence of signs of suspicion of an invasive cervical lesion the patient should be referred to a specialized unit for specific gynecological study.



2.1.1. Material and methods

Prior to sample collection, the whole of the cervix should be exposed and macroscopically assessed with the use of a speculum. The cytology smear should obtain a sample of the external surface (ectocervix) and of the cervical canal (endocervix).

Two devices have traditionally been used (a spatula for the exocervical smear and a cotton swab or a cytobrush for the endocervical smear). At present, there are also sampling devices with which a single smear of the exocervix and endocervix can be made. Both methods are effective. If the smear is done with the single device (for collection of exo- and endocervical material) it is advised to center the device on the cervix and turn the bristles at least 5 times on the specimen [5]. For separate smears, the spatula is applied on the ectocervix and may be of wood or plastic, although the latter material seems to be preferable for reading in liquid medium. The cytobrush collects material from the endocervix, and it preferred over cotton swabs [6].

The transfer of the cervical smear differs according to whether conventional or liquid cytology is performed. For the conventional or classical cytology on a slide, the material obtained from the ectocervix should be carefully extended on the first half of the glass. Then, it is extended on the second half of the slide perpendicular to the former material collected with the cytobrush, slowly turning it on the glass. The material placed on the glass should occupy the whole surface but should not be lumpy or have a thick layer since reading will be inadequate in these areas. After depositing the sample, this should be fixed with a spray, applied at a distance of 15.20 cm so that a homogeneous layer remains on the sample avoiding smearing of the sample.

In the case of liquid cytology, the spatula and the cytobrush or the single sampling device are introduced into the preserving transportation fluid and shaken vigorously for several seconds so that the exfoliated cells become loose and remain in suspension. If the smear is made with the single sampling device with plastic bristles, the device should be pushed against the bottom of the vial 4-5 times in order to separate the bristles and for the material to fall.

Both the classical cytology on slides and liquid cytology are acceptable methods for screening, although the technology in liquid medium is preferable in most European and

American clinical guidelines. There are several reasons which justify the preference for liquid cytology. On one hand, liquid cytology allows the possibility of automatizing the processing and reading. In addition, the liquid medium technique can eliminate the erythrocytes, and thus, the difficulty of obtaining smears in cases with vaginal bleeding is less relevant, thereby reducing the rate of inadequate samples. Another important advantage of liquid cytology is the possibility of using the same material for the cytological study and to carry out molecular determinations such as human papilloma virus (HPV) detection, the HPV genotype or dual p16/Ki76 staining [7].

Recommendation:

- A cytological smear should obtain samples of the exocervix and the endocervix.
- Cytological smears should preferentially be done in liquid medium with a plastic spatula or cytobrush or with a single sampling device. Conventional smears on slides are acceptable.

2.1.2. Reports

The cytology report should include:

- A description of the type of study: conventional, liquid medium and/or HPV test.
- Whether the sample is adequate or not.
- Interpretation of the result.
- A description of any auxiliary test or automatic revision made and the notes or suggestions of the pathologist.

In 1988 the terminology for reporting the cytology result was standardized using the Bethesda system, having been reviewed on several occasions, the last being in 2014 [8]. The Bethesda terminology is considered the “official” terminology to describe cytological findings.

Squamous cell abnormalities are reported using the term “SIL” meaning squamous intraepithelial lesions [9]. Since 1988, cytological SIL alterations have been divided into two categories based on a different prognosis: LSIL (low grade squamous intraepithelial lesion) usually corresponds to low histological grade lesions (LSIL/CIN1) and HSIL (high grade squamous intraepithelial lesion) is most frequently associated with high grade histological lesions (HSIL/CIN2-3) and cancer. The results of the cytology test do not represent a definitive diagnosis since this should always be confirmed by histology. The definitive diagnosis should always be made by colposcopy-guided biopsy.

The time from sample collection and the availability of the cytological report should not exceed 6 weeks [10].

Recommendation: cytological reports should be made according to the Bethesda terminology.

2.2. SAMPLE COLLECTION FOR HPV TESTING

The determination of HPV in screening has the principal advantage of increasing the sensitivity and efficacy compared with cytology and can increase the interval between smears [11, 12]. The lower specificity of this screening method may be compensated by the selection of HPV positive patients by reflex cytology and the study of molecular biomarkers related to HPV infection [10, 13].

More than 140 methods for HPV detection are available. At present, only 4 have been approved by the Food and Drugs Administration (FDA) for the detection of HPV for health care purposes: Hybrid Capture, Cervista, Cobas 4800 and APTIMA [10]. The Cobas 4800 is the only method approved by the FDA and the European Medicines Agency (EMA) for populational screening. Among the multiple methods of HPV determination, their validity for clinical use is accepted provided that there is an optimal balance of clinical sensitivity and specificity for the detection of \geq HSIL/CIN2 similar to that demonstrated in clinical studies with hybrid capture (reference test) [14, 15].

Recommendation: Tests to determine HPV must be approved by regulating agencies (FDA and/or EMA) or fulfill the criteria of equivalence of sensitivity and specificity.

2.2.1 Material and methods

The samples for HPV testing should be obtained from the endocervix and the TZ using the spatula and the cytobrush or the single sampling device in a similar way to cytology smear collection (see section 2.1.1). The material is deposited in the transport medium.

Most liquid cytology systems can use the same specimen for HPV determination. There are other methods of self-collection or HPV testing in urine, but at present their use has no clinical application.

Recommendation:

- Smears for HPV determination should be obtained from the endocervix and the transformation zone.
- Smears for HPV determination should be obtained in liquid medium with a plastic spatula and cytobrush or with a single sampling device.

2.2.2 Reports

The tests for HPV testing may be used as a primary tool for CC screening (exclusively or as a co-test if HPV testing and cytology are performed together), or as a reflex test

after an abnormal cytology result such as, for example an ASCUS [16]. In the latter case, the extra transport liquid of the cytology study is used to determine the presence of HPV.

The information provided in the HPV test reports depends on the test used. The HPV tests approved by the FDA include hybrid capture (Hybrid Capture® 2 [HC2]), Cervista® HPV HR Test and APTIMA® HPV Test, which group the results for all high risk HPV types (that is, reports a positive result if any high risk type is present but does not describe any specific type). Cobas 4800 especially identifies HPV types 16 and 18 and groups the result of the other 12 high risk types (high risk HPV other than 16/18). This latter test is the only HPV test explicitly approved for screening. Other tests which are currently marketed fulfill the prevailing requisites for their use in populational screening [10].

Recommendation: Depending on the method chosen, reports of HPV test results in primary screening will provide information about a positive high risk HPV result or report the specific genotype or the positivity for HPV 16 and 18 genotypes.

2.3 SAMPLE COLLECTION IN SPECIAL CLINICAL SITUATIONS

Some situations may present specific characteristics. Each patient should be considered individually and adopting the strategies necessary for correct sample collection is fundamental for cytologic evaluation.

2.3.1 Cervical stenosis

Severe cervical stenosis (often as a result of previous surgery) frequently impedes cytological sample collection of the complete transformation zone. Access to the cervical canal can be achieved by cervical traction with Pozzi forceps and/or cervical dilatation [17]. Another option is to perform the cytological smear after dilatation maneuvers. In difficult cases in which scarce material is collected, it is preferable to obtain a smear for HPV testing [10].

Recommendation: In cervical stenosis an endocervical smear may be performed after dilatation. In difficult cases it is preferable to obtain a smear for the HPV test.

2.3.2 Cervicitis, leukorrhea, contaminants.

In the case of abundant leukorrhea, the surface of the cervix may be gently cleaned with a swab eliminating the excess of vaginal secretion and mucosity before performing the cytology test without interfering with the results. Cytology can identify several infectious agents which cause leukorrhea (for example, Actinomyces, Trichomonas vaginalis, candida, herpes virus), but it is not a method to diagnose alterations in vaginal secretion. On signs of cervicitis it is preferable to carry out local and/or systemic, empiric or specific treatment after fresh smear or culture, and after several weeks the screening sample can again be attempted.

The use of a lubricant prior to introducing the speculum has no adverse impact on the interpretation of the classical cytology and has been evaluated in several studies [18, 19].

In general, it is logical to think that the sample in liquid medium is less affected by leukorrhea or other vaginal contaminants (creams, semen, etc.) than the classical glass sample.

Recommendation: In cases of cervicitis it is preferable to delay cervical sampling until after undergoing specific treatment.

2.3.3 Severe atrophy

In post menopausal patients atrophy may hinder sample taking and impede endocervical sampling, thereby increasing the number of inadequate cytologies due to an absence of cylindrical epithelial cells or of the transformation zone. Treatments with local estrogen or even with misoprostol have been proposed to facilitate endocervical access and repeat the sampling [19, 20]. At present, HPV detection is the reference technique for this limitation. If the cytology does not show abnormalities and the HPV test is negative, the screening is assumed to be normal. In special cases or in cases in which repeated samples have been deficient, estrogen treatment may be administered in order to repeat sample collection after 6-8 weeks [12, 17].

Recommendation: In cases of severe atrophy treatment with topical estrogens may be administered before the cytology or HPV testing.

2.3.4 Previous hysterectomy

Patients undergoing total hysterectomy with no previous history of SIL/CIN should not continue with the screening [2], since primary cancer of the vagina is the least frequent of the genital tract (0.69 cases per 100,000) [21]. The frequency is comparable to breast cancer in males or penile cancer.

Different studies including more than 10,000 women with hysterectomy due to benign disease found a reduced number of cases of vaginal SIL (less than 1%) and no case of vaginal cancer after a follow-up of up to 20 years [22-25]. Therefore, independently of age, screening for the detection of cancer of the vagina with any technique is not justified in patients with no history of SIL/CIN undergoing hysterectomy.

Women with a history of a lesion \geq HSIL/CIN2 treated or spontaneously resolved continue to have a 5 to 10-fold greater risk of developing CC within the following 20 years than the general population [10]. These patients should therefore continue screening. A plastic spatula is used to obtain the cytology sample and/or for determination of HPV from the vaginal fundus. In cases of subtotal hysterectomy, screening is the same as in women with an intact uterus.

Recommendation: women with hysterectomy due to SIL/CIN should continue to be screened for at least 20 years.

2.3.5 Previous radiotherapy

There is no evidence as to which strategies are the most ideal in women undergoing radiotherapy for cancer of the cervix, rectum, bladder or other pelvic organs. These cases are not submitted to standard screening protocols and individualized clinical gynecological control should be implemented [2].

2.3.6 Absence of endocervical cells or cells from the transformation zone

In cases in which the cytology results show an absence of endocervical cells or cells from the transformation zone, in the absence of other abnormalities, the result is considered negative provided that the sample is adequate for evaluation.

When the cytology is reported as inadequate for evaluation, several possibilities may be considered: 1) perform a HPV reflex test in the same sample (if this is negative it can be assumed that the screening is negative); 2) if HPV determination is not available treatment with estrogens may be carried out and the sample repeated (ideally the co-test) in 6-8 weeks [17].

If the cytology is repeatedly inadequate for evaluation because of an absence of endocervical cells or cells from the transformation zone, the patient should be referred to colposcopy.

Recommendation: Cytology results without cellular alterations reported as “adequate but limited by the absence of endocervical cells or cells from the transformation zone” are considered to be negative.

2.3.7 Repeated inflammatory or hemorrhagic cytology results

Inflammatory or hemorrhagic cytology results are more frequently reported when conventional cytology is used. In some cases, this alteration conditions inadequate sampling. Cytology samples in liquid medium minimize the number of inadequate samples due to inflammation or hemorrhage.

However, in either case, this result implies a lower sensitivity, and therefore, there is a possibility that an inflammatory or hemorrhagic sample may underdiagnose premalignant lesions of the uterine cervix.

In a study including 420 samples, 30 (8.6%) showed persistent inflammatory changes at one year. These patients were referred to colposcopy which found four cases of LSIL/CIN1 (13.3%) and one case of HSIL/CIN2 (3.3%) [26].

If the cytology is inadequate due to inflammation or hemorrhage, the sample should be repeated after specific treatment. In cases with three inadequate cytologies due to inflammation or hemorrhage the preferable option is to

perform HPV testing and act according to the result obtained [2]. If an HPV test is not available the patient should be referred to colposcopy.

3. Guidelines for referring a patient to colposcopy. Standards of quality.

3.1 WAITING TIME TO PERFORM COLPOSCOPY IN ASYMPTOMATIC PATIENTS WITH AN ABNORMAL SCREENING TEST RESULT

With abnormal cervical screening test results a colposcopic examination should be performed as well as evaluation of the lower genital tract [27]. Depending on the organization of health care and screening, the patient is referred to a specific unit for performing this study. It is very important to ensure that the time between the screening test results and the colposcopic examination does not imply a worsening in the prognosis, especially in cases of greater risk or on suspicion of invasive lesions. Some studies have shown that the prognosis of an underlying malignant lesion is directly related to a delay in implementing adequate treatment [2, 28-30].

The risk of a severe cervical lesion largely depends on the abnormality found in the screening test. This aspect conditions the recommended interval of time to perform the evaluation of the patient.

In this regard, there are many publications in which the recommendations are not completely homogeneous and are based on territorial health care policies [30].

In general, earlier evaluation is recommended for more severe abnormalities (alterations \geq HSIL/CIN2) compared to alterations of a lesser grade. Nonetheless, most guidelines recommend that women with abnormal detection tests should be evaluated within a “reasonable time” taking into account not only the risk of high grade lesions or underlying cancer but also the emotional stress associated with waiting when screening test results are abnormal [29].

3.1.1 Cytology showing atypical squamous cells of undetermined significance (ASCUS)

This is the most common cytological alteration. The global prevalence of HPV infection in women with ASCUS ranges from 33-51% [27] and varies based on age. The presence of lesions \geq HSIL/CIN2 in women with ASCUS cytology results with a positive HPV determination is between 5-12% and between 0.1-0.2% for CC [27].

In the different guidelines published it is described that in cases with an ASCUS cytology that is positive for the HPV test, the recommended evaluation time should be between 6 and 12 weeks [2, 30].

Recommendation: colposcopic evaluation of a patient with ASCUS cytology and positive HPV results should be performed within 8 weeks.

3.1.2 Cytology with low grade squamous intraepithelial lesion (LSIL)

LSILs are found in 2-3% of all cytological studies. Approximately 12-16% of these alterations correspond to a lesion \geq HSIL/CIN2 after a colposcopy and biopsy study [27], and the risk of CC is estimated as having a grade similar to the ASCUS cytological result [31]. The National Health Service (NHS) and the American Society for Colposcopy and Cervical Pathology (ASCCP) recommend that in these cases a colposcopic examination should be performed within 6 to 12 weeks [2, 30].

Recommendation: Colposcopic evaluation should be performed within 8 weeks in a patient with LSIL cytology.

3.1.3 Cytology showing high grade squamous epithelial lesion (HSIL)

This cytological result is found in 0.5 to 1% of all screening cytologies.

In cases with a cytology of HSIL, the definitive histological diagnosis shows a lesion \geq HSIL/CIN2 in approximately 60% of the cases and CC in 2% [27]. Taking into account the high risk of the presence of an underlying lesion \geq HSIL/CIN2, there is wide consensus regarding the need to perform colposcopic evaluation within a period of no greater than 4 weeks after the HSIL cytological result [2, 29, 30], which would adjust the treatment time to within a safe interval.

Recommendation: Colposcopic evaluation should be performed within 4 weeks in a patient with HSIL cytology.

3.1.4 Cytology showing atypical squamous cells which cannot rule out a high grade lesion (ASC-H)

The diagnosis of uncertain atypical squamous cells that cannot rule out a high grade intraepithelial lesion (ASC-H) is also infrequent (between 0.27 and 0.6% of all screening cytologies). This result represents a medium-term risk of lesions \geq HSIL/CIN3 of 26 to 68% [27].

There is no firm consensus in the literature defining the time at which these ASC-H alterations should be evaluated. Nonetheless, considering the high probability of the presence of a severe underlying lesion, rapid evaluation times of between 2 to 6 weeks have been described in the literature [2, 29, 30, 32].

Recommendation: Colposcopic evaluation should be performed within 4 weeks in a patient with ASC-H cytology.

3.1.5 Atypical glandular cells (AGC) that cannot rule out a high grade lesion (AGC-H)

The finding of atypical glandular cells (AGC) is very infrequent, representing approximately 0.4% of all cytologies, and they are associated with a wide range of both benign and malignant alterations [27]. The nomenclature establishes several terms attempting to orient the origin of the glandular elements found in the sample (endocervical, endometrial or non specific) or indicating the suspicion of malignant squamous disease (AGC-H).

Although the term AGC suggests glandular pathology, this result is more frequently associated with squamous cervical lesions (SIL/CIN of any grade) than with glandular lesions, with there being an elevated probability of diagnosing lesions \geq HSIL/CIN2 (9-54%) [27]. In general, in young women with AGC-H cytology results there is a greater prevalence of lesions \geq HSIL/ CIN2, while in women over 35 years of age a greater prevalence of glandular pathology is observed [27]. Glandular and squamous lesions can frequently coexist (half of the cases diagnosed with adenoma in situ [AIS] are also diagnosed with CIN). Therefore, in cases with AGC cytology the diagnosis of CIN does not totally exclude an AIS or adenocarcinoma.

Lastly, AGC can also be associated with carcinomas not related to HPV. Thus, in cases with AGC cytology, a negative HPV test does not totally exclude the possible presence of an invasive lesion. In these cases, a negative HPV test identifies a subgroup with greater risk of endometrial than cervical neoplasia [27].

In women with AGC or AGC-H cytologies, there is no consensus in the literature as to the time within which these alterations should be evaluated. Nonetheless, in view of the high probability of a severe underlying lesion, rapid evaluation times of between 2 to 6 weeks have been described [2, 29, 30, 32].



Recommendation: Colposcopic evaluation should be performed within 4 weeks in a patient with AGC or AGC-H cytology.

3.1.6 Cytology showing adenocarcinoma in situ (AIS) or carcinoma

This cytology result suggests the possible presence of a very severe or invasive squamous or glandular cervical lesion, and therefore, cervical evaluation by colposcopy should be performed as soon as possible. The guidelines recently published by different scientific societies recommend that in no case should the colposcopy study be performed later than 2 weeks after the receipt of the cytological results [2, 29, 30].

Recommendation: Colposcopic evaluation should be performed within 2 weeks in a patient with AIS cytology

3.1.7 Positive HPV test and negative cytology

Patients with a positive HPV test and negative cytology present a 5-10% risk of a lesion \geq HSIL/CIN2 at 5 years. In this case, there is no consensus as to the best therapeutic attitude to be taken. However, a conservative approach of repeating the HPV test at 12 months has shown a sensitivity for detecting a lesion \geq HSIL/CIN2 that is comparable to immediate colposcopy and with the great advantage of substantially reducing the number of colposcopies.

If the HPV test continues to be positive after one year, colposcopy evaluation is indicated [27]. Here the review of the standards has a lower grade of consensus. Some scientific societies recommend that the colposcopic evaluation of these patients should not exceed more than 26 weeks [30], while other societies recommend that these women be evaluated within a period of 6 to 12 weeks [2], since the risk of a HSIL/CIN2 lesion is similar to that presented by women with ASCUS and a positive HPV test or with LSIL [31, 33]

Recommendation: Colposcopic evaluation of patients with negative cytology and a persistent positive HPV test for at least one year should be performed within 16 weeks.

3.2 WAITING TIME TO PERFORM COLPOSCOPY IN PATIENTS WITH SYMPTOMS OR WITH SUSPICIOUS FINDINGS IN THE ROUTINE GYNECOLOGICAL EXAMINATION

On certain occasions we may find patients with a symptomatology suggesting the presence of a severe cervical lesion, or an asymptomatic woman with a cervical examination suspected of presenting CC (friable, with ulcerated lesions, bleeding). With these findings the patient should be referred to specialized consultation for colposcopic evaluation.

3.2.1 Women with symptoms suggestive of cervical cancer (CC)

The symptoms which most often suggest an invasive process are [34]:

- Spontaneous, irregular and repeated genital bleeding.
- Repeated bleeding during coitus.
- Anomalous vaginal fluid (watery, mucoid, bad smelling). Although it is not a specific finding and may be confounded with symptomatology of vulvovaginitis, it should be taken into account, especially if the patient presents negative cultures.

In these circumstances, if there is clinical suspicion of the presence of an invasive cervical lesion, the genital tract should be assessed immediately by performing a colposcopy. Most scientific societies recommend a colposcopic evaluation within a period of no greater than 3 weeks [2,29, 30].

Recommendation: In patients with symptoms suggestive of CC colposcopic evaluation should be performed within 2 weeks.

3.2.2 Macroscopically abnormal cervix in the screening test sample

In asymptomatic cases in which the cervical examination suggests the presence of a malignant lesion, the possibility of performing cervical biopsy within the shortest time possible or even at the same time as the screening should be evaluated if there is adequate material.

In these women it is recommended to take a biopsy of the most suspicious area, attempting to avoid zones of necrotic appearance in which the histological evaluation normally does not achieve an adequate yield [34]. In addition, endocervical curettage should be performed independently of the result of the cervical cytology.

If it is not possible to directly obtain a sample, the patient should be referred to the Colposcopy Unit within a period of 2 weeks [2, 29, 30].

Recommendation: Colposcopy should be performed within 2 weeks in women with a macroscopically abnormal cervix in the screening sample.

3.3 Waiting time between confirmed histological diagnosis and colposcopy and treatment

All patients who are candidates to receive treatment should previously undergo an exhaustive colposcopic study performed by specialized personnel.

All the treatments of high grade premalignant lesions should be carried out in centers of colposcopy units which are adequately equipped and have specialized professionals.

The patients should be informed of the need for and type of treatment and must give consent, preferably signed (if consent is verbal, this should be reported in the clinical history).

When treatment is indicated in women with HSIL/CIN2-3, the procedure should be performed with a period of less than 8 weeks.

Among patients treated with excisional procedures:

- The percentage of cases with excision of a single surgical piece should be greater than 80%.
- The proportion of severe hemorrhagic complications (requiring additional treatment) should be less than 5%.
- The proportion of readmission due to treatment-related complications should be less than 2%.

Recommendation:

- All cervical treatments require a previous colposcopic study performed in a Colposcopy Unit by specialized professionals.
- The treatment of HSIL/CIN2-3 should be carried out in less than 8 weeks.
- Excisional procedures should present less than 5% of hemorrhagic complications and less the 2 % of readmissions.

4. Colposcopy instruments and material

4.1 COLPOSCOPY

A colposcopy is a low resolution, stereoscopic, binocular, field microscope which has a powerful light source and is used for visual examination of the cervix and the rest of the lower genital tract. The colposcope is an essential tool for the diagnosis of preneoplastic lesions.

The colposcope was designed by Hans Hisselmann in 1925 with the aim of facilitating early detection of cervical changes preceding the development of CC. Since then, this tool has become a key tool for the secondary prevention of CC. In the last years, colposcopes have advanced, improving the resolution and adapting accessories in order to obtain, store and export videos and digital images. These improvements in the colposcopic images facilitate control of the quality of the diagnostic or auditory images to evaluate the efficacy of the study as well as carry out teaching activities with high resolution monitors [35].

4.1.1 Elements making up a colposcope

The head of the colposcope is the essential part of this instrument and is made up of the following elements [36]:

- **Lens:** colposcopes have two binocular lens situated in straight optic tubes which allow adjustment of the dioptries to individually correct refraction errors. The angle of the binocular tubes in relation to the observation line from the eye to the cervix can be inclined (45°) or straight (180°). The focal distance or the distance between the colposcope and the area examined is determined by the curvature of the lens. It is fundamental for the focal distance to be sufficiently long to introduce the instruments necessary to obtain samples, biopsies or to perform treatments. In general, colposcopes have an adjustable focal distance of between 200 and 350 mm to easily adapt any type of forceps or procedure.
- **Focus:** the colposcope is focused by displacing the head of the colposcope in relation to the patient (macrometric focus) or using a focusing adjustment knob (micrometric focus).
- **Filters:** green or blue filters are available for all colposcopes, and they act by impeding the transmission of red light, highlighting the view of the blood vessels located in the stroma and facilitating evaluation of their characteristics.
- **Magnification:** most colposcopes have a magnification changer and some make progressive magnification with zoom capacity. Usually low magnification is used (x2 to x6) to evaluate the external genitals, a medium magnification (x8 to x15) is used for the vulva, vagina and cervix) and a high magnification (x15 to x25) is used to assess fine, specific, details such as glandular orifices, vascular patterns, etc. In general, the greater the magnification the lesser the field of view and the lesser the illumination of the object of interest. In practice, a magnification greater than 15-20 is rarely used.
- **Light source:** Visualization of the cervix and vagina requires good illumination. Over the years many types of light sources have been used and have evolved in parallel with the technological advances (incandescent light bulbs, tungsten halogen and arc lamps). The current colposcopes have cold xenon or LED light which provides brighter illumination and generates less heat. It is important for the light source of the colposcope to provide good illumination to the whole field of observation, and therefore, it must be potent, and it should be possible to adjust the intensity to achieve adequate illumination to the area to be examined. The location of the lamp should also be accessible to facilitate changing. In the colposcopes currently available, the lamp is set outside the head and the light passes through a fiber optic cable. This cable allows the use of lamps of greater intensity.
- **Adjustable arm and stand:** the head of the colposcope is joined to the central axis and in turn has an adjustable articulated arm which can move in all directions. The colposcope can be fixed to a examination table, set up on a pedestal or be adapted to a giratory arm subjects to the wall or ceiling. However, in general, the base is usually a wide platform which acts as a counterweight and has wheels for purposes of mobility.

4.1.2 Colposcope accessories.

In the last years many accessories have been adapted to colposcopes to optimize examination of the anogenital tract and visualize the images on monitors or to capture and transfer videos or digital images. Among all these accessories the following are of note:

- Image capture systems of both standard and high definition. These systems can store, view and review the images at a later time. The resolutions now available range from 640×480 to 1920×1080 pixels.
- Tactile monitors, for the visualization and management of the digital colposcope systems.
- Integrated registry systems allow the acquisition and availability of patient information. To do this, structured databases, generally the SQL type, are used, which include the different examinations, images and videos in the same registry of the patient.
- Tools for the integration of the information systems of the colposcope to the hospital information systems. The information stored in the colposcope system can be integrated into the Picture Archiving and Communication System (PACS) using Digital Imaging and Communication in Medicine standards (DICOM) or Health Level
- Seven (HL7). These systems not only satisfy the legal requisites regarding patient data protection, but this archiving system also provides structured management of each study performed allowing flexibility and facility to follow the disease [37].

4.2 INSTRUMENTS FOR COLPOSCOPY CONSULTATION

A colposcopy study requires a series of materials and instruments to evaluate the lower genital tract. The objective of the instruments used in the colposcopy examination is to facilitate access and allow magnified inspection and collection of samples for histologic study.

The instruments necessary to perform a colposcopy can be grouped into three categories: 1) material to facilitate access for colposcopic viewing, 2) fungible material, and 3) material necessary to obtain samples.

4.2.1 Instruments for colposcopy access and viewing

In order to carry out a colposcopy examination it is necessary to have material to achieve access to and expose the cervical and vaginal surface. The instruments which should be used are described below:

- **Vaginal speculum.** This instrument is made up of two valves with a mechanism to separate these valves and widen the opening or maintain it opened to provide visualization of the whole cervix and vagina. There are several valve separation and fixation systems. Vaginal speculums are available in different lengths and widths. The most standard widths are 16, 24 and 36 mm, and the remaining are special sizes. Vaginal speculums may be metallic (reusable) or plastic (disposable). The metallic speculums are usually covered with isolating material and may be available in a fume extraction tube (usually used in surgical procedures).
- **Vaginal retractor.** With this instrument the lateral walls of the vagina can be retracted to facilitate view of the cervix. In determined patients, especially obese or pregnant women in the 2nd or 3rd trimester, the vaginal walls tend to prolapse on placement of the speculum, thereby making visualization of cervix difficult. In extreme situations the vaginal walls may even totally hide the cervix. One alternative to the use of the vaginal retractor is to use a sheath of the ultrasonographic vaginal probe or a condom to cover the valves of the speculum. Once the speculum has been placed or just before placement, a cut is made at the point so that when the speculum is opened, the sheath or condom impede the prolapse of the vaginal walls towards the mid-line.
- **Endocervical speculum.** This instrument allows visualization of the endocervical canal in cases in which the transformation zone is not completely viewed or a lesion which extends to the interior of the canal is identified. This speculum has two narrow opposing valves of 1.5 to 2 cm which are placed inside the external cervical orifice and are then gently opened in order to observe the endocervical canal.

4.2.2 Fungible material

Swabs and gauzes are used to clean the flow or mucous impeding correct colposcopic evaluation as well as to apply acetic acid and lugol solution in the study area.

4.2.3 Instruments for collection of histological samples

The colposcopic examination frequently determines the presence of lesions requiring histological study. The instruments necessary for doing biopsies are specific according to the area to undergo biopsy.

- **Biopsy punch forceps:** biopsy forceps are especially designed to obtain small tissue samples (2-5 mm). They are formed by a handle and a biopsy head at the distal end. This biopsy head is composed of a jaw with a part which punches and cuts. Different models are commercialized (Burke, Kevorkian, Tischler, Schubert, Schumaker etc.) with small differences in design, shape and jaw characteristics (round, oval, triangular, square-shaped). With the wide availability of different biopsy forcep models the biopsy can be individualized adapting the histological sample to the characteristics of the cervix of the patient.
- **Endocervical curettage:** This is performed to obtain histological samples from the endocervical canal. The instrument used is a hand-held curette which has a handle to grasp and a slightly curved cutting head or end. A small indentation in the rod indicates alinement of the instrument with respect to the distal cutting edge. The cutting edge may be rectangular and in some models may have a basket in which the tissue obtained is collected.
- **Dermatological punch:** although this instrument is not specifically used in biopsy sampling with colposcopy, it is an essential tool for examination of the lower genital tract. This instrument has a circular hollow blade for obtaining histological material from vulvar-perineal lesions. There are different sizes to obtain a cylinder of cutaneous tissue of different diameters. The punch is rotated in order to obtain a cylinder of tissue which is extracted after excising the base. The biopsy should include all the dermoepidermal thickness.

4.2.4 Other materials

Different instruments are often used to facilitate exposure or traction of the tissue to be examined.

- **Pozzi forceps:** this instrument fixes the cervix. It is useful in situations in which the biopsy forceps slip on the epithelial surface or when the ligaments of the pelvic floor are lax or there is uterine hypermobility.
- **Hooks:** these are hook-shaped metallic rods which are not sharp at the end in order to avoid tearing. They are especially useful in vaginoscopy of patients with previous hysterectomy since they allow traction and visualization of the fundus of the vaginal pouch and the angles of the colpotomy (dog ears). They also facilitate punch forcep biopsy of lesions in smooth vaginal walls in which the punch biopsy alone cannot become fixed to the tissue to be extracted.

4.3 ACETIC ACID

- **Composition:** 3-5% glacial acetic acid in distilled water [38]. Concentrations at 5% produce more rapid and durable histological response than 3%.
- **Mechanism of action:** the exact mechanisms of how acetic acid whitens the lesional areas are unknown. Two mechanisms which may occur together have been postulated. On one hand, acetic acid temporarily dehydrates the cells, reducing the nucleus/cytoplasm relationship. The refraction of the light on the surface of the cervix produces a visualization of the tissue, which is more intensive and prolonged according to the cellular density of the epithelium. On the other hand, it has been suggested that there may be a possible precipitation or reversible coagulation of cellular proteins such as cytokeratins and nuclear proteins. In dysplastic processes in which the nuclei are larger, there is more protein precipitation, and therefore, less absorption of light, generating an acetowhite epithelium [39].
- **Method of use:** acetic acid may be applied using a dampened swab or with direct instillation or pulverization on the cervix. Acetic acid should act for at least 20 seconds before withdrawal in order to see acetoreactivity (speed at which the acetowhite images appear). Depending on the grade of the lesion, more

or less waiting time will be needed for observing abnormal images.

- **Adverse effects:** in general, acetic acid is well tolerated with only some cases presenting mild irritation and itchiness which ceases spontaneously. Allergic reactions are very rare.

4.4 LUGOL SOLUTION

- **Composition:** Lugol iodine solution is composed of potassium iodine (10 g), distilled water (100 ml) and iodine crystals (5 g) [37]. This solution is unstable at room temperature and has an expiration period of 3-6 months.
- **Mechanism of action:** Lugol solution has avidity for glucogens found in the intermediate layer of the squamous epithelium of the cervix and vagina, producing a reddish-brown color which is more or less intense based on the quantity of glucogen in the cells. Since the cylindrical epithelium does not have glucogen, it does not present changes in color or presents a very light brown color. The squamous epithelium of immature metaplasia, menopause or inflammatory processes has a lower glucogen content, presenting areas of lesser or disperse uptake that are badly defined. Dysplastic epithelium and cancer have no glucogen, and therefore, when the lugol solution is applied, it acquires a mustard yellow or golden yellow saffron color. Neither do zones of leucoplasia or hyperkeratosis take up iodine. Condylomas may not become stained or staining may be variable.
- **Method of use:** Lugol solution is applied in the same way as acetic acid, using a swab by direct instillation or pulverization. In this case, it is not necessary to wait since the staining effect is very rapid, but it may be necessary to continue with the staining to obtain an homogeneous color.
- **Adverse effects:** this solution does not normally produce adverse effects, although in some cases it produces mild irritation with itchiness which spontaneously ceases. However, some sensitive patients may present an allergic reaction to iodine.

4.5 HEMOSTATIC SOLUTIONS

Biopsy of the cervix is a usual procedure in the study of intraepithelial lesions. Bleeding is usually minimal and self-limiting since tissue resection with the instruments used does not usually exceed 5 mm of surface and 2 mm of depth. The most frequent hemostatic products used after biopsy are silver nitrate sticks and iron perchlorate or Monsel's solution.

Silver nitrate sticks. These belong to the group of so-called antiseptic and disinfectant medications. Although their indication in the summary of product characteristics is for warts and skin granulomas, mouth ulcers and epistaxis, they can also be used to perform hemostasis after cervical biopsy [39].

- **Composition:** they are commercialized in the form of plastic sticks of 2.4 mm in diameter and 9.5 cm in length with a small head of 42.5 mg of silver nitrate at one of the ends.
- **Mechanism of action:** induce hemostasis by chemical cauterization.
- **Method of use:** apply the end of the stick to the center of the biopsied zone for a few seconds. This cauterizes the tissue, acquiring a white color, and contact to the surrounding epithelium should be minimal.
- **Adverse effects:** they present no secondary effects except in the case of excessive use which produces a dark gray color in the cervix.

Monsel's solution. Leon Monsel described the solution given his name in 1856 as a potent hemostatic agent. At present, Monsel's solution is used as a topical hemostatic agent in minor surgical procedures such as biopsies in gynecology, proctology, dermatology, otorhinolaryngology and odontology. In a recent study it was reported that compared to "wait and see", the application of Monsel's solution showed a significant reduction in bleeding at 6 hours after cervical biopsy [40].

- **Composition:** ferric subsulfate (15 g), ferrous sulfate powder, sterile water for mixing (10 ml) and glycerol starch (12 g). In addition to the solution there are two other pharmaceutical forms of therapeutic utility in paste and gel form, with the same pharmacological properties as the solution. The semisolid forms are more easily applied on the target tissues, and it has been shown that they have many more irritating

characteristics than the solution [37]. The expiration period is 6 months.

- **Mechanism of action:** solutions with iron salts for topical use have astringent and hemostatic properties. The action is due to the ferric ion which is a potent protein precipitant [41].
- **Method of use:** a cotton swab with the solution is gently pressed onto the bleeding surface for several seconds to avoid the hemostatic scab falling on withdrawal of the swab. It should be applied after completing the biopsy because it may interfere with the interpretation of the histological result [42].
- **Adverse effects:** no relevant adverse effects have been described.

4.6 MAINTENANCE OF COLPOSCOPY MATERIAL

Maintenance of the colposcopic equipment and sterilization of the instruments are two fundamental processes for achieving both optimum performance in the study of the lower genital tract and to guarantee safety in the transmission of infections among patients.

After use of the colposcope, it should be adequately cleaned and covered in order to avoid the accumulation of dust in the lens. The lens should be cleaned with specific material for this use. Avoid the use of paper or gauzes which may scratch the lens. The fiber optic cables should be protected against bumps, torsions or folding to impede rupture of the fiberglass.

With use, biopsy forceps may become blunt or the articulation which opens or closes the forceps may harden, especially if sterilized in the autoclave on metal trays and they are not packaged prior to sterilization. Biopsy forceps which have become blunt obtain tissue samples with more artefacts due to tissue crushing and produce more pain, and therefore, it is important to maintain these forceps in good state and to periodically sharpen them.

Disinfection/sterilization of the instruments used is an essential process to ensure that these are free of infectious agents and may be safely reused in diagnostic and surgical processes [43].

Reuse of material implies carrying out the following procedures: decontamination, cleaning and sterilization or high grade disinfection.

- **Decontamination:** this is a series of measures adapted to ensure that the use of a medical instrument is safe due to a reduction in contamination by microorganisms. This process can inactivate the hepatitis B virus and HIV. After use, the instrument is placed in a plastic recipient with chlorine solution at 0.5% for 10 minutes.
- **Cleaning:** this process is crucial to ensure that the instruments are safe and aseptic. Energetic manual cleaning with water and liquid soap or detergent eliminates biological material such as blood, fluids and tissue residue. If biological residue remains present, this converts the instruments into a reservoir of germs.
- **Sterilization:** This consists in destroying all the microorganisms present on the instrument by exposure to physical or chemical agents. This process eliminates all microbial life forms, including bacterial spores. The sterilization process is fundamental to safely reuse instruments in clinical settings. Two sterilization methods are described:
 - **Sterilization by high pressure saturated steam (Autoclave):** this is done by placing uncovered instruments into an autoclave for at least 20 minutes at a temperature between 121-132°C.
 - **Chemical sterilization:** this consists in submerging the instruments in a solution of glutaraldehyde at 2-4 % for 20 minutes or in formol at 8% for 24 hours. This is an alternative to steam sterilization. It requires special manipulation with gloves. Instruments sterilized by glutaraldehyde or formol should be rinsed with sterile water prior to use since these chemical products leave residue on the instruments. In general, steam sterilization is preferred over chemical sterilization because, among other reasons, glutaraldehyde is very expensive and formol is very irritating to the skin, lungs and eyes.
- **Decontamination of consultation surfaces.** The auxiliary tables, colposcope, electrosurgical equipment, vapor aspirators, lamps, etc. should be decontaminated after each procedure using a chlorine solution at 0.5%, ethylic alcohol or isopropyl at 60-90% or other chemical disinfectants such as iodine fluorides.

5. Nomenclature and description of colposcopic findings

5.1 TERMINOLOGY

As mentioned in previous sections, colposcopy is a structured and orderly examination of the cervix which has the objective of interpreting colposcopic findings (colposcopic impression) and direct the biopsy to obtain histological confirmation of a determined lesion.

To do this, it is very important for the nomenclature to be uniform for good reproducibility. For this objective, it is fundamental to have a terminology developed by the consensus of professionals and scientific societies involved in colposcopy. Along history multiple colposcopic classifications have been used and modified according to the new knowledge acquired.

At present, 2 colposcopic classifications are the most commonly used in health care practice: the classification proposed by the International Federation of Cervical Pathology and Colposcopy (IFCPC) [1] (Table 5.1) and the classification of the American Society for Colposcopy and Cervical Pathology (ASCCP) [44].

The classification proposed by the IFCPC [1] is the most internationally accepted. The last update of this classification was carried out by a committee made up of 13 colposcopists who are representatives of different scientific societies around the world and was presented in Río de Janeiro in 2011 (Table 5.1). With respect to the previous classification, the principal novelties of the new classification are:

1. The concept of adequate examination (replacing the classical concept of satisfactory colposcopy).
2. The description of the lesions in relation to size, localization and location with respect to the transformation zone.
3. Two new signs have been included in the section on grade 2 changes (inner border sign and the ridge sign).
4. The classification and terminology for vaginal lesions has been included.

In 2016, the ASCCP constituted a working group (WG1) to review and update the colposcopic terminology of the IFCPC as well as analyze the benefits and potential unwanted

effects of the same based on review of the data published in the literature [44]. The most notable changes included in the last ASCCP classification compared to that by the IFCPC are the following: 1) the concept of adequate or inadequate and the types of TZ have been replaced by a description as to whether the cervix can or cannot be visualized and the reason for non visualization. 2) it should be reported whether the squamocolumnar junction can or cannot be completely visualized without discussing the types of TZ. The reason for this is that the concept of type 2 TZ is little reproducible and is of scarce interest in the management of the lesion. 3) replacement of the nomenclature “grade 1 or 2” changes by low or high grade changes, since these terms are better correlated with cytological and histological terminology. The principal differences between the IFCPC and ASCCP terminology are shown in table 5.2.

Table 5.3 shows the different colposcopic classifications over time and the most relevant changes made.

The present guidelines have adopted the terminology of the IFCPC (Rio de Janeiro 2011) [1] which, in addition to being the most commonly used, this terminology was achieved by consensus and is the “official” terminology in Europe.

Recommendation: The colposcopic terminology that should be used in clinical practice is that of the IFCPC 2011 Classification.

5.2 ACCURACY OF COLPOSCOPIC DIAGNOSIS

The main objective of the colposcopic terminology is to obtain the best correlation between the colposcopic changes described and the histological lesion. Globally, colposcopy is a more or less subjective and operator-dependent evaluation technique and thereby presents a poor interobserver correlation even among expert evaluators. In addition, colposcopy is a dynamic technique

and loses validity when interpreting static images.

The highest degree of concordance is achieved in the interpretation of acetowhite images with a kappa index of 0.37, 95%CI (0.30-0.45) [49]. However, if only the acetowhite changes are assessed, the correlation is lower than if the evaluation of the border of the lesion and the vascular pattern are included [50].

Some studies have reported a good correlation of the colposcopic classification with the histology of the lesion [51] while other studies have found a poor correlation,

suggesting that the grade of concordance depends on the skill and experience of the colposcopist [35]. The grade of concordance is greater in high grade lesions or when the epithelium is normal and is very low in cases of low grade lesions [51, 52]

The technology used for colposcopic evaluation is considered to be a factor with considerable repercussion. At present, high definition colposcopic equipment can obtain high quality images providing greater diagnostic accuracy. Some recent studies using last generation colposcopes have obtained a very good correlation between the

Table 5.1: Colposcopic classification of the International Federation of Cervical Pathology and Colposcopy (IFCPC) 2011 [1]

Colposcopy terminology of the cervix of the IFCPC 2011 ¹			
General Evaluation		<ul style="list-style-type: none"> Adequate/ inadequate due to... (i.e.): cervix not clear due to inflammation, bleeding, scarring). Visibility of the squamocolumnar junction completely, partially or not visible. Types of transformation zone 1,2,3	
Normal colposcopic findings		Original squamous epithelium: <ul style="list-style-type: none"> Mature Atrophic Columnar epithelium <ul style="list-style-type: none"> Ectopy Metaplastic squamous epithelium <ul style="list-style-type: none"> Naboth cysts Glandular openings and/or glandular crypts Deciduosis in pregnancy	
Abnormal colposcopic findings	General principles	Location of the lesion: inside or outside the transformation zone, clockwise location of the lesion. Lesion size Number of quadrants of the cervix covering the lesion, size of the lesion as percentage of cervix.	
	Grade 1 (Minor)	Thin acetowhite epithelium. Irregular border	Fine mosaic, Fine pointed
	Grade 2 (Major)	Dense acetowhite epithelium. Rapid appearance of acetowhite epithelium. Open glandular orifices with thickened edges	Thick mosaic, Thick pointed, Delimited borders, Sign of the inner border limit, Ridge sign
	Not specific	Leukoplasia (keratosis, hyperkeratosis), Erosion Lugol solution (Schiller test): positive/negative	
Suspicion of invasion		Atypical vessels Additional signs: thin vessels, irregular surface, exophytic lesion, necrosis, ulceration (necrotic), nodular tumoration.	
Miscellaneous finding		Congenital transformation zone, condyloma, polyp (exocervical/ endocervical) Inflammation	Stenosis, Congenital abnormality, Post-treatment abnormality, Endometriosis

Table 5.2. Differences between the ASCCP 2017 and the IFPC 2011 terminology [44]

	ASCCP 2017	IFCPC 2011
General impression: visibility of the cervix	Totally /Not totally visible	Adequate/Inadequate
General impression: visibility of the squamocolumnar junction	Totalmente /No totalmente visible	Completely/Partially/Not visible
General impression: type of TZ	Not used	Type 1,2 or 3 TZ.
Abnormal colposcopic findings	Low grade changes/ High grade changes	Grade 1 (minor) Grade 2 (major)
Type of excision	Not considered	Excision type 1, 2 or 3

Table 5.3. Terminology used in the different classifications over time

Author/ Year	Normal findings	Abnormal findings	Other terms
Hinselmann 1933 [35]	Thick leukoplasia	Mosaic leukoplasia mosaico	Cervicouterine ectopy
Coppleson 1960 [45]	Grade I, not suspicious, White semitransparent epithelium, flat, with indistinct borders	Grade II, suspicious white, opaque epithelium with very suspicious defined Grade III borders	Transformation zone (TZ)
IFCP Graz 1975 [46]	Normal colposcopy	Atypical TZ	Colposcopy not satisfactory. Miscellaneous
Reid 1985 Puntaje [45]	Category 1, benign, Minor dysplasia	Category 2, intermediate Category 3, suspicious	4 criteria: Border, color, vessels, iodine uptake
IFCP Roma 1990 [47]	Normal colposcopy Cylindrical epithelium: ectopy	Abnormal colposcopy inside or outside the TZ. Mosaic/ Fine pointed/coarse	Miscellaneous not acetowhite
IFCP Barcelona 2002 [48]	Type 1, 2, 3 TZ.	Minor/major changes. Suggestive of high/Low grade lesion	Colposcopy suggestive of invasive cancer
IFCP Rio de Janeiro 2011 [1]	Includes metaplasia and deciduosis	Grade 1 changes. Grade 2 changes. Lesion location.	Includes description of vaginal lesions.
		Quadrants occupied New signs	Incorporates types of excision
ASCCP 2017 [44]	Includes ectopy, Naboth cysts, glandular crypts, metaplasia and deciduosis	Localization and size of the lesion. Low/high grades/invasive changes. New signs	Miscellaneous: polyp, inflammation, congenital TZ, Post-treatment

colposcopic classification and the biopsy results (kappa 45.8% vs.74.1%) [53].

With regard to the colposcopic signs included by the IFCCP in the last classification, one study which evaluated lesion size, in addition to the 4 variables of the Reid index, obtained an increase in the specificity but at the expense of lower sensitivity [54]. Along the same line, another retrospective study in 335 patients showed an elevated specificity and positive predictive value for the diagnosis of lesions \geq HSIL/CIN2 for the inner border sign, the rag sign and the ridge sign [55].

Another comparative study of 525 colposcopies reviewed by 13 experienced colposcopists showed a good correlation with the high grade lesions using the IFCCP 2011 classification, with a sensitivity and specificity of 63.64% and 96.01%, respectively. They also found 2 signs to have predictive value: the inner border sign and the ridge sign, with less agreement for defining the TZ [56].

Recommendation:

- The principal objective of colposcopy terminology is to obtain the best correlation between the colposcopic findings and the histologic lesion.
- Acetowhite changes have a greater grade of correlation, and this increases with evaluation of the vascular pattern and the borders of the lesion.
- Some recently introduced colposcopic signs (inner border sign, ridge sign and the rag sign) have an elevated specificity and positive predictive value for lesions \geq HSIL/CIN2

5.3 BENEFITS OF COLPOSCOPY

Historically, before colposcopy became a part of secondary CC prevention programs, most women with cytological alterations underwent conization or hysterectomy with the consequent associated morbidity [44]. At present, colposcopy is a fundamental technique in screening programs.

The results of screening tests condition the risk of carrying a lesion \geq HSIL/CIN2. According to the level of risk, women

are referred to colposcopy to confirm the presence of a lesion and orient the management approach to treatment or follow-up.

The main advantages of colposcopy in the evaluation of the risk of lesions \geq HSIL/CIN2 are:

1. Colposcopy can detect premalignant lesions of the lower genital tract.
2. Colposcopy can determine the most adequate biopsy site.
3. Colposcopy can facilitate and individualize treatments.
4. Colposcopy allows the follow-up of intraepithelial lesions which may be treated or followed without treatment. At present, in young women with small-sized lesions \geq HSIL/CIN2, conservative management is accepted. Colposcopy is a key element in the follow-up of these lesions [57].

It was recently proposed to include the impression of the colposcopic results with those of the screening test to standardize the risk of lesion [58]. This suggestion should not be confounded with the use of colposcopy as the first step in screening. Colposcopy is not recommended for routine gynecological evaluation of women since this indication has not shown any benefit in the early diagnosis of HSIL lesions [57].

Colposcopy before “see and treat”. The option of see and treat should be exceptional and reserved for patients in whom follow-up is not possible and colposcopy results show grade 2 changes. As advantages, colposcopy avoids underestimation of the biopsy and reduces patient anxiety. However, the most important risk is the elevated percentage of conizations with a negative histology [57].

Intraoperative colposcopy. This procedure can reduce treatment in specific cases with possible spontaneous regression.

Recommendation:

- The use of colposcopy shows greater benefits in the detection of lesions (guides biopsy and allows histological confirmation).
- Conization should be performed under colposcopic control.

5.4 POTENTIAL HARMFUL EFFECTS OF COLPOSCOPY

As an examination technique, colposcopy does not present any contraindications. It may be used in patients with cervicitis and may even contribute to the diagnosis of this inflammatory process. Both anticoagulation and even active bleeding are not contraindications, although they may induce difficulties [28]. The risks and morbidity associated with colposcopy are considered to be very low (table 5.4) [44]. The main drawbacks of colposcopy can be summarized as follows:

- **Pain.** Colposcopy is not considered to be a painful examination, and therefore, the administration of analgesic drugs are not necessary prior to the procedure. In a review of 19 randomized studies, there were no differences in the grade of pain among patients who received oral analgesics versus those who received placebo [59].
- **Anxiety.** The grade of anxiety during colposcopy (which may cause greater perception of pain and discomfort) and the possible benefit of strategies to reduce this sensation have been analyzed [60]. There is sufficient scientific evidence to demonstrate the negative psychological effects women present when they are informed of an abnormal result of the cervical study and the associated need to perform more tests. One recent study confirmed the negative psychological impact of colposcopy, although the results could not determine the factors which might predict this impact [61]. Effective information and communication are crucial to reduce patient anxiety. In addition, some studies have described a reduction in anxiety with the use of music or demonstrating the colposcopic images during the examination. However, a recent prospective study including 225 colposcopists concluded that the use of videocolposcopy does not reduce either anxiety or pain [62]. The utility of informative pamphlets seems evident in the reduction of the grade of sexual dysfunction which some women present in association with having undergone colposcopy [60].
- **Inadequate use of colposcopy.** As mentioned in the previous section, colposcopy has not shown to be an effective technique for primary screening of CC, and therefore, it should not be used for this indication [63].

- **Colposcopy performed by unexperienced professionals.** The principal harm induced is underdiagnosis of high grade lesions or cancer. False negative results in colposcopy are very related to the experience of the professionals and the number of biopsies performed [44]. On the other hand, excessive performance of biopsies and unnecessary procedures may induce potential harm related to insufficient professional training.
- **Anaphylactic reaction to lugol solution.** Isolated cases have been described including clinical manifestations of pruritis, vaginal edema, hypotension, tachycardia and breathing difficulties. The symptomatology usually remits upon withdrawal of the saline lugol solution [64].

Recommendation:

- The principal harmful effects of colposcopy reported by patients are pain and anxiety.
- Underdiagnosis or an excess number of unjustified biopsies are the potential harmful effects associated with colposcopy procedures performed by unexperienced professionals.

Table 5.4. Potential harmful effects of colposcopy			
Adverse effects	Result	Evidence	Treatment
Pain	No pain compared with placebo	Mild-Moderate	NO
Anxiety	Produces anxiety	Mild-Moderate	Videocolposcopy does not seem effective. Music may reduce anxiety.
Inadequate use of the technique	Unnecessary procedures, over treatment.	Not applicable	Follow guidelines and precise indications.
Scarce experience of the professional	Risk of underdiagnosis of HSIL histological lesions or cancer.	Mild	The formation of specialized units and expert colposcopists reduces the risk of underdiagnosis.
Others, anaphylaxia to lugol solution	Isolated case	Not applicable	Elimination of lugol

6. Standards of quality in colposcopic diagnosis

6.1 REGISTRY OF THE CLINICAL HISTORY OF PATIENTS REFERRED TO COLPOSCOPY

6.1.1 Anamnesis (pathological, gynecological and obstetric history)

Anamnesis prior to colposcopy should be exhaustive and include the general medical/surgical history as well as the gynecological and obstetric history of the patient and specific history related to diseases of the lower genital tract (cytologies, HPV tests, colposcopies and treatments) [65].

Questions related to the history of sexual relations may be embarrassing and stressful to some women, being an aspect which may have negative repercussion on the sincerity and quality of the responses [66]. Therefore, it would be better to avoid questions about sexual relations at the beginning of the consultation and wait until the patient feels more comfortable and a climate of trust has been achieved.

Likewise, women consulting for a colposcopy may be uncomfortable in the presence of persons other than the physician and may need to be accompanied by someone they trust. The consultation should not include more persons than strictly necessary.

Quality anamnesis should include [65]:

- Smoking habit.
- Date of last period (rule out pregnancy if in doubt).
- HIV
- Any type of immunosuppression.
- Parity
- Current hormonal situation: fertile age/pregnancy/menopause.
- Current contraception.
- History of hysterectomy or previous treatments for intraepithelial lesions.
- History of SIL (cervical, vaginal, vulvar or anal).
- Date and result of all the previous screening tests and biopsies available.
- Vaccination against HPV (including vaccination date and type of vaccine).

- Vacunación contra el VPH (incluyendo fecha de vacunación y tipo de vacuna)

Recommendation: On the first visit anamnesis should be exhaustive and include patient history (parity, HIV/immunosuppression), hormonal situation, contraception and data on premalignant disease (HPV vaccination, date and result of screening tests, history of SIL and previous treatments).

6.1.2 Indications for performing colposcopy

The exact indication to perform a colposcopy and the result of the screening tests (cytology/HPV test) that have led to this study should be reported in the clinical history of all cases [2, 65].

The fundamental objective of colposcopy is secondary prevention of CC. To fulfil this objective there are different indications for performing a colposcopy:

1. Initial study after an abnormal cytology result/HPV test.
2. Follow-up of patients with intraepithelial lesion before or after treatment. It is therefore essential to know the indication for performing the colposcopy and the results of the tests leading to this indication. Knowledge of previous screening results (cytology/HPV test) improves the sensitivity of the colposcopic impression for high grade lesions [2].

Recommendation: prior to performing a colposcopy it is essential to know the indication and the results of the screening tests.

6.1.3. Verbal information and informed consent

All patients should receive verbal information prior to colposcopy and this should always be registered in the

clinical history of the patient. In addition, it is recommended to give the patient a document (Annex 1) describing the characteristics of colposcopy and to which the patient authorizes and agrees to undergo the procedure. In this case, informed consent (Annex 2) should be included in the clinical history.

According to recommendations, other scientific societies have indicated the importance of informed consent. The National Health Service (NHS) states that to achieve minimal quality 95% of the women should receive verbal information prior to colposcopy

[2]. The American Society for Colposcopy and Cervical Pathology (ASCCP)

considers informed consent to be a basic element that must be obtained before all colposcopy procedures [65].

Recommendation: prior to colposcopy women should receive verbal information regarding the characteristics of the procedure and ideally informed consent should be obtained.

6.2 COLPOSCOPIC EXAMINATION

6.2.1 Cervical examination

The cervical examination by colposcopy should follow a systematic method [67, 68]:

- Revise the instruments to be used.
- Place the patient in a dorsal lithotomy position and cover the patient to make her feel more comfortable.
- Sit comfortably beside the colposcope.
- Turn on the colposcope and adapt the interpupillary distance and focus the lens to the personal characteristics of the examiner.
- Visualize the vulva and the perianal area with white light and at a magnification (x4) and on the appearance of any abnormality immediately perform a specific study or postpone this study until the end of the cervical examination.
- Introduce a speculum of adequate size and length into the vagina. It is important to move the speculum carefully, avoiding brusque movements which might produce pain to the patient and ensure that the cervix and/or vagina is not injured, thereby avoiding the appearance of any lesion which could additionally hinder the examination. In special cases a gynecological lubricant can be used to facilitate maneuverability.
- Using saline solution, carefully clean any secretions making visualization of the cervix and the vagina difficult. If overlapping of the vaginal walls is present, retract the wall using vaginal side-wall retractors, and if these are not available, apply a condom or glove finger with both ends open onto the blades of the speculum as indicated in section 4.2. If the cervix is in a position making observation difficult, attempt to correct this by the placement of gauze packing at the end of the vaginal pouch.
- Visualize the vaginal-cervical anatomy, mucosal trophism and the presence or absence of signs of infection with white light and low magnification (x4).
- Examine the vascular pattern with the green filter. The vessels should be observed at low light and great magnification. Do not apply acetic acid or collect any sample before performing the vascular evaluation.
- Obtain samples if indicated.
- Apply acetic acid to the cervix at 3.5% either directly (gauze or cotton swabs) or using a pulverizing device as indicated in section 4.3 of the guidelines. Avoid excessive rubbing or knocking the cervix in order not to produce unnecessary erosions or hemorrhages.
- With white light and low and high magnification carefully visualize the changes produced.
- Determine if colposcopy is adequate or not.
- Identify the squamocolumnar junction and categorize the transformation zone.
- Identify and evaluate the characteristics of the colposcopic findings at the level of the cervix, endocervix and vaginal pouch fundus.
- Make digitalized images whenever possible to include in the clinical history of the patient.
- Apply lugol solution in the same way as acetic acid to specify the topography and extension of a suspicious zone. Before the procedure ensure that the patient is not allergic to iodine.
- Make targeted biopsies in indicated cases and coagulate bleeding zones of the area biopsied.
- Carefully withdraw the speculum. If the women reports significant stinging after the examination due to transitory dehydration produced by the solutions

used, a vaginal moisturizer may be applied before withdrawal of the speculum.

- Revise the samples to ensure correct identification before sending them for analysis.

Recommendation: colposcopic examinations should always be performed following a systematic method.

6.2.2 Examination of the vagina

Vaginal examination by colposcopy (vaginocopy) is a technical challenge for a colposcopist and a more uncomfortable and lengthy process for patients. The surface examined is much greater than in the cervix. The vaginal mucous presents a large quantity of rough areas or folds and the blades of the speculum do not allow visualization of 360° at one time, making it necessary to repeat the application of the fluids used (acetic acid and lugol) and rotations of the speculum.

The general principals and methodology are similar to those described in the case of colposcopy. Of note are a series of specific nuances [67]:

- The patient is placed in a dorsal lithotomy position, but the examination can be facilitated by raising the buttocks 5-10 degrees.
- The size of the speculum should have sufficient depth to observe the distal vagina but should also allow easy rotation.
- It is preferable to use acetic acid at 5%, since this solution more rapidly demonstrates the presence of lesions (if present).
- Since the effect of lugol solution does not disappear over time, the use of this solution is especially important because it can detect small lesions which may not have been observed in the examination with acetic acid.
- Strict order should be followed in order to ensure that no zone remains unexamined [69]. The examination begins in the fundus of the vaginal pouch by lateral mobilization of the cervix with a gauze or spatula. In patients who have previously undergone hysterectomy, a hook, endocervical speculum or polyp forceps may be useful to reach these angles. Then, the middle and outer thirds of the vagina are examined, and afterwards, with careful rotation of the speculum, the anterior and posterior walls of the vagina are evaluated.

Recommendation: colposcopic evaluation of the vagina should be systematically performed and may be facilitated using low magnification and lugol solution.

6.2.3 Examination of the vulva

Colposcopic examination of the vulva (vulvoscopy) can identify subclinical lesions not observed in the general examination and helps to define the extension of the disease and guide biopsy [70].

Examination under low magnification is used for the general evaluation of the vulva and greater magnification is used for in depth examination of small lesions.

It is important to take the following aspects into account in vulvar examinations [71]:

- Acetic acid solution should be of 5%, and you should wait between 3 to 5 minutes in order for it to be effective in the areas of the keratinized epithelium [72].
- Whitening of determined areas after applying the acetic acid presents a low specificity since the vulvar epithelium, mainly at the level of the introitus, frequently reacts diffusely to acetic acid in the absence of disease.
- Abnormal vascular patterns can be observed as pointed and mosaic, although there is no analogy between the colposcopic changes described in the cervix and those found in the vulva.

Recommendation: colposcopic evaluation of the vulva can be performed using low magnification and acetic acid solution at 5%.

6.3 REPORTING AND REGISTRY OF COLPOSCOPIC FINDINGS

6.3.1 Description of colposcopic findings

The description of the colposcopic findings is a medical document which facilitates the follow-up of patients, orientation of clinical approaches following diagnosis and

the evaluation of discordant results. For all these reasons, this description should be meticulous and exhaustive. At present, the description of an examination constitutes one of the most relevant indicators of quality of Lower Genital Tract Disease Units [65].

Evaluation of the cervix and the squamocolumnar junction. The recommendations of the principal scientific societies of lower genital tract disease and colposcopy coincide in that adequate or inadequate visualization of the cervix, the squamocolumnar junction and the description of the type of TZ (1, 2, 3), according to the IFCPC classification criteria [1] is an important indicator of quality. Their importance mainly lies in that the diagnostic/therapeutic management of determined cytological alterations is conditioned by these indicators.

The description and registry of the visualization of the cervix (adequate or inadequate) should be made in 100% of the colposcopies carried out (minimum required 70%) [2, 73]. The description and registry of the squamocolumnar junction and the type of TZ should be made in 100% of the colposcopies (minimum required 70%) [29, 74-76].

Evaluation of the lesion (type of lesion, size, localization, visibility, semiology).

Evaluation of the lesion is a fundamental aspect for establishing an adequate correlation between the different diagnostic tests (cytology, HPV test, colposcopy) and the provisional and/or definitive histological study. A lack of documentation may lead to over/underestimation of the results of these tests and colposcopic impression.

The description and registry of the characteristics of the lesion (type of lesion, localization in the cervix, complete or incomplete visibility and semiology) should be made in all the cases (minimum required 90%) [77] according to the IFCPC nomenclature [1].

Knowledge of the localization of the lesion in the cervix and its size are fundamental for planning the most adequate clinical approach (treatment or follow-up). The lack of documentation of these aspects may lead to inappropriate clinical actions, and in the case of surgical treatment, insufficient or excessive resections, with the subsequent

negative repercussions. An observational study in patients with HSIL cytology reported that the probability of finding carcinoma lesions is related to the absolute size of the lesion and the percentage of the TZ affected [78]. These data are a practical demonstration of the importance of reporting the information of the characteristics of the lesion in all colposcopies [29].

Lastly, complete or incomplete visualization of the lesion may condition the clinical approach or the efficacy of the treatment. The current clinical guidelines accept that this information should be registered in at least 70-100% of the colposcopies performed [2, 29, 73]. However, a systematic review showed that the presence of infiltrating lesions is more frequent when the upper limit of the lesion cannot be visualized because of being introduced into the endocervical canal (61% of microinvasion, 71% of invasive disease). This demonstrates the importance of reporting all the information which may be relevant in the treatment and follow-up of the patient.

Recommendation: description of the colposcopic findings should be strict and exhaustive.

6.3.2 Registry of colposcopic data and images (diagrams, photos)

Registry of the colposcopic images (ideally with colpophotographies or if not available, with diagrams or schemas) should be done in 100% of the cases (minimum required 70%).

These images and schemas should be included with the colposcopy report and be available among the printed materials available when necessary. It is recommendable to include them in the electronic clinical history of the patients [65].

Iconographic registry of the colposcopic findings (colpophotography) and representation in graphic schemas is an essential part of the work to be carried out by colposcopists. In addition, it can evaluate the correlation of the results (cytology and/or HPV test, histology and colposcopic impression) of the lesions, and monitor and assess the follow-up of treated patients and of lesions not candidates for treatment.

Recommendation: registry of colposcopic images is essential (preferably with colpophotographies in the electronic history). Another option is to register the colposcopic findings as schemas or diagrams.

6.3.3 Reporting of colposcopic impression

The colposcopic impression should be reported in 100% of the colposcopies (minimum required 80%) [29, 73, 75, 76].

Reporting of the colposcopic impression should also be made taking into account the IFPC classification [1]. This parameter is related to the quality of the colposcopic prediction and has the objective of achieving a high positive predictive value of findings classified as grade 2 for the histological diagnosis of lesions \geq HSIL/CIN2.

In most cases, colposcopic findings classified as grade 2 changes should be correlated with a histological diagnosis of \geq HSIL/CIN2 (>75%) [79].

Recommendation: on completing the colposcopic examination the colposcopic impression should be reported according to IFPC terminology in all the cases.

6.4 COLPOSCOPY-GUIDED BIOPSY

6.4.1 Adequacy of the biopsies

In most cases, the detection of an abnormal cervical screening test implies the need to perform colposcopy and colposcopy-guided biopsy. Colposcopy shows the architectonic pattern of the epithelium and classifies each image as abnormal according to the alterations presented (grade 1 and grade 2 changes or changes suggestive of carcinoma) according to the characteristics defined in the classification of the International Federation for Cervical Pathology and Colposcopy (IFPC)

[1]. Directed biopsy obtains a confirmatory histological diagnosis and orients the most adequate treatment planning [82].

In general lines, colposcopy-guided biopsy is recommended in cases with cytology findings \geq HSIL and whenever an abnormal TZis observed. Pregnancy is an exception [2].

Colposcopy-guided biopsy consists in obtaining one or several samples of the abnormal cervical epithelium. This procedure does not require the administration of anesthesia [83]. It is usually carried out with punch forceps. The use of small diathermic loops is also possible and may improve the quality and quantity of tissue resected without increasing the pain to the patient during sample taking [84, 85]. The order for sample taking should be from back to front to avoid bleeding, which would hinder visualization of the remaining areas to be biopsied, and preferably of the area closest to the TZ (centripetal localization) since this is where the higher grade lesions are usually found. In the case of lesions suspected of invasion, avoid taking the samples from the zones showing necrosis. For the cervical biopsy to be representative of the sample it must contain epithelial and stroma tissue. The percentage of adequate biopsies for histological diagnosis should be greater than 90% [2].

The efficacy of the colposcopy to detect SIL/CIN and invasive lesions is largely conditioned by the experience of the colposcopists and their capacity to interpret the colposcopic findings and adequately target the biopsies to the zones in which the colposcopic impression suggests greater lesional grade.

Among expert colposcopists there is little interobserver variability in characterizing normal epithelium with grade 2 changes (suggestive of lesions \geq HSIL/CIN2) or with lesions suggestive of invasion. This variability increases in the case of grade 1 changes (suggestive of LSIL/CIN 1), although the definitive diagnosis of these entities is achieved by the histological study [51].

The selection of the most significant lesional area to perform the directed biopsy is conditioned by the subjectivity of the colposcopic impression. A metaanalysis including 32 studies with close to 8000 biopsies evaluated the diagnostic yield of the colposcopic impression. After biopsy, all the patients underwent excisional therapy, and the histological diagnosis was considered the gold standard. The sensitivity and specificity of the colposcopy to detect HSIL/CIN2 lesions in the conization piece differed according to whether

the result of the directed biopsy was LSIL/CIN 1 (91% and 25%, respectively) or \geq HSIL/CIN2 (81% and 63%, respectively) [86].

Retrospective studies have shown that compared to excisional histological diagnosis, directed biopsy may both “overestimate” the grade of the lesion when it is small since the biopsy has divided the fragment with the greatest abnormality, and more often, it may “underestimate” the severity of the lesion (4.3% and 57.1% in HSIL/CIN2 lesions) [2].

Although colposcopy is a fundamental examination in the secondary prevention of CC, it continues to be a subjective and operator-dependent technique, and therefore, the reproducibility of the colposcopic impression and the directed biopsy is limited, and the sensitivity and specificity for the diagnosis of lesions \geq HSIL/CIN2 is lower than what has classically been reported. The most important factors contributing to this limitation are:

- Lack of standardization in colposcopic terminology.
- Lack of consensus recommendations on how to perform a colposcopic examination.
- Lack of reliable and measurable measures of quality control.
- Use of colposcopy in the hands of non expert professionals.

Other factors which may contribute to over or under diagnosis of a lesion \geq HSIL/CIN2 are:

- Patient age.
- Menopausal status.
- Visibility of the squamocolumnar junction.
- Size of the lesion.
- Endocervical extension.
- Number of biopsies performed [58, 87].

Recommendation:

- Cervical biopsy should always be guided by colposcopy. The sample should be selected from areas showing greatest abnormality and should contain adequate representation of the epithelium and the stroma (percentage of satisfactory biopsies greater than 90%).
- Selection of the most significant epithelial area to perform the directed biopsy should take the colposcopic impression into account.

6.4.2 Number of biopsies

Traditionally, it has been recommended to take a single biopsy sample selected from the colposcopic area presenting the greatest abnormality. Recent studies have shown that correct diagnosis is not achieved with a single biopsy in up to 40% of precursor lesions. An increase in the number of biopsies is translated into an increase in the sensitivity of colposcopy to detect lesions \geq HSIL/CIN2 [58].

Data from the National Cancer Institute Biopsy Study demonstrate that performing a second or third biopsy in areas with small colposcopic alterations of the TZ increases the sensitivity to detect precancerous lesions from 61% to 86% or 96%, respectively [88]. Thus, the objective is to find a balance between achieving greater sensitivity to detect precursor lesions and adjusting the number of biopsies in order to avoid unnecessary procedures in the colposcopic examination. Although the characteristics of the lesions and the risk of the patient presenting lesions \geq HSIL/CIN2 should be evaluated, in general, it is recommended to perform directed biopsies mapping the different abnormal colposcopic areas (generally between 1 to 4 biopsies according to the extension and complexity of the lesion).

Recommendation:

- Taking a single directed biopsy of the colposcopic area with the greatest abnormality has a lower sensitivity for the detection of lesions \geq HSIL/CIN2 than multiple biopsies.
- Based on the characteristics of the lesion and the risk of lesions \geq HSIL/CIN2, it is recommended to perform directed biopsies of the different abnormal colposcopic areas.

6.4.3 Cervical biopsy sampling according to level of risk

In cases with an abnormal screening test, the ASCCP [58] recommends adapting the colposcopy and biopsy sampling based on the level of risk of \geq HSIL/CIN2.

This risk mainly depends on:

- The cytology results.
- The presence of infection by HPV genotypes 16/18.
- Colposcopic impression.

The combination of these markers can stratify the population into high and low risk of underlying \geq HSIL/CIN2. Based on this evaluation of risk the ASCCP recommends:

1) Not to perform biopsies if there is a low risk of \geq HSIL/CIN2. This recommendation is applicable in women fulfilling all of the following criteria:

- Cytology showing minor alterations (<HSIL).
- HPV other than 16/18.
- Colposcopic impression without acetowhite areas of metaplasia or other visible abnormalities.

Many studies have shown that there is a very low risk of \geq HSIL/CIN2 in women classified as having low risk. A prospective study carried out in the United Kingdom reported that the probability of detecting a precursor lesion in the successive years is very low [89]. To the contrary, biopsy sampling is recommended even when the colposcopic impression does not suggest a significant lesion (acetowhite areas compatible with metaplasia or another minor abnormality), since not performing a biopsy increases the risk of underdiagnosing \geq HSIL/CIN2 lesions.

2) Perform direct biopsies if there is high risk of \geq HSIL/CIN2 lesions. This recommendation is applicable in women over the age of 25 years, who are not pregnant and who have at least two of the following criteria:

- HSIL cytology.
- Infection by HPV16 or 18.
- Colposcopic impression with grade 2 changes.

If multiple biopsies are made and are negative, strict control should be performed according to the norms of the prevailing clinical guidelines. Data from the National Cancer Institute Biopsy Study demonstrate that if multiple biopsies are negative, the negative predictive value (NPV) (that is, the probability of absence of a lesion \geq HSIL/CIN2) is high [88].

3) Immediate excisional treatment in the presence of high risk of \geq HSIL/CIN2. This recommendation may be acceptable in selected cases and implies fulfilling the same criteria as in the point above.

The results of a systematic review on the see and treat strategy showed that 89% of women with HSIL based on cytology have a lesion \geq HSIL/CIN2 in the excisional piece. This percentage is greater if the colposcopic impression is of grade 2 changes or the HPV test is positive for HPV types 16 or 18 for which immediate treatment is acceptable.

Recommendation:

- Directed biopsy sampling should take into account the level of risk of lesions \geq HSIL/CIN2 which depends on the cytology results, the presence of HPV16/18 and the colposcopic impression.
- Do not perform biopsies in women with low risk of lesions \geq HSIL/CIN2: cytology $<$ HSIL, no HPV 16/18 and normal colposcopic impression.
- Perform multiple biopsies in women over 25 years of age, not pregnant, with high risk of lesions \geq HSIL/CIN2 and at least 2 factors: HSIL cytology, HPV 16 or 18, colposcopic impression with grade 2 changes.
- Perform immediate excisional treatment if there is a high risk of lesions \geq HSIL/CIN2, and this can be performed in selected cases fulfilling the criteria mentioned in the previous point.

Recommendation:

- Non directed biopsy sampling (within the transformation zone) can be carried out in cases in which the colposcopic impression does not show evidence of a lesion and there is a risk of lesions \geq HSIL/CIN2.
- Non direct biopsy sampling should never be performed in cases with a low risk of lesions \geq HSIL/CIN2.

6.4.5 Endocervical study (biopsy with curettage or cytological smear)

Histological evaluation of the endocervical canal is an integral part of the study in women with an abnormal screening test result. However, the role of endocervical biopsy is controversial due to the discomfort and pain produced in patients, and moreover, it has limitations in relation to sample quality, sensitivity and false positive and negative results.

The procedure consists in introducing a curette into the cervical canal (fenestrated Novak cannula or fenestrated kevorkian curette) and debride the four quadrants to obtain strips of epithelium which are representative of all the endocervical surface. The sample should be sent for histological study separately from the other cervical samples since it is important to register the endocervical location of the lesions. On occasions, the endocervical sample may contain cells of the ectocervix in which a positive result may lead to overtreatment. This most frequently occurs in cases in which the TZ is in the endocervical canal such as in the case of menopausal women or in those who have previously undergone excisional therapy.

An endocervical biopsy is considered inadequate when there is a lack of sufficient evaluable tissue. This is reported in up to 20% of cases. An inadequate biopsy should not be interpreted as a negative result, and therefore, if the result affects the approach to be followed, then the possibility of obtaining a new sample should be considered. This decision should be individualized since there are cases, especially in menopause, in which it is practically impossible to obtain adequate histological material. Endocervical study is indicated when the colposcopic lesion shows an endocervical

6.4.4 Non directed biopsies

The term “non directed biopsy” applies to cervical biopsies which are randomly taken from inside the transformation zone, despite having a normal colposcopic impression (without acetowhite areas or with \leq grade 1 alterations suggesting SIL/CIN). Some studies highlight the value of non directed biopsies when there is a risk of lesions \geq HSIL/CIN2 [58].

Many studies have shown that non directed biopsies of the TZ with a normal colposcopic impression is not effective in cases with a low risk of lesions \geq HSIL/CIN2 (cytology $<$ HSIL and HPV 16 or 18 infection) [90].

This stratification of risk can thereby adapt the colposcopy procedure to each case. At the end of this stratification we can either not perform a biopsy in cases with a low risk of lesions \geq HSIL/CIN2, or to the contrary, perform immediate treatment without previous biopsy in cases in which the risk is elevated. In the remaining intermediate cases, taking multiple biopsy samples when the colposcopic results are normal (with no clear evidence of grade 1 or 2 lesions) or when there are minimal acetowhite areas seems to be of value since this can increase the detection of high grade precursor lesions.

component. The results of an endocervical biopsy can lead to the diagnosis of 5-15% of patients with lesions \geq HSIL/CIN2. Therefore, this procedure increases the diagnostic sensitivity fundamentally in menopausal women. In addition, it can obtain samples of non contiguous lesions which are a characteristic feature of glandular lesions, and therefore, on suspicion of a possible glandular lesion an endocervical study should always be performed [91]. Endocervical biopsy carried out immediately before treatment has shown a low sensitivity for detecting glandular alterations (false negative rate of 59-78%) [92].

It is also recommended to perform an endocervical biopsy immediately after conization. A post-treatment endocervical study is, moreover, a better predictive factor of lesional persistence affecting the margins, despite some series describing false negative rates of 58-67% [2, 92].

Endocervical curettage is contraindicated during pregnancy [82].

In the last years, the limitations of biopsy or endocervical curettage have favored evaluation of the role of cytological smears or endocervical brushing. According to data in the literature, endocervical brushing shows a sensitivity of 77-93% versus 36-64% for endocervical curettage, although the specificity of the former is lower (26-38%), with a percentage of false positive results of 28-75% due to probable contamination of the samples with cells from the exocervix [93, 94].

One randomized clinical trial evaluated the role of endocervical brushing and endocervical curettage associated with colposcopy-guided biopsy. The sensitivity of the direct biopsy was 96% with a specificity of 95%. When direct biopsy was associated with endocervical curettage, the values were 82% y 88%, respectively [95].

One additional advantage reported for endocervical brushing is the low percentage of inadequate samples due to lack of tissue (approximately 2%) compared to 20% for endocervical curettage [95]. Together with greater tolerability of endocervical brushing and a lower cost, these data justify the utility of this technique in the study of the endocervical canal versus endocervical curettage, although a positive result should be interpreted with caution to avoid overtreatment [96].

Recommendation:

- Endocervical study with curettage or brushing should be performed when the colposcopic lesion shows an endocervical component (more frequent in menopause or post-treatment).
- Endocervical study immediately after conization is indicated since it has an elevated predictive value of lesional persistence.
- Endocervical curettage is contraindicated during pregnancy.

6.5 REPORTING AND REGISTRY OF BIOPSIES

6.5.1 Localization, number of biopsies and characteristics of the areas selected for biopsy.

It is fundamental to correctly report and register the number of biopsies performed, their exact localization in the cervix and the colposcopic characteristics of the areas selected for biopsy. This information contributes to determining the most adequate clinical approach to take. Description of the localization can be performed based on the four quadrants of the cervix or according to a clockwise distribution. To do this, diagrams or graphic schemas should be used with a registry format that depends on the institution in which the sample taking is performed [91].

In the case of multiple biopsies, these should be identified separately according to the localization in the cervix and fixed in formal at room temperature for posterior histological analysis, the report of which should include [84]:

- Sample size (mm).
- Type of tissue.
- Sample quality.
- Absence or presence of lesion.
- Lesional grade and/or type of lesion.
- Presence of changes associated with HPV infection (koilocytes, dyskeratosis).
- Characterization of non neoplastic lesions.
- Stromal reaction (presence and extension of inflammatory or desmoplastic reaction)
- In the case of invasion, depth and lateral extension,

presentation of lymphovascular involvement and grade of differentiation.

Recommendation:

- It is essential to correctly report and register all cervical biopsies (number, localization and colposcopic characteristics).

6.5.2 Endocervical study (biopsy with curettage or cytological smear)

Reporting of the endocervical biopsy is analogous to that of exocervical biopsies. In this case the endocervical biopsy with curettage is a single sample that should contain material of all the endocervical canal. Cytological brush smear should only contain the material obtained from the endocervix, avoiding, whenever possible, exocervical contamination.

6.6 Reporting of the results to the patient and follow-up

The patient should receive verbal and written information of the results of the studies performed. The histopathological reports should be available within a relatively short period of time after biopsy. Delay in the diagnosis may have repercussions in relation to a delay in the treatment of potentially invasive lesions and patient anxiety [73].

The negative psychological impact which an abnormal screening test result has in women and the consequent colposcopic evaluation requires adequate communication

between the physician and the patient. The transmission of adequate information and having the patient participate in decision making has shown a reduction in anxiety throughout the process, thereby favoring compliance and follow-up [2].

The patient should be given written material of the verbally transmitted information (for example, using support material such as <http://www.aepcc.org/pacientes/>) which can help to clarify doubts arising after the medical visit and reduce the need to search for additional information at sources of non contrasted quality. When the results of the screening tests have been integrated with the colposcopic and histological findings, the therapeutic strategy should be planned as well as the most adequate follow-up in each case. This information should be registered in the clinical history and clearly reported to the patient in the simplest and most comprehensible way and within the shortest time possible.

Recommendation:

- Following biopsy the histological report should be available within a period of less than 4 weeks.
- The patient should receive verbal and written explanations of the results of the colposcopy and the complementary studies performed.

7. Colposcopy units. Standards of quality and recommendations.

7.1 STANDARDS OF QUALITY OF A COLPOSCOPY UNIT

Colposcopy Units should have clinical protocols which follow the national guidelines. These protocols should be accessible and open and submitted to periodic updating. In addition, standards of quality should be documented and periodic controls should be carried out to evaluate their fulfillment.

Ideally, the members of the unit team should be accredited for their activity and continuing education should periodically be made.

It is essential for a Colposcopy Unit to have an established circuit of reporting of any error, difficulty or need (table 7.1 shows a list of fundamental points which should make up the standards of quality of Colposcopy Units)[2, 74, 97].

Table 7.1: Standards of quality in Colposcopy Units.

- Good practice guidelines.
- Equipment.
- Diagnostic strategy.
- Maximum referral times after abnormal cytology.
- Referral criteria for colposcopies different from abnormal cytology.
- Test in colposcopy.
- Procedure protocols.
- Informed consent for the procedures.
- Organization with assignment of functions of the members.
- Multidisciplinary work.
- Training and accreditation of the colposcopists.
- Databases.
- Definition of standards by processes.
- Standards for colposcopy.
- Reduce patient anxiety.
- Follow-up of patients who do not attend visits.

7.1.1 Coordination and management of the Colposcopy Unit.

Colposcopy Units should be coordinated or directed by a professional with great experience in this area.

Unit coordinator: Colposcopy teams should have a coordinator. The coordinator should be the person of reference of the team and should supervise the correct functioning of the unit, ensuring fulfillment of good practice and standards of quality as well as the follow-up and updating of the protocols. It is recommended that the coordinator be a colposcopist with wide experience and is accredited in colposcopy. The coordinator should be involved, moreover, in the definition of the criteria of patient referral to the Colposcopy Unit and should have a direct relationship with the team colposcopists, the pathologists and the other professionals who work in the unit.

Head of the Department: Depending on the size of the unit and structure of the work center, both figures (Unit Coordinator and Head of Department) should be assumed by the same person. If this is not so, there should be fluid periodic communication between the two. The Head of the Department is responsible for ensuring the execution of the patient referral circuits to the unit.

7.1.2 Quality control of the Colposcopy Unit

Quality control of the activities carried out in the Colposcopy Unit should periodically be performed.

Ideally, an annual audit of the indicators of quality specified in the present guidelines should be carried out. All the team should know the results of the audit and make a joint analysis of the results. This audit can be made by members of the AEPCC-Guidelines Colposcopy Unit but other pathologists and midwives from primary care responsible for screening can also intervene.

Quality control of a Colposcopy Unit is not possible without

detailed collection of the data of health care activity of the unit. It is fundamental to have a systematic data collection system which facilitates evaluation of the activity of the unit in order to perform adequate quality control.

The indicators which can be audited in a Colposcopy Unit are shown below:

1. Number of positive directed biopsies by each colposcopist and altogether.

Recommendation: the percentage of positive directed biopsies for lesions should be $\geq 80\%$.

2. The level of concordance between the diagnostic impression of the colposcopy and the result of the biopsy. All the units should obtain annual data of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) together and separately for abnormal grade 1 and 2 colposcopic findings.

Recommendation: Globally, in the diagnosis of a lesion colposcopy should have a sensitivity $\geq 80\%$ and a specificity $\geq 70\%$

3. Number of conizations annually.

Recommendation: The number of conizations performed each year should be registered.

4. Number of conizations performed in the outpatient setting (in the consulting office and with local anesthesia).

Recommendation: the percentage of conizations performed in the outpatient setting should be $\geq 70\%$.

5. Percentage of conizations performed under colposcopic control.

Recommendation: the percentage of conizations performed under colposcopic control should be $\geq 90\%$.

6. Percentage of treatments carried out with each therapeutic modality (diathermic loop, excision or laser vaporization, cryotherapy, follow-up without treatment, etc.).

Recommendation: The type of treatment carried out should be registered in all the cases.

7. Number of conizations with a histological diagnosis of a lesion \geq HSIL/CIN2.

Recommendation: Lesions \geq HSIL/CIN2 should be confirmed in $\geq 70\%$ of the conization pieces.

8. Number of cone biopsies without histological lesions (blank cones).

Recommendation: The percentage of conizations with histological lesions should be $\leq 15\%$.

9. Percentage of conizations with affected margins. The number of margins affected in each case and their localization (exocervical, endocervical or deep) should be specified.

Recommendation: The percentage of conizations with lesion-positive margins should be $\leq 20\%$ ($\leq 15\%$ of endocervical margins).

10. Percentage of cases treated of HSIL/CIN with cytology \geq HSIL/CIN2 at 6 and 24 months after treatment.

Recommendation: The percentage of cytologies \geq HSIL/CIN2 at 6 months should be $\leq 10\%$ and $\leq 5\%$ at 24 months.

11. Fulfillment of waiting times from diagnosis to colposcopy.

Recommendation: The percentage of fulfillment of recommended waiting times should be $\geq 90\%$.

12. Fulfillment of administration of the vaccine against HPV post-conization in communities in which the vaccine is funded.

Recommendation: The percentage of meeting the HPV vaccine schedule in women after conization (according to the protocols of each autonomous community this percentage should be $\geq 90\%$).

13. Registry of claims or complaints by patients.

Recommendation: Register the number of claims and complaints annually and analyze the reasons for them.

14. Number of sessions in the Colposcopy Unit and interdisciplinary sessions established in the unit.

Recommendation: Register the annual number of unit and interdisciplinary sessions carried out.

At present, there is great concern about establishing

homogeneous criteria of quality and a grade of fulfillment to ensure excellence in the care given to patients in colposcopy. Table 7.2 shows the European standards of quality established by the European Federation of Colposcopy in Paris in 2017.

7.1.3 Information and communication with the patient

Communication with the patient is key in the perception of quality of a Pathology Unit of the Lower Genital Tract. There is evidence of the negative psychological repercussion which informing a patient of an abnormal cytology result or an HPV test has on the patient. Clear, adequate information notably reduces the level of anxiety and favors posterior treatment and follow-up.

Before screening tests and colposcopy, all women should receive verbal/written information of the objectives of these studies. They should also be given verbal/written information of the results of these tests and of the colposcopy. Likewise, all women with abnormal results should receive written information about the clinical approach to be followed. The time from these tests to obtaining the results should be as short as possible.

Table 7.2. European Standards of Quality - Paris - 2017

Parameter	%
The type of TZ (1,2,3) should be reported in colposcopy.	100%
Percentage of cases with colposcopy prior to treatment due to abnormal cytology results.	100%
Percentage of women with definitive histological diagnosis of \geq HSIL/CIN2 in biopsies or excisional treatments.	85%
Percentage of excisional or conization lesions which are border-free.	$> 80\%$
Number of low grade colposcopies (individual) performed per year after abnormal screening cytology results.	> 50
Number of high grade colposcopies (individual) performed per year after abnormal screening cytology results.	> 50

The results of the tests and the follow-up policy should be reported to the general practitioner.

Recommendation:

- Patients should be correctly informed (preferably in writing) of the objective of the screening tests and the possibility of complementary studies ($\geq 90\%$) and of the results of screening tests and colposcopy ($\geq 90\%$).
- The results should be reported to the patient within a maximum of 8 weeks.

7.1.4 Certification

All colposcopists should have a training program or should have received specific training to achieve accreditation in colposcopy. All training programs should fulfill national and European standards.

Recommendation: The members of a Colposcopy Unit should be accredited (ideally $\geq 50\%$).

7.1.5 Coordination with screening programs

The coordinator of the Colposcopy Unit or the Head of Department should have consensus with the levels of primary care in relation to the flow of patients referred according to the screening framework recommended in national and/or local guidelines.

Consensus regarding referral circuits should be established for each of the diseases which can be referred to the Colposcopy Unit. The circuits established should be accessible and available for consultation and review.

At a national level, the clinical approach to follow in patients undergoing CC screening should be performed according to the published clinical guidelines (APECC-Guidelines on Screening and AEPCC-Guidelines on Prevention available at: <http://www.aepcc.org/aepcc-guias/>) [27, 33] following the referral circuits established with the primary care centers.

Recommendation: Colposcopy Units should coordinate and achieve consensus regarding the flow of patients referred from screening programs based on regional or national guidelines.

7.2 PERSONNEL, INSTALLATIONS AND EQUIPMENT IN THE COLPOSCOPY UNIT

7.2.1 Staffing

The personnel adscribed to a Colposcopy Unit should have experience in pathology of the lower genital tract.

Medical personnel:

The number of professionals is based on the work volume of the Colposcopy Unit, and these personnel should know the national screening and clinical approaches in depth as well as all the treatment techniques.

Staffing of a Colposcopy Unit should be able to assume the waiting times established in the standards of quality of the present guidelines in the case of abnormal screening tests, the performance of treatment and visits for results and follow-up of their process.

Ideally, the personnel of the Colposcopy Unit should have sufficient time available to correctly provide the care and carry out internal controls of quality, team meetings, and internal and multidisciplinary sessions. It is also important to have time for pregraduate and postgraduate teaching and continuing education.

Nursing personnel:

Nursing personnel in the Colposcopy Unit should be qualified and have specific training and experience in the support and clinical approaches in women consulting for suspicion of a preneoplastic lesions or cancer and its treatment. These personnel should be integrated into the team and actively participate in the unit. This participation should include their attendance to internal meetings, knowledge of the standards of quality and commitment to correct functioning of the unit.

In the case of having more than one nurse, one nurse

should be responsible for nursing in the unit. Continuing education should be ensured among all the nursing staff related to the unit.

The responsibilities of the nursing staff of the Lower Genital Tract Unit are:

- Control of fungible and non fungible material.
- Control of material for treatment in the consulting office.
- Collection of data of cytological smears and biopsies of the patient consulting.
- Identification of samples and sending of the samples to central services.
- They may be in charge of user satisfaction surveys.

Recommendation:

- The medical personnel of the Colposcopy Unit should be experienced and staffing and organization should ensure correct care, quality control, teaching and continuing education.
- Nursing personnel should be qualified and integrated into the functioning of the unit.

7.2.2 Installations and equipment

Colposcopy Units should fulfill all the health care requirements of safety and access to first aid. They should be correctly equipped for the diagnosis, treatment, collection and storage of clinical data and images. They should also have an area dedicated to management and for administrative personnel.

All the equipment should be regularly revised to guarantee correct functionality at all times. The privacy of the consulting office and especially the place where the colposcopic examination is performed should be ensured and at least one accompanying person should be allowed to be present, if the patient wishes.

Recommendation: The installations and equipment of the Colposcopy Units should fulfill the health care requirements of safety, equipment and privacy.

7.3 Equipment in the Colposcopy Unit for diagnosis by colposcopy.

1. Colposcope with magnification (different ranges from 23 to 24), filters.
 - a. Exterior screen.
 - b. Camera for photos and videocolposcopy.
 - c. Image archiving system.
 - d. System for colposcopy report with photos incorporated.
2. Types of spatulas and cytobrush for liquid based cytology medium..
3. Adequate liquid medium diagnostic vials.
4. Saline solution.
5. Acetic acid at 5%
6. Cotton swabs for use of acetic acid.
7. Lugol solution.
8. Cotton swabs for application of lugol solution.
9. Speculums of different sizes.
10. Speculums for evaluation of the endocervix.
11. Forceps for selective biopsy.
12. Novak and/or Cornier cannulas and/or curette or cytobrush for endocervical sampling.
13. Vials with formol duly accredited for each patient.
14. Monsel's solution or silver nitrate sticks for cauterization of post-biopsy bleeding.
15. Hemostratic gauzes.
16. Punch forceps of different sizes.

7.4 Equipment of the Colposcopy Unit for outpatient conization.

1. Non conductive speculums with smoke aspiration system.
2. Smoke aspiration system.
3. Electrosurgical current system including cutting and coagulation.
4. Dispersive plate for closing the electrical circuit.
5. Local anesthesia plus vasoconstrictor.
6. 25-27 gauge needles for the application of anesthesia.
7. Diathermic loops of different sizes.
8. 3 or 5 mm ball electrodes for coagulation.

7.3. Organization and administrative management

As in any working group the Colposcopy Unit should have a work organigram showing the functions and responsibilities of each member of the team and to ensure the availability of adequate material resources in order for each member of the team to adequately carry out their work.

The Colposcopy Unit requires administrative support which is essential for: 1) facilitating communication and appointment making with patients, 2) managing the relationship with other departments of the center, and 3) collaborate in data collection.

Each medical consultation should include a specialized nurse.

Recommendation: The organization of the Colposcopy Unit requires a specific organigram and administrative support as well as specialized nursing personnel.

7.3.1 Organization and meetings of the Colposcopy Unit and with multidisciplinary teams.

The team of a Colposcopy Unit should periodically meet for the presentation of clinical cases and review of relevant clinical aspects or therapeutic indications.

The meetings of the unit are especially useful for:

- Raising questions of team logistics.
- Presenting the results of the audits of standards of quality and evaluate options for improvement.
- Discuss projects for improving specific aspects of the unit.
- Present and discuss investigation projects and their results.
- Periodically review the unit protocols.

In addition, it is recommended to establish periodic multidisciplinary meetings with related departments (pathologists, dermatologists, internal medicine physicians, hematologists...). These meetings are essential for

designing common protocols, establishing agreements for patient referral and to coordinate diagnostic and therapeutic procedures as well as joint evaluation in complex cases.

Recommendation:

- Specialists in the Colposcopy Unit should periodically meet (preferably every 1 or 2 weeks).
- Multidisciplinary meetings with specialists related to the Colposcopy Unit should be held every trimester.

7.4 CLINICAL DOCUMENTATION

All the activity of the Colposcopy Unit should be documented in a standardized format. All the documentation and data of the patients should follow the legal requirements of data protection.

All the documents which professionals should collect, store or provide to the patient are described below.

1. Clinical history of the patient. This should include:

- Personal history, including allergies, toxic habits, diseases, usual treatments, immunodepressive treatments, HIV status, diseases involving immunosuppression.
- Gynecological history, including parity (abortions, miscarriages, deliveries, type of delivery, age at first delivery), menarchy, menogram and date of last period, menopause, local hormone treatment, systemic hormone replacement treatment, contraception (type, length of contraception, contraception in the last 6 months), sexual activity (age at first coitus, number of sexual partners), HPV vaccine status, previous treatments of the cervix, vagina and vulva, previous screening (last cytology, result, history of SIL).
- Reason for consultation for the current episode.
- Physical examination including the report of the colposcopy examination, if biopsies have or have not been performed as well as the number and localization of the biopsies.

2. Informed consent. Required for each procedure.

- Colposcopy (Annex 2).

- Cervical treatments: conization, cryotherapy, ablative or excisional treatments with CO2 laser.
- Treatments of the vulva or vagina: incisional or excisional procedures, ablative treatments with cryotherapy or CO2 laser.

Informed consent is obtained according to the prevailing legal requirements. In cases of electronic clinical data systems, it is recommended to scan the consent forms and include them with the documents of the clinical history of the patient.

3. Indication of follow-up. After each visit the patient should receive clear information as to when a new visit should be made and how to structure the follow-up. Ideally, the patient should leave with the visit and the specific appointment programmed for the next control.

4. Images and archiving of the colposcopic images.

Colposcopic examination of the lower genital tract may be documented by colpophotographies or videos. These images constitute very valuable information of the clinical history and ideally should be archived or included in the electronic clinical history. In the general consent or specific consent form the patient should expressly authorize the capture and storage of these images.

5. Discharge report after treatment. After any treatment, especially if this is excisional, a discharge report should be provided which specifies the procedure performed as well as the recommendations that the patient should follow in the days after the intervention and the alarm signs which could lead to consultation to the reference unit. This information should be provided in written form in order to contribute to the safety of the patient, reduce patient anxiety and favor adherence to the indications.

6. Discharge from the Colposcopy Unit. Document to be given to the patient which should include:

- Reason for consultation.
- Results of the studies performed.
- Treatments performed.
- Evolution and follow-up.
- Reason for discharge.
- Specific follow-up schedule to be carried out with the reference gynecologist and/or primary care physician in the patient's health care center.

7. Informative documents for the patients. This type of informative document or pamphlet should describe the most frequent processes related to diseases of the lower genital tract and HPV infection (conization, HPV infection, vaccination for HPV, vulvar and vaginal disease, etc.).

7.5 COLPOSCOPY TRAINING, CERTIFICATION AND CONTINUING MEDICAL EDUCATION.

7.5.1 Training and certification of colposcopists.

In all Colposcopy Units at least 50% of the colposcopists should be accredited in colposcopy by the AEPCC.

All colposcopists should have minimum experience, which, according to the European standards of quality (Paris 2017), includes:

- Number of low grade colposcopies (individual) performed at one year after an abnormal screening cytology result (> 50).
- Number of high grade colposcopies (individual) performed after an abnormal screening cytology result (>50).

7.5.2 Content of the training and evaluation.

Colposcopy training involves some minimum requirements [98-100].

Minimum general training required in colposcopy

- Understand the development of cervical neoplasia.
- Ensure that the colposcopy procedure complies with the recommendations of health and safety.
- Treat patients according to the criteria of national guidelines.
- Provide adequate information prior to the colposcopy.
- Answer questions related to management of the lesion.
- Communicate with other health care professionals.
- Understand the national screening guidelines.
- Be able to carefully report the results.
- Provide data to the national health care system.



Basic examination: minimum requirements.

- Be able to write the clinical history.
- Examine the vagina.
- Examine the vulva.
- Place and adjust the colposcope.
- Be able to place the patient in the position to perform the colposcopy.
- Be able to insert the vaginal speculum.
- Use the endocervical speculum.
- Report the colposcopic findings.
- Provide adequate information after the colposcopy.

Colposcopic procedure.

- Perform cervical sampling.
- Perform bacteriological smears.
- Examine the TZ with transparent and green filters.
- Examine the TZ with acetic acid.
- Perform the Schiller test.
- Describe the changes with acetic acid and the Schiller test.
- If indicated, perform biopsies (cervix, vagina and vulva).

Documentation of the colposcopy

- Make the colposcopy report using the IFCPC nomenclature.
- Produce report with the diagnosis and indications of follow-up and/or treatment.

Therapeutic procedures

- Perform excisional treatments with local anesthesia.
- Perform excisional treatments with general anesthesia.
- Perform ablative treatments with cryotherapy. Electrocoagulation, CO₂ laser (if this equipment is available in the unit).

Patient communication skills

- The result of an abnormal cytology produces patient anxiety, and therefore, education on the transmission of information should be promoted to reduce patient

anxiety and facilitate follow-up prior to performing colposcopy.

- The woman should receive verbal and written information prior to colposcopy.
- Advice should be integrated in the care.
- Communication of the results of tests and treatment plans should be informed directly to the patient, and this information should always be provided in writing.
- There should be a professional who is responsible for standards of quality and to monitor the same at least annually.
- The audit of the results should be global and personalized.
- The nurses of the unit should be qualified and have experience in the support and management of suspicion of preneoplastic lesions or cancer and their treatment.

7.5.3 Maintenance of clinical skills and continuing medical education (CME)

All the members of the Colposcopy Unit should perform a sufficient number of cases annually to maintain their clinical skills as stated in the standards of quality of these Clinical Guidelines.

Continuing medical education is the responsibility of each member of the team as well as the unit. Periodical updating of the references and review of the protocols in the unit should be made in addition to attendance to local, national and international congresses.

Sessions of bibliographic review and updating should be promoted within the unit.

8. Infections, cytology and colposcopy

In addition to detecting premalignant lesions of the cervix (fundamental objective), cervical cytology and colposcopy can also detect infectious agents or changes suggestive of determined infections. However, their diagnostic yield for this objective is very low, and they should therefore not be exclusively used for the diagnosis of infections of the lower genital tract.

8.1 SAMPLE COLLECTION FOR THE STUDY OF INFECTIONS IN THE COLPOSCOPY CONSULTATION.

This aim of this section is not to describe the treatment and most adequate clinical approach to each infection. In fact, it is not indicated to use the CC screening visit for taking samples for the screening of some frequent genital infections such as chlamydia or gonorrhoea.

This statement is justified based on the fact that gonococcal infection, and especially, infection by chlamydia are very frequent in very young women (during the first years of sexual life). For this reason, the screening of these infections is recommended in women under the age of 25.

On the other hand, CC screening is indicated above the age of 25 years, when the incidence of these infections is lower [10]. There is no evidence supporting the screening of these infections or showing cost-effectiveness in women over the age of 25 [2].

However, since conventional cervical cytology or liquid-based cytology medium can identify determined microorganisms, this section schematically covers the approach to these findings in the cytological reports.

Recommendation: It is not justified to use the CC screening visit to perform the screening of infections of the lower genital tract.

8.2 APPROACH TO INFECTIONS FOUND IN CYTOLOGY CITOLOGÍA

Although it is not the primary objective, the accuracy of the diagnosis of these infections varies among the different microorganisms in question [101].

The most frequent infections described in cytology reports are shown below, although their description in the current terminology of the Bethesda system is not obligatory.

8.2.1 Actinomyces

Cytological examinations have a low sensitivity, specificity and positive predictive value for the detection of actinomyces.

Infection by actinomyces is detected in 7% of women using an interuterine device (IUD) and is very infrequent in women without an IUD. Women carrying actinomyces are usually asymptomatic. After cytological detection the significance of the prognosis is very low in the absence of specific symptoms [2].

In women with a cytological diagnosis of actinomyces who are completely asymptomatic, treatment or IUD extraction is not indicated [102]. To the contrary, in symptomatic women, the IUD should be extracted and specific follow-up should be made to ensure the resolution of the infection. In these cases it should be ensured that the patient uses adequate contraception to avoid the risk of unwanted pregnancy [2].

Recommendation: Cytological detection of actinomyces has a low sensitivity, specificity and PPV. In asymptomatic women it is not necessary to extract the IUD or administer specific treatments.

8.2.2 Trichomonas vaginalis

Trichomoniasis is the most frequent, non viral, sexually transmitted disease (STD). Although some patients with this infection present cervicitis, leukorrhoea and signs of vulvar irritation, most (70-85%) have minimum symptomatology



[103]. Therefore, a significant number of women without symptoms or who do not present any evident cervicitis may be diagnosed with this infection by cytology. However, microscopic study of fresh tissue presents a sensitivity of approximately 50% to detect infection by *Trichomonas vaginalis* [104].

In cases with cytological results showing infection by *Trichomonas vaginalis*, treatment is indicated in both the patient and her partner.

Recommendation: Cytological detection of *Trichomonas vaginalis* may occur in patients who are asymptomatic or without signs of cervicitis. In all the cases, treatment should be indicated in both the patient and her partner.

8.2.3 *Candida* species

Vulvovaginitis by *Candida* is very frequent, with approximately 70-80% of women presenting at least one episode along their lives, and more than 40% present several episodes. Asymptomatic colonization for *Candida* or for other fungal species is also very frequent (10-20% are asymptomatic carriers) [104]. Therefore, it is relatively frequent for cervical cytology to report the presence of *Candida*. Nonetheless, cytology is considered to be a scarcely sensitive method among diagnostic procedures to detect *Candida* species.

The mere presence of *Candida* in the cytology study of asymptomatic patients is not an indication to receive treatment. In some cases the presence of spores is indicative of the reproductive activity of the microorganism, and thus, the probability of presenting symptoms and requiring treatment.

In cases in which the cytological report describes the presence of *Candida*, the coexistence of other associated infections should be ruled out.

Recommendation: Cytological detection of *Candida* is frequent, although this method is considered to have a low sensitivity. This finding is not an indication for treatment in asymptomatic patients. Other associated infections should be ruled out.

8.2.4 Bacterial vaginosis

Bacterial vaginosis is the replacement of the normal vaginal flora constituted by *Lactobacillus* spp. by anaerobic bacteria such as *Prevotella* spp. or *Mobiluncus* spp. It is considered to be a polymicrobial infection and is the most prevalent vaginal infection among women of reproductive age in developed countries [105]. It is one of the most frequent causes of malodorous leukorrhea, although an elevated percentage of women with bacterial vaginosis present scarce symptoms or are asymptomatic.

The presence of clue cells or cervical-vaginal cells covered by coccobacilli adhered to their surface and associated with a reduction or absence of lactobacilli is a characteristic cytological sign associated with bacterial vaginosis. However, the presence of these cells alone is not diagnostic of infection.

The diagnosis of bacterial vaginosis is based on the presence of clinical (Amsel criteria) or cytomorphologic criteria (Gram staining), and in some cases, even requires confirmation by biochemical criteria.

Recommendation: Cytological detection of bacterial vaginosis is frequent. The presence of characteristic clue cells is not diagnostic of infection. The diagnosis and treatment should be based on clinical criteria.

8.2.5 *Chlamydia trachomatis*

The sensitivity of cytology for the diagnosis of *Chlamydia* is very low (approximately 30%). Liquid-based cytology samples are considered adequate for the detection of *Chlamydia* using nucleic acid amplification testing (NAAT), although the sensitivity may be slightly lower than that obtained in samples of vaginal or cervical lavage.

The detection of chlamydia is of no interest in CC prevention programs but may be of interest in symptomatic women or in those suspected of having inflammatory pelvic infection.

Recommendation: Cytological detection of chlamydia tracomatis has a very low sensitivity. This finding is of interest in symptomatic women or in those with pelvic inflammatory disease. Liquid-based cytology samples are adequate for performing NAAT techniques.

8.2.6 Neisseria gonorrhoeae

Cytology may show the presence of intracytoplasmatic diplococci suggestive of infection by Neisseria gonorrhoeae; however, this procedure is not diagnostic since other common non pathogenic species of neisseria present similar findings [2]. Therefore, confirmatory tests based on amplification methods (NAAT) are always necessary.

Cervical samples by liquid cytology are adequate for the preservation of DNA, and thus, for the detection and confirmation of this infection.

Although the detection of N. gonorrhoeae is not of interest in CC prevention programs, it may be indicated to perform the study in liquid cytology samples in symptomatic women with suspicion of inflammatory pelvic infection.

Recommendation: Cytological detection of intracytoplasmatic diplococci is not always diagnostic of infection by Neisseria gonorrhoeae (always requires confirmation techniques). Liquid cytology samples are adequate for performing NAAT techniques.

8.2.7 Herpes Simplex Virus (HSV)

Cytology may show findings suggestive of herpes simplex virus (cells with a multinucleated appearance and peripheral margination of chromatin to the nuclear membrane or ground glass appearance, and occasionally intranuclear eosinophilic or viral inclusions are observed).

The specificity of cytology for this infection is high, but the

sensitivity is less than 40% [101]. Therefore, with this finding in cytology the patient should be evaluated and questioned about lesions or genital discomfort, and additional tests should be performed such as polymerase chain reaction (PCR).

Recommendation: The specificity of cytology for the detection of findings suggestive of herpes simplex is high, but the sensitivity is low. Specific techniques such as PCR are needed for confirmation. Liquid-based cytological samples are adequate for these techniques.

8.3 Communication of the results to the patient.

The cytology or colposcopic results of patients attended for CC screening may find alterations suggestive of or confirming genital infection. In some cases, specific treatment is indicated and in others the patient should be reevaluated with specific tests to confirm the diagnosis or refer the patient to a clinic specialized in STD.

Communication of the results should take into account the impact that knowledge of being a carrier of a potential sexually transmitted infection may have on the patient or partner. Protocols should be established to determine in which cases the study should be amplified or in whom additional confirmatory tests should be made in both the patient and the partner and in which cases it is possible to administer treatment and specific follow-up.

Recommendation:

- Cytology may suggest or confirm genital infection. Protocols should determine in which cases the study should be amplified or treatment and specific follow-up should be performed in both the patient and the partner.
- On communicating the presence of an STD after the cytology results, the impact this may have on the patient and her partner should be taken into account.

9. Colposcopy standards in special situations

9.1 PREGNANCY

Colposcopy in pregnant women should be performed whenever there is an indication, and the main objective should be to rule out invasive cancer. The great difficulty in evaluating the cervix during pregnancy makes it essential for the procedure to be performed by experienced professionals within a Colposcopy Unit. The cervix undergoes notable changes during pregnancy. On one hand, the endocervical columnar epithelium shows hypersecretion which extends outward in the ectocervix facilitating vision of the squamocolumnar junction. Vascularization increases with certain venous stasis and edema. The stroma may also show decidual changes or decidualis which may affect small isolated areas or diffusely extend throughout the cervix. All of this leads to a cyanotic and edematous appearance which is characteristic of the cervix in pregnant women and which bleeds easily, further hindering colposcopy, especially in the last trimester and in multiparous women.

The incidence of CC in pregnancy is low ranging, from 1-5 to 15.6 cases per 100,000 deliveries [106, 107]. Approximately, 1 to 3% of CC are diagnosed during pregnancy or postpartum [108]. Five percent of pregnancies may present an abnormal cervical screening result [109].

For some women pregnancy may be the first opportunity for cervical screening. In addition, a diagnosis of CC is more probable in women who have never undergone screening tests.

The first visit during pregnancy should include a review of the screening history, and in the absence of a screening history, a cervical smear should be made for HPV testing and/or cytology based on the corresponding screening protocol. It must be remembered that the use of an endocervical brush is not advised.

The indications for referring a pregnant woman for colposcopy study are:

- LSIL cytology: colposcopy is the preferential option although not imperative. The low risk of occult carcinoma or lesion which progresses to carcinoma

justifies a conservative approach, and therefore, colposcopy may be deferred until 6 weeks after delivery.

- Suspicion or confirmation of LSIL/CIN 1 or less: defer the control until after delivery.
- HSIL cytology: immediate colposcopy.
- On suspicion or histological confirmation of HSIL/CIN2-3 trimestral colposcopic control is recommended during pregnancy, with a new evaluation postpartum.
- Positive HPV test with the presence of HPV 16 or 18 genotypes: colposcopy is the preferred option [110], especially if there is a concomitant abnormal cytology result. If the cytology is negative a conservative approach may be taken and colposcopy may be deferred until 6 weeks after delivery.
- Clinical or colposcopic suspicion of invasive cancer: an adequate biopsy is required to achieve a diagnosis. A biopsy that only suggests SIL/CIN does not reliably rule out invasion. In these cases, conization is indicated despite a risk of hemorrhage of approximately 25%. The main objective of cervical biopsy during pregnancy is to rule out an invasive lesion, and therefore, it is always recommended on cytological or colposcopic suspicion of infiltration.

In general, and except for invasive cancer, the treatment of high grade cervical lesions should be deferred until 6 weeks after delivery and preferably before 3 months.

Recommendation:

- Colposcopy should be performed in pregnant women whenever there is a precise indication, and it should be carried out by experienced professionals in Colposcopy Units.
- Colposcopic evaluation during pregnancy is more complex due to physiological changes in the cervix.
- The main objective of colposcopy in pregnancy is to rule out CC. On clinical and colposcopic suspicion, biopsy or even conization should be performed.

9.2 MENOPAUSE

Colposcopy is more difficult in menopausal women due to the physiological changes presented in the cervix in relation to a deficiency of estrogen and epithelial atrophy. In most cases, the squamocolumnar junction is not visible for being in the interior of the cervical canal (type 3). Atrophy and epithelial thinning easily produces bleeding and de-epithelization which makes the colposcopy inadequate. In addition, in an elevated percentage of cases, ACsUS or LSIL cytology in menopausal women is due to atrophy and estrogen deficit. Therefore, the application of local estrogens during 6-8 weeks in postmenopausal women with marked atrophy and ASCUS or LSIL before repeating the cytology is an acceptable option which improves the cytological and colposcopic study [111].

Prospective studies have shown that the incidence of cervical lesions and CC is low in postmenopausal women with previously normal screening results. In addition, they confirm that hormone replacement therapy with estrogens and progesterone has no significant effect on the positivity of the HPV test or abnormal cytologies [112-114].

Postmenopausal bleeding is not an indication for performing preventive cervical screening regardless of whether the patient has correctly followed the cervical screening program or not. Since postmenopausal hemorrhage may be the first symptom of genital cancer, the patient should immediately be referred to a gynecologist for undergoing the pertinent diagnostic tests. Any delay in diagnosis can severely worsen the prognosis.

Recommendation:

- Colposcopy is more difficult in menopause because of the associated atrophy.
- Treatment with topical estrogens may facilitate both evaluation of the cytological sample as well as interpretation of colposcopy.
- Postmenopausal genital hemorrhage is not an indication for screening but rather for gynecological examination to rule out an eventual gynecological cancer.

9.3 USE OF CONTRACEPTIVES

The possible carcinogenic effect of oral contraceptives has been analyzed in numerous studies. One systematic review of 28 studies found that, in comparison with women who never used oral contraceptives, the relative risk (RR) of CC increased with an increase in the length of use of oral contraceptives. The results were similar for both squamous carcinoma and adenocarcinoma. The risk decreased with discontinuation of the contraceptive pill [114, 115].

Although HPV is a necessary cause of CC, it has also been associated with other risk factors such as elevated parity and the use of oral contraceptives. In a recent prospective study of a cohort of 308,036 women, the duration of use of oral contraceptives during more than 15 years was associated with a significant increase of HSIL/CIN2-3 and cancer, compared to women who had never taken them, suggesting that there are hormonal factors of risk for cervical carcinogenesis [116].

However, on weighing the risks and benefits, the World Health Organization (WHO) does not recommend any change in the practice of oral contraceptives. Adherence to the current cervical cancer screening schedules should minimize the greater risk of cervical cancer associated with these hormonal risk factors.

Recommendation:

- The benefits and risk of the use of contraceptives should be evaluated individually in patients with premalignant cervical lesions or HPV infection.
- The WHO does not recommend any change in the schedules which may represent an increase in unwanted pregnancies.

9.4 HYSTERECTOMY

The approach in any patient in whom hysterectomy is indicated depends on two factors: 1) the presence of SIL/ CIN at the time of the hysterectomy 2) previous screening results.

Patients who have undergone hysterectomy for CC or endometrial cancer should follow the pertinent gynecological oncology protocol. Patients with subtotal hysterectomy should follow cervical screening the same as the general population.

Total hysterectomy in patients with SIL/CIN.

At present, hysterectomy is not a treatment of choice for SIL/CIN. It is only justified if associated with benign disease such as myomas or prolapse or when conservative treatment is not possible due to persistence of SIL/CIN.

The risk of SIL/ vaginal intraepithelial neoplasia (SIL/VaIN) after hysterectomy for SIL/CIN is 5%. A joint analysis of 4 series with 1,149 patients controlled over 5 to 20 years detected 61 cases of SIL/VaIN (5.3%), 3 of which progressed to cancer [117-120]. In most cases, the development of SIL/ VaIN post-hysterectomy is the consequence of persistence or reinfection by HPV and is rarely due to incomplete resection of SIL/CIN [121, 122].

Relatively frequently SIL/VaIN develops in the epithelium which may remain buried in the scar of the vaginal fundus and angles. This conditions a greater limitation for diagnosis, increasing the risk of developing an occult cancer which may debut as an endopelvic tumor growth [123].

Prior to surgery a thorough colposcopy with lugol staining should be performed to determine the status of the vaginal vault and rule out a possible SIL/VaIN.

Patients with SIL/CIN treated by hysterectomy should undergo a co-test at 16, 18 and 36 months after treatment. In the presence of a positive HPV test and/or abnormal cytology, the patient should be referred for a vaginoscopy [110].

If the vaginal margin is affected with an intraepithelial neoplasia, and the controls are negative, periodic follow-up should be carried out. Cases of invasive neoplasia in the vaginal vault have been described after more than 20 years.

Total hysterectomy for adenocarcinoma in situ (AIS).

Annual control of the vaginal vault should be made with co-test for at least 20 years. At present, there are no data supporting the discontinuation of control [110, 9]. In the presence of a positive HPV test and/or abnormal cytology,

the patient should be referred for vaginoscopy.

Total hysterectomy for benign processes.

In patients requiring hysterectomy for disease not related to HPV, it is necessary to include a review of the screening history in the preoperative study, and in the absence of screening, an HPV test and cytology should be performed [2]. Patients with a positive result should be referred to colposcopy for evaluation prior to surgery.

- With a normal cervical screening history (negative HPV test and cytology). Patients do not require to follow the screening program.
- With no history of or unknown cervical screening. Perform co-test in vaginal vault. If the result is negative, further control is not necessary. In the presence of a positive HPV test and/or abnormal cytology, refer the patient to colposcopy.
- Following treatment of HSIL/CIN2-3, with controls of complete cure and no evidence of cervical disease, follow with routine screening of the vaginal vault until completing 20 years of follow-up.

Recommendation:

- Women with negative screening and hysterectomy for disease not related to HPV should discontinue screening.
- Women treated with hysterectomy for HPV-related diseases should undergo the corresponding post-treatment follow-up and afterwards continue with screening for at least 20 years.

10. Colposcopy practice according to the level of risk

The principal objective of CC screening is to reduce the incidence and mortality of this neoplasm by the detection and treatment of lesions with a risk of progression (HSIL/CIN2-3). The risk of presenting or developing a HSIL/CIN2-3 should determine the frequency and intensity of follow-up or the type of treatment so that similar risk carries similar interventions [124].

The introduction of new diagnostic tests into clinical practice and the conjugation of new molecular, morphologic and colposcopic markers has led to more precise prevention of CC and facilitates more accurate quantification of the risk of having or developing this cancer. This information allows the planning of strategies of clinical practice based on more rational use of the tests and greater optimization of the resources, which translates into more efficient screening. Estimation of the risk of HSIL/CIN2-3 or CC is the result of the combination of the different tests performed, and when the level of risk is the same, the same clinical strategy should be considered.

10.1 DEFINITION OF RISK OF PREMALIGNANT CERVICAL LESION ACCORDING TO MOLECULAR, MORPHOLOGIC AND COLPOSCOPIC MARKERS.

The screening of CC has classically been based on cervical cytology. In most cases, an abnormal cytology implies the need for colposcopy and directed biopsies with the objective of obtaining histological confirmation. Therefore, the histological diagnosis is considered the gold standard which largely determines the clinical approach.

The incorporation of the test for HPV detection and genotyping into clinical practice as well as other molecular markers and their combination with morphological (cytology) and colposcopic markers provides greater potential in the stratification of risk of a premalignant lesion. The greater or lesser probability of identifying a lesion \geq HSIL/CIN2 using these procedures can classify patients into a level of high, low or null risk.

Women with negative cytology and HPV test have a very low risk of presenting a precursor lesion in the following 5 to 10 years and present virtually no risk of developing a CC in this period. To the contrary, patients with HSIL cytology, a positive HPV test (especially for genotypes 16 or 18) and a colposcopy with grade 2 changes present an 80% probability of having a lesion \geq HSIL/CIN3 within the following 2 years. This information justifies clinical decision making based on the knowledge and quantification of risk of precancer estimated by the result and the combination of the different screening tests as has been described in different prospective studies and clinical trials [124].

Table 10.1 shows some levels of risk for HSIL/CIN3 according to the cytology and HPV test results as well as the clinical proposals for follow-up [124].

Patients referred to the Colposcopy Unit for an abnormal screening test have a wide range of risk of having SIL/CIN. This risk may be estimated by the result of the screening test and molecular tests together with the colposcopy images. Along the same line, the ASCCP [58] recently proposed a series of recommendations based on a systematic review of published evidence in which the procedures to be performed are indicated based on the estimation of risk of presenting HSIL/CIN3. This risk is evaluated from the results of 3 parameters:

- Cytology result (morphological marker).
- Determination of HPV with genotyping (molecular marker).
- Initial colposcopic impression (colposcopic marker).

The combination of these markers of risk can stratify the population into three groups of risk (table 10.2). The need to perform biopsies is determined according to the level of risk established [58].

Recommendation:

- In the case of an abnormal result of the screening tests the markers of risk are evaluated: cytology (morphological), HPV test (molecular) and colposcopic impression (colposcopic). The need for directed biopsies is established according to the level of risk.
- Women with a low risk of lesion \geq HSIL/CIN2 are those who fulfill the criteria of: cytology $<$ HSIL, negative HPV 16/18 and normal colposcopy.
- Women with a high risk of lesions are those who fulfill at least 2 criteria of: cytology \geq HSIL, AGC or ASC-H; positive HPV 16/18; colposcopy with grade 2 changes.
- Women with intermediate risk of lesion \geq HSIL/CIN2 are those who are not included in the previous 2 groups.

Table 10.1. Risk of premalignant cervical lesion based on the screening tests and tools proposed for clinical follow-up.

Scenario of screening or clinical management	Cytology result	Result of oncogenic HPV test	Clinical proposal for follow-up	Absolute risk of precancer CIN3a
Screening	Negative	HPV -	Routine	< 2%
Screening/Triage	ASCUS	HPV -		
Post-colposcopy ^b		VPH -		
Screening Screening Screening Post-colposcopy ^b LLETZ	Negative LSIL ASCUS Negative	HPV + HPV - HPV +	12 months	2 – < 10%
Screening /Triage Screening post colposcopy ^b Post LLETZ Screening	ASCUS LSIL > ASCUS	HPV + HPV + HPV +	Colposcopy Colposcopy/Treatment	>10% > 40%
Post-colposcopy ^b CIN2 biopsy	HSIL	HPV +	Treatment? Treatment	> 40%
Colposcopy grade 2	HSIL	VPH +	Treatment?	> 60%

a. Risk until the following screening round - b. Results of cytology and HPV test in the control at 6 months after colposcopy. [124]Reproduced from Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M. Risk assessment to guide the prevention of cervical cancer. *Journal of Lower Genital Tract Disease*, Volume 12, Number 1, 2008, 1-7.

Table 10.2: Level of risk of having SIL/CIN based on cytology, HPV test and colposcopy.

Low risk (Fulfill the following 3 criteria):	High risk (Fulfill at least 2 of the following criteria):	Intermediate risk (cases not included in the 2 previous groups).
<ul style="list-style-type: none"> • Cytology < HSIL • Negative HPV 16/18 • Normal colposcopy 	<ul style="list-style-type: none"> • Cytology ≥ HSIL, AGC or ASC-H • Positive HPV 16/18 • Colposcopy with grade 2 changes. 	

Number and type of biopsy taken in colposcopy

Numerous studies have demonstrated that taking a single directed biopsy in the zone with the greatest colposcopic abnormality may not diagnose between one third to more than half of SIL/CIN (Table 10.3). It is recommended to perform directed biopsies mapping the different abnormal colposcopic areas (see section 6.4).

10.2 COLPOSCOPIC PRACTICE IN WOMEN WITH LOW RISK OF PRECANCER

In this regard the ASCCP [58], and based on the stratification of risk obtained with the markers described above, have

established that non directed biopsies or at random biopsies should not be carried out in patients with a very low risk referred to colposcopy (cytology < HSIL, HPV test not 16 or 18 and colposcopy without grade 2 changes).

Many studies have shown that women with cytology results < LSIL, HPV infection by genotypes other than 16 or 18 and normal colposcopy or with grade 1 changes have a low risk of presenting an underlying lesion ≥ HSIL/CIN2 (Table 10.4). In these cases it is recommended to perform a directed biopsy in the abnormal areas of acetowhite epithelium, metaplaia or another abnormality. Not performing directed biopsy in these situations implies a risk of underdiagnosing a lesion ≥ HSIL/CIN2.

Table 10.3. Increase in the rate of detection of premalignant lesions with an increase in the number of biopsies.

Study	Population	Endpoints	1 biopsy	2 biopsies	3 biopsies	4 biopsies
ALTS trial [87]	Multicenter ALTS trial, in the USA	2 years ≥CIN3	142/208 (68.3%)	108/132 (81.8%)	35/42 (83.3%)	NA
Pretorius et al. [125]	SPOCCS, China	Cross-sectional ≥CIN3	141/122 (63.5%)			198/222 (89%)
Van der Marel et. al. [126]	EVAH study, The Netherlands and Spain	Cross-sectional ≥CIN2	136/263 (51.7%)	159/263 (60.4%)		
Wentzensen et al. [88]	Biopsy study, USA	Cross-sectional HSIL+	157/252 (60.6%)	222/252 (85.6%)	246/252 (95.6%)	252/252 (100%)

ALTS indicates ASCUS-LSIL Triage Study; NA not applicable; CIN: intraepithelial cervical neoplasia; HSIL high-grade squamous intraepithelial lesion.

SPOCCS, Shanxi Province Cervical Cancer Screening Study; EVAH, Evaluando la Visual Apariencia de las lesiones cervicales y su diagnóstico histológico, genotipo del virus del papiloma humano y otros parámetros virales. [58] Reproduced from Wentzensen N, M Schiffman, Silver MI, Khan MJ, Perkins RB, Smith KM, MD, Gage JC, Gold MA, Conageski C, Einstein MH, Mayeaux EJ, Waxman AG, Huh WK, MD, Massad LS. ASCCP Colposcopy Standards: Risk-Based Colposcopy Practice. J Low Genit Tract Dis 2017;21: 230–234.

Table 10.4. Risk of premalignant cervical lesion in women with a normal colposcopy normal and previous low risk.

Study	n	HSIL/CIN2	HSIL/CIN3	Proportion HSIL/CIN2	Proportion HSIL/CIN3
ATHENA	660	15	6	0.0227	0.0091
ALTS trial	402	4	2	0.0100	0.0050
BD Oncoclarity	1572	25	11	0.0159	0.0070
Biopsy Study	38	3	0	0.0789	0.0000
Pool estimado	2672	47	19	0.015	0.004

10.3 COLPOSCOPY PRACTICE IN WOMEN WITH HIGH RISK OF PRECANCER

In women stratified in the high risk group [58], that is, those presenting at least two of the following parameters (HSIL cytology, positive HPV test for genotype 16 and/or 18 and colposcopy with grade 2 changes), it is recommended to immediately perform colposcopy with multiple directed biopsies (preferably of all the abnormal areas). Even in selected cases it is acceptable to perform excisional treatment without a confirmatory biopsy. If in cases undergoing biopsies, these do not show a lesion \geq HSIL/CIN2, then an endocervical study should be carried out [30, 33, 75].

A systematic review of the see and treat strategy in women with HSIL cytology found that in 89% the excisional procedure confirmed the presence of a lesion \geq HSIL/CIN2 [127], while other studies reported lower values (Table 10.5). The 2012 clinical guidelines of the ASCCP consider performing immediate direct treatment in women with cytological HSIL. Table 4 shows the risk of precancer in the different studies in women with HSIL and colposcopy with major grade 2 changes or HPV16 positive and colposcopy with grade 2 changes which substantially exceed the rate of risk of HSIL in whom immediate treatment can be recommended [58].

In order for this strategy based on the stratification of risk to be successful, it is necessary for determined conditions to be met [58]:

- The markers of evaluation of risk must be reliable

and reproducible. The parameters of high risk (HSIL cytology and colposcopy with grade 2 changes) and those of low risk (cytology $<$ HSIL and normal colposcopy) are more reproducible than the intermediate categories of cytology and colposcopy.

- The estimations of risk for specific strata should be comparable among populations. A systematic review of the publications showed that the variability in the evaluation of risk for different strata was low.
- The strategy must be able to be used in clinical practice. Dividing the population into a few strata with different levels of risk is clinically more practical and facilitates management.

In summary, the evaluation of risk of HSIL/CIN in a colposcopy visit can modify the procedures, adapting them to the risk of each woman. In this way, when the risk is low it is possible to observe and follow the patient without performing a biopsy and treat without histological confirmation when the risk is higher. For women in all the other risk groups, taking multiple directed biopsies including the areas with a minimum acetowhite epithelium is important to improve the detection of SIL/CIN in the colposcopy visit.

At present, other biomarkers which may provide greater accuracy in the evaluation of risk are under investigation [131], among which the following are of note:

- **Dual p16/Ki67 staining:** Positive results for this test are positively related to the histological grade of the cervical lesion. Although the study results are discordant, some have shown that dual staining is useful for the selection of HPV positive women with normal cytology who would present a high probability

of an underlying lesion \geq HSIL/CIN2 [132]. There is currently an automated detection system for p16 / Ki67 to improve the stratification of risk of CC [133].

- **DNA methylation:** The utility of epigenetic alterations in the detection of premalignant lesions of the cervix with capacity of progression (HSIL/CIN3) has been evaluated. Epigenetic silencing of tumor suppressor genes by hypermethylation of the promoter is one of the earliest epigenetic alterations in many neoplasms in oncologic transformation and may be an early marker of malignant transformation. Many studies related to the hypermethylation of different genes involved in the development of cervical cancer such as CADM-1, MAL, FAM have been performed.
- **MCM2/TOP2A (ProEx C):** Recent studies of transcriptional profiles have identified 2 proteins

related to the cellular cycle, and the maintenance of minichromosome protein-2 (MCM2) and topoisomerase II (TOP2A), the genes of which are over expressed in Ω CC [134] and are detectable by microarray-based technology. ProEx C is a new immunohistochemical marker for the detection of the MCM2 and TOP2A proteins. Increased expression of these proteins seems to be associated with HPV 16 and HSIL [135]. Different combinations of cytological evaluation, HPV test and ProExC staining have been compared, and it was found that primary screening based on the DNA of high risk HPV followed by ProExC triage was the best screening strategy for detecting \geq HSIL/CIN2

Table 10.5. Risk of lesion \geq HSIL/CIN2 in women with previous high risk.

Stratum	Study	Author	Population	N	\geq CIN2	Proportion \geq CIN2
HSIL sólo		Aue Aungkul et al. [128]	HSIL	133	119	0,89
			HSIL	1781	1643	0,92
	ALTS	Bosgraaf et al.[129].[88]	ASCUS/LSIL	411	246	0,60
	BD		HPV +	124	105	0,85
	Biopsy Study		\geq ASCUS	206	127	0,62
	Pooled Estimate			2655	2240	0,79 (0.61-0.93)
High grade colposcopy and HSIL		Aue_Aungkul et. al. [128]	HSIL	110	102	0,93
			HSIL	1543	1473	0,95
	ALTS	Bosgraaf et al.[129]		155	122	0,79
	BD			17	13	0,76
	Biopsy Study			108	81	0,75
	Pooled Estimate			1933	1791	0,86 (0,73-0,95)
High grade colposcopy and HPV 16/18 +	DSI Trial	Zaal et al. [130]	BMD Twice	18	17	0,94
	ALTS			182	133	0,73
	BD			31	19	0,61
	Biopsy Study			83	65	0,78
		Pooled Estimate			314	234
HSIL y HPV 16/18 +	ALTS			171	128	0,75
	BD			46	31	0,67
	Biopsy Study			91	67	0,74
		Pooled Estimate			308	196
High grade colposcopy HSIL and HPV 16/18 +	ALTS			105	90	0,86
	BD			9	8	0,89
	Biopsy Study			57	45	0,79
		Pooled Estimate			171	143

CIN: cervical intraepithelial neoplasia; HSIL high grade squamous intraepithelial lesion; ASCUS atypical squamous cells of undetermined significance. ALTS, ASCUS/LSIL Triage study for cervical cancer; BD, Beckton Dickinson; DSI, Dynamic Spectral Imaging; BMD, borderline mild dyscariosis. [58] Reproduced from Wentzensen N, M Schiffman, Silver MI, Khan MJ, Perkins RB, Smith KM, MD, Gage JC, Gold MA, Conageski C, EinsteinMH,Mayeaux EJ, Waxman AG, Huh WK, MD, Massad LS. ASCCP Colposcopy Standards: Risk-Based Colposcopy Practice. J Low Genit Tract Dis 2017;21: 230–234.



11. Summary of the recommendations and standards of quality in colposcopy.

2. SAMPLE COLLECTION FOR THE SCREENING OF CERVICAL CANCER

Recommendations

2.1 Cytological smear

- Ideally the cytological smear should be done when the patient is not menstruating.
- The presence of signs of suspicion of an invasive cervical lesion implies the need to refer the patient for a specific gynecological study.
- The cytological smear should obtain samples from the exocervix and endocervix.
- The cytological smear should preferably be done in liquid medium with a plastic spatula and cytobrush or with a single device. Conventional smear and extension on a slide is acceptable.
- The cytological reports should be made according to the Bethesda terminology.

2.2 Sample collection for HPV testing

- The HPV testing test should be approved by the regulatory agencies (FDA) or fulfill the criteria of equivalence of sensitivity and specificity.
- The HPV sample should obtain material from the exocervix and the transformation zone.
- The HPV sample should preferably be made in liquid medium with a plastic spatula and cytobrush or with a single device.
- According to the method selected, in primary screening the report of HPV test result should provide information of a positive high risk HPV test or specifically for each of the genotypes or for genotypes 16 and 18.

2.3 Sample collection in special clinical situations

- In cases with cervical stenosis, the endocervical sample may be obtained after dilatation. In difficult cases it is preferable to take a sample for the HPV test.
- In cases of cervicitis, it is preferable to defer the cervical sampling until after performing a specific treatment.
- In the case of severe atrophy, treatment with topical estrogens can be performed before the cytology or making an HPV test.
- Screening in women with hysterectomy for SIL/CIN should continue for at least 20 years.
- Adequate cytology without cellular alterations but limited due to the absence of endocervical cells or cells from the transformation zone is considered negative.
- In cases of inadequate cytology limited by the absence of endocervical cells or cells from the transformation zone, the reflex HPV test or co-test may be performed after treatment with estrogens.

3. GUIDELINES FOR REFERRING A PATIENT TO COLPOSCOPY. STANDARDS OF QUALITY.

Recommendations

3.1 Waiting time to perform colposcopy in asymptomatic patients with an abnormal result in the screening tests.

- Colposcopic evaluation of a patient with ASCUS cytology and a positive HPV test should be performed within 8 weeks.
- Colposcopic evaluation of a patient with LSIL cytology should be performed within 8 weeks.
- Colposcopic evaluation of a patient with HSIL cytology should be performed within 4 weeks.
- Colposcopic evaluation of a patient with ASC-H cytology should be performed within 4 weeks.
- Colposcopic evaluation of a patient with AGC or AGC-H cytology should be performed within 4 weeks.
- Colposcopic evaluation of a patient with AIS cytology should be performed within 2 weeks.
- Colposcopic evaluation of a patient with a persistent HPV positive test of at least 1 year and negative cytology should be performed within 16 weeks.

3.2 Waiting time for performing colposcopy in patients with symptoms or suspicious findings in the routine gynecological examination.

- Colposcopic evaluation of a patient with symptoms suggestive of CC should be performed within 2 weeks.
- Colposcopic evaluation of a patient with a macroscopically abnormal cervix in the screening sample should be performed within 2 weeks.

3.3 Waiting time between confirmed histological diagnosis after colposcopy and treatment.

- All cervical treatments require a previous colposcopy study performed in a Colposcopy Unit by specialized professionals.
- The treatment of HSIL/CIN2-3 should be performed in less than 8 weeks.
- Excisional procedures should present less than 5% of hemorrhagic complications and less than 2% of readmissions.

5. NOMENCLATURE AND DESCRIPTION OF COLPOSCOPIC FINDINGS.

Recommendations

5.1 Terminology

- The colposcopic terminology of the IFCPC 2011 Classification should be used in clinical practice.

5.2 Accuracy of colposcopic diagnosis

- The principal objective that colposcopy terminology should pursue is to obtain the best correlation between the colposcopic findings and the histological lesion.
- Acetowhite changes have a greater grade of correlation, and this increases with the evaluation of the vascular pattern and borders of the lesion.
- Some recently introduced colposcopic signs (inner border or white on white, ridge sign and rag sign) have an elevated specificity and PPV for lesions \geq HSIL/CIN2.

5.3 Benefits of colposcopy

- The use of colposcopy shows its greatest benefits in the detection of lesions (guides biopsy and allows histological confirmation).
- Conizations should be performed under colposcopic control.

5.4 Potential harmful effects of colposcopy

- The principal harmful effects of colposcopy reported by patients are pain and anxiety.
- Underdiagnosis or the excess of non justified biopsies are the principal potential harmful effects associated with colposcopy performed by unexperienced professionals.

6. STANDARDS OF QUALITY IN COLPOSCOPY DIAGNOSIS (I)

Recommendations

6.1 Registry of the clinical history of patients referred to colposcopy

- Anamnesis in the first colposcopic visit should be exhaustive and include the patient's history (parity, HIV/immunosuppression), hormonal situation, contraception and data on premalignant disease (HPV vaccination, data and result of the screening tests, history of DIL and previous treatments).
- Prior to colposcopy it is essential to report the indication and the result of the screening tests.
- Prior to colposcopy women should receive verbal information regarding the characteristics of the procedure, and ideally, they should provide informed consent.

6.2 Colposcopic examination

- The colposcopic examination should always be performed following a systematic methodology.
- Colposcopic evaluation of the vagina should be systematic and may be facilitated using low magnification and lugol solution.
- Colposcopic evaluation of the vulva can be facilitated using low magnification and acetic acid solution at 5%.

6.3 Reporting and registry of colposcopic findings.

- Description of the colposcopic findings should be exhaustive and rigorous.
- Colposcopic evaluation of the visualization of the cervix, description of the squamocolumnar junction and the type of transformation zone should be performed in all the cases.
- In the case of a cervical lesion, colposcopic evaluation of the characteristics of the lesion (type, localization in the cervix, visibility and semiology) is mandatory.
- Registry of the colposcopic images is essential (preferably by colpophotographies in the electronic clinical history). As an option they may be registered using schemas or diagrams.
- On completion of the colposcopic examination, the colposcopic impression should be reported according to the IFCPC terminology in all the cases.

6. STANDARDS OF QUALITY IN COLPOSCOPIC DIAGNOSIS (II)

Recommendations

6.4 Colposcopy-guided biopsies

- Cervical biopsy should always be guided by colposcopy. The sample should select areas of greatest abnormality and should contain an adequate representation of the epithelium and the stroma (percentage of satisfactory biopsies greater than 90%).
- Selection of the most significant epithelial area to perform the directed biopsy should take the colposcopic impression into account.
- Taking a single directed biopsy of the colposcopic area with the greatest abnormality has a lower sensitivity for the detection of a lesion \geq HSIL/CIN2 than the taking of multiple biopsies.
- Based on the lesion characteristics and the risk of lesions \geq HSIL/CIN2, directed biopsies of the different abnormal colposcopic areas are recommended (generally between 1 to 4).
- Directed biopsies should take into account the level of risk of a lesion \geq HSIL/CIN2 which depends on the cytology result, the presence of HPV 16/18 and the colposcopic impression.
- Do not perform biopsies in women with a low risk of lesion \geq HSIL/CIN2: cytology $<$ HSIL, no HPV 16/18 and a normal colposcopic impression.
- Perform directed biopsies in women over 25 years of age, not pregnant, with a high risk of lesion \geq HSIL/CIN2 and at least 2 factors: HSIL cytology, HPV 16 or 18, colposcopic impression with grade 2 changes.
- If there is a high risk of lesions \geq HSIL/CIN2, immediate excisional treatment can be performed in selected cases if they fulfill the criteria in the previous point.
- Non directed biopsies (within the transformation zone) can be performed in cases in which the colposcopic impression shows no evidence of lesion but there is a risk of
 - HSIL/CIN2.
- Non directed biopsies should never be performed in cases with a low risk of lesions \geq HSIL/CIN2.
- Endocervical study with curettage or brush should be performed when the colposcopic lesion shows an endocervical component (more frequent in menopause or post-treatment).
- An endocervical study immediately post-conization is indicated since it has an elevated predictive value of lesion persistence.
- Endocervical curettage is contraindicated during pregnancy.

6.5 Reporting and registry of biopsies

- It is essential to correctly report and register all the cervical biopsies (number, localization, and colposcopic characteristics).
- Following biopsy sampling the histological report should be available within a time of less than 4 weeks.
- Patients should receive verbal and written communication of the colposcopy results and of the complementary studies performed.

7. COLPOSCOPY UNITS. STANDARDS OF QUALITY (I)

Recommendations

7.1 Standards of Quality of the Colposcopy Unit.

- The percentage of positive directed biopsies for lesions should be $\geq 80\%$
- Globally, the sensitivity and specificity of colposcopy in the diagnosis of lesions \geq HSIL/CIN2 should be $\geq 80\%$ and $\geq 70\%$, respectively.
- The number of conizations performed per year should be registered.
- The percentage of conizations performed in the outpatient setting should be $\geq 70\%$.
- The percentage of conizations performed under colposcopic control should be $\geq 90\%$.
- The type of treatment performed in all cases should be registered.
- A lesion \geq HSIL/CIN2 should be confirmed in $\geq 70\%$ of the conization pieces.
- The percentage of conizations without histological lesions should be $\leq 15\%$.
- The percentage of conizations with lesions positive for lesion should be $\leq 20\%$ ($\leq 15\%$ of endocervical margins).
- The percentage of HSIL cytologies at 6 months should be $\leq 10\%$ and $\leq 5\%$ at 24 months.
- The percentage of compliance with recommended waiting times should be $\geq 90\%$.
- The percentage of compliance with the vaccination schedule for HPV in women after conization (according to the protocols of each autonomous community) should be $\geq 90\%$.
- The annual number of claim or complaints should be registered and analysis of the reasons for these claims should be performed.
- The annual number unit or interdisciplinary sessions should be registered.
- Correctly report (preferably in writing) the objectives of the screening tests and the possibility of complementary studies ($\geq 90\%$) and the results of the screening tests and colposcopy ($\geq 90\%$).
- The patient must be informed of the results within a maximum of 8 weeks.
- The members of the Colposcopy Unit should be accredited (ideally $\geq 50\%$).
- The Colposcopy Units must coordinate and achieve consensus regarding the referral of patients from screening programs based on regional or national guidelines.



7. COLPOSCOPY UNITS. STANDARDS OF QUALITY (II)

Recommendations

7.2 Personnel, installations and equipment of a Lower Genital Tract Unit.

- The medical personnel of the Colposcopy Unit should be experienced and staffing and organization should allow correct patient care, quality control, teaching and continuing education.
- The nursing personnel should be qualified and integrated in the functioning of the unit.
- The installations and equipment of the Colposcopy Units should fulfill the health care requisites of safety, equipment, and confidentiality.

7.3 Organization and administrative management

- The organization of the Colposcopy Unit requires a specific organigram and administrative support as well as specialized nursing personnel.
- The specialists of the Colposcopy Unit should periodically meet (preferably every 1 or 2 weeks).
- Multidisciplinary meetings with specialists related to the Colposcopy Unit should be held every trimester.

7.4 Clinical documentation

- The clinical activity of the Colposcopy Unit requires documentation which is standardized according to the prevailing legislation.
- The principal documentation refers to: clinical history, informed consent, authorizations, discharge reports, and informative documents.
- Informed consent registered in the clinical history should be obtained in > 95% of all the procedures performed.

8. INFECTIONS, CYTOLOGY AND COLPOSCOPY

Recommendations

8.1 Sample collection for the study of infections in the colposcopy visit.

- A screening visit for CC cannot be used to perform screening for infections of the lower genital tract.

8.2 Action towards infections found in cytology

- Cytological detection of actinomyces has a low sensitivity, specificity, NPV and prognostic value. In asymptomatic women neither IUD extraction nor specific treatment is necessary.
- Cytological detection of Trichomonas vaginalis can occur in asymptomatic patients or in women without signs of cervicitis. In all the cases, both the patient and partner should receive treatment.
- Cytological detection of Candidas is frequent, although this method is not considered to be very sensitive. In asymptomatic patients, this finding is not an indication for treatment. Other associated infections should be ruled out.
- Cytological detection of bacterial vaginosis is frequent. The presence of characteristic clue cells is not diagnostic of infection. The diagnosis and treatment should be based on clinical criteria.
- Cytological detection of Chlamydia tracomatis presents a very low sensitivity. This finding is of interest in symptomatic women or in those with inflammatory pelvic disease. Liquid cytology samples are adequate for performing NAAT techniques.
- Cytological detection of intraplasmatic diplococci is not always diagnostic of infection by Neisseria gonorrhoea (confirmatory techniques are always required). Liquid cytology samples are adequate for performing NAAT techniques.
- The specificity of cytology for the detection of findings suggestive of herpes simplex is high, but the sensitivity is low. Specific techniques such as PCR are necessary for confirmation. Liquid cytology samples are adequate for performing these techniques.

8.3 Informing patients of the results

- Cytology may suggest or confirm a genital infection. There should be protocols regarding in which cases the study should be widened or treatment or specific follow-up should be performed in both the patient and her partner.
- On informing the patient of the presence of a STD in the cytology results, the impact this may have on the patient and partner should be taken into account.

9. COLPOSCOPY STANDARDS IN SPECIAL SITUATIONS

Recommendations

9.1 Pregnancy

- Colposcopy in pregnant women should be performed based on a specific indication by experienced professionals and in Colposcopy Units.
- Colposcopic evaluation during pregnancy is more complex due to the physiological changes in the cervix.
- The principal objective of colposcopy in pregnant women is to rule out CC. On clinical and colposcopic suspicion, biopsy or even conization should be performed.

9.2 Menopause

- Colposcopy during menopause is more difficult due to the associated atrophy.
- Treatment with topical estrogens can facilitate both evaluation of the cytological sample as well as interpretation of the colposcopy.
- Postmenopausal genital hemorrhage is not an indication for screening but rather for gynecological examination to exclude an eventual gynecological cancer.

9.3 Use of contraceptive

- The benefits and risk of taking contraceptives by patients with premalignant cervical lesions or HPV infection should be individually evaluated.
- The WHO does not recommend any change in schedules which may induce an increase of unwanted pregnancies.

9.4 Hysterectomy

- Women with negative screening results and hysterectomy for any disease not related to HPV should discontinue screening.
- Women treated with hysterectomy for diseases related to HPV should undergo the corresponding post-treatment follow-up and continue with screening for at least 20 years.

10. COLPOSCOPY PRACTICE ACCORDING TO THE LEVEL OF RISK

Recommendations

10.1 Definition of risk of premalignant cervical lesion according to molecular, morphologic and colposcopic markers.

- On abnormal results in the screening tests the markers of risk are evaluated: cytology (morphological), HPV test (molecular) and colposcopic impression (colposcopic). The need for colposcopy and directed biopsies is determined depending on the level of risk.
- Women with a low risk of lesion \geq HSIL/CIN2 are those who fulfill the criteria of: cytology $<$ HSIL, negative HPV 16/18 and normal colposcopy.
- Women with a high risk of lesion \geq HSIL/CIN2 are those who fulfill at least 2 criteria of: cytology \geq HSIL, AGC or ASC-H; positive HPV 16/18; colposcopy with grade 2 changes.
- Women with an intermediate risk of lesion \geq HSIL/CIN2 are those who are not among the previous 2 groups.

STANDARDS OF QUALITY IN COLPOSCOPY PRACTICE

Waiting times for performing colposcopy	Standard fo quality	Recommendation
Asymptomatic patients with ASCUS cytology	< 8 weeks	≥ 80% of the cases
Asymptomatic patients with LSIL cytology	< 8 weeks	≥ 80% of the cases
Asymptomatic patients with HSIL cytology	< 4 weeks	≥ 80% of the cases
Asymptomatic patients with ASC-H cytology	< 4 weeks	≥ 80% of the cases
Asymptomatic patients with AGC and AGC-H cytology	< 4 weeks	≥ 80% of the cases
Asymptomatic patients with AIS cytology	< 2 weeks	≥ 80% of the cases
Asymptomatic patients with negative cytology and persistent positive HPV determination	< 12 weeks	≥ 80% of the cases
Patients with symptoms compatible with CC	< 2 weeks	≥ 80% of the cases
Patients suspected of having an infiltrating lesion in the cervix	< 2 weeks	≥ 80% of the cases

Information to patients	Standard of quality	Recommendation
Information of screening tests (preferably written material)	Percentage of women informed	≥ 90%
Information regarding screening results	Percentage of women informed	≥ 90%
Information of clinical action derived by the results of the screening tests	Percentage of women informed	≥ 90%
Waiting time to inform of result of screening tests	< 8 weeks	≥ 90%
Informed consent for procedures	Completed	≥ 90%

Training, sessions	Standard of quality	Recommendation
Training of physicians in the unit		
Accreditation for colposcopy	Percentage of accredited physicians in the unit	≥ 50%
Sessions		
Unit sessions	Every 1-2 weeks	Register annual number
Multidisciplinary sessions	Every trimester	Register annual number

Health care activity in colposcopy	Standard of quality	Recommendation
Description and registry of the characteristics of the lesion (type of lesion, localization, visibility and semiology)	Document	≥ 90%
Colposcopic impression	Document	≥ 90%
Grade 2 colposcopic changes	Correlation with ≥HSIL/CIN2	≥ 70%
Direct biopsies	Adequate for evaluation	≥ 90%
Directed biopsies	Direct biopsies positive for SIL/CIN	≥ 80%
Sensitivity of colposcopy	Percentage of patients with HSIL/CIN correctly diagnosed	≥ 80%
Specificity of colposcopy	Percentage of patients without SIL/CIN correctly diagnosed	≥ 70%
Conizations	Number of cases per year	Register
Outpatient conizations (in consulting office with local anesthesia)	Porcentaje del total de conizaciones	≥ 70%
Conizations under colposcopic control	Percentage of total number of conizations	≥ 90%
Conizations with lesion ≥ HSIL/CIN2	Percentage of total number of conizations	≥ 70%
Conizations without histological lesion	Percentage of total number of conizations	≤ 15%
Conizations with positive margins	Percentage of total number of conizations	≤ 20%
Conizations with positive endocervical margin	Percentage of total number of conizations	≤ 15%
Persistence/recurrence of lesion ≥ HSIL/CIN2	At 6 months after treatment	≤ 10%
Persistence/recurrence lesion ≥ HSIL/CIN2	At 24 months after treatment	≤ 5%
HPV vaccination in conized women (according to protocol in each autonomous community)	Percentage of women vaccinated	≥ 90%
Claims and complaints	Number and reasons	Register

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Annex 1

Information for patients [80, 81]

What is colposcopy / vaginoscopy / vulvoscopy?

This procedure is carried out to explore the cervix / vagina / vulva using a low magnification lens called “colposcope” which can examine the zone with the greatest accuracy. After applying a series of liquids, premalignant lesions of the epithelium become visible, and we can observe their size and exact localization. If any alteration suggestive of a lesion is visualized, a small biopsy of the abnormal area will be performed. With the analysis of the biopsy sample, the diagnosis can be obtained. This diagnosis, together with the characteristics of the colposcopy examination and the characteristics of the patient are essential to define which cases should be treated or should simply undergo periodic controls.

Why is necessary to perform this examination?

Colposcopy/vaginoscopy/vulvoscopy is a test performed by a gynecologist specialized in colposcopy. This procedure is used to study the cervix/vagina/vulva in depth and detect whether there are any abnormalities which should be treated or controlled without treatment.

It is advisable to perform this test for several reasons. The most frequent cause is an alteration in the screening tests (cytology or human papilloma virus test). In this case, colposcopy can visualize lesions (if present), their localization and their characteristics.

The information obtained with the test is important for deciding the most adequate clinical action to take with the patient.

Do I need any preparation before the examination?

- Do not apply any cream or treatment to the external genital region during the two days before the test.
- Do not have sexual relations during the two days before the test.
- If you have your period on the day of the test it is better to delay the examination.

What does the examination consist of?

Colposcopy / vaginoscopy / vulvoscopy is performed in the consulting office similar to the usual gynecological examination. It lasts approximately 10-15 minutes and does

not usually produce additional disturbances to those which occur with cytology sampling or the human papilloma virus test.

During the test a transparent liquid called acetic acid will be applied to the vulve/vagina/cervix, and sometimes another dark colored liquid is applied called lugol. These liquids highlight abnormal areas facilitating the identification of lesions. On some occasions, there may be a slight, non painful, sensation of burning or stinging which disappears after a few minutes.

If it is necessary to take a biopsy this will be done at the same time. Biopsy sampling is not usually painful, but some disturbance may be felt, although, in general, this is well tolerated. In some localizations it may be necessary to also use local anesthetics to allviate the sensation of pain and the application of substance to avoid bleeding afterwards. In exceptional cases and in very specific genital zones, the use of other methods such as small sutures may be necessary to avoid bleeding. If any sample is obtained, this will be sent to a laboratory for analysis.

Recommendations after the examination

- Most women can return to normal activity immediately after this test. Some women feel discomfort or mild genital cramps which generally disappear within one or two hours. If necessary, an analgesic medication used normally can be taken.
- It is advised to use a sanitary pad to protect your underwear during the hours after the test to avoid staining by the liquids used, especially the lugol solution (iodine solution). Due to the use of these liquids it is possible that you will have brown or black vaginal secretions during the following days.
- If a biopsy has been taken do not use creams or treatments (except if specified) in the zone. In addition, do not have sexual relations or immersion baths or vaginal douches in the following two days.
- If a biopsy has been taken, there may also be genital bleeding/spotting which should be scarce and of short duration. To the contrary it is advised to be visited again.



Annex 2 Informed consent

This informative document aims to explain, as simply as possible, the intervention called

colposcopy, vaginoscopy, vulvoscopy

as well as the most important aspects of the post-intervention period and the most frequent complications which may appear as a consequence of the intervention. This document has the objective of providing you with adequate information prior to your consent to undergo the intervention according to the Regulating Basic Law of the autonomy of the patient and the rights and obligations related to clinical information and documentation (41/2002).

Mr./Ms. cwith ID/passport nº.....as the patient.

I DECLARE

that the medical team attending me has informed me of the need to undergo the test described.
Informed consent for performing colposcopy / vaginoscopy / vulvoscopy.

1. I have satisfactorily been informed by Dr of the following points: that is, what colposcopy / vaginoscopy / vulvoscopy is, how it is performed, why it is performed, the possible risks and the possible disturbances or complications of the procedure. In addition, I have been advised of the precautions that should be taken after the procedure.

2. Description of the procedure to be authorized: **colposcopy / vaginoscopy / vulvoscopy:**
Colposcopy /vagoscopy /vulvoscopy is carried out to explore the cervix / vagina / vulva using a low magnification lens called "colposcope" which can examine the zone with greater accuracy. After applying a series of liquids, the pre-malignant lesions of the epithelium become visible, and we can observe their size and exact localization. If any alteration suggestive of a lesion is visualized, a small biopsy of the abnormal area will be performed. With the analysis of the biopsy the diagnosis can be obtained. This diagnosis is essential to define which cases should be treated or should simply undergo periodic controls according to the grade and characteristics of the lesion and the patient.

3. The complications and/or risks of the procedure are:
- Pain during and after the procedure (generally mild) which requires the use of analgesics and/or may trigger vagal reaction requiring specific measures of action (medication, observation).
 - Adverse reactions and/or allergies to the products and/or drugs (local anesthetics, hemostatic drugs) used during the procedure.
 - Bleeding during and after the procedure (generally mild) requiring suture points and emergency care (exceptionally).
 - Infections of the biopsy site requiring health care and complementary treatments.

4. Due to my current situation the doctor has informed me that complications may increase or appear (specify):
.....
.....
.....

5. The doctor has explained that the sample obtained during the procedure will be sent for analysis. The results of this analysis will be reported to me, or failing that, my family and/or legal representative. In addition, the doctor has explained to me and I have understood that depending on the results of this analysis another type of study may be necessary, and on occasions, determined surgical procedures.

6. The doctor has explained to me the possibility of performing photographs and/or videos of the images of the procedure for medical purposes and for scientific investigation, ensuring at all times the anonymity of all the data which could facilitate recognition of my person.
Under the conditions described, I authorize / do not authorize (cross out what is not applicable) the taking of photographs and/or videos of images of the procedure.

7. I have understood the explanations given to me in clear simple language, and the doctor attending me has allowed me to make comments and has clarified all my questions/doubts. I also understand that at any time and without any explanation I can revoke the consent which I now render.

8. I thereby state that I am satisfied with the information received and under such conditions I give my consent to undergo a colposcopy / vaginoscopy / vulvoscopy.

Annex 2 Informed consent

Consequently, I render my Consent for the performance of the procedure described.

SIGNATURE OF THE PATIENT

SIGNATURE OF THE INFORMING PHYSICIAN

Date:

Date:

Name of the legal representative in the case of patient disability indicating the relationship of this person with the patient (father, mother, tutor, etc.).

Name and surname..... ID n°

As the.....

SIGNATURE OF THE REPRESENTATIVE

Date:

REVOCACTION

Mr/Mswith ID/passport n°..... As the patient, or in his/her absence, Mr/Ms.....with ID/passport n°....., as legal representative and/or tutor of the patient of legal age, state that I REVOKE the consent rendered on the date of

Signature: Physician Signature: The patient

Signature: Legal representative/relative



