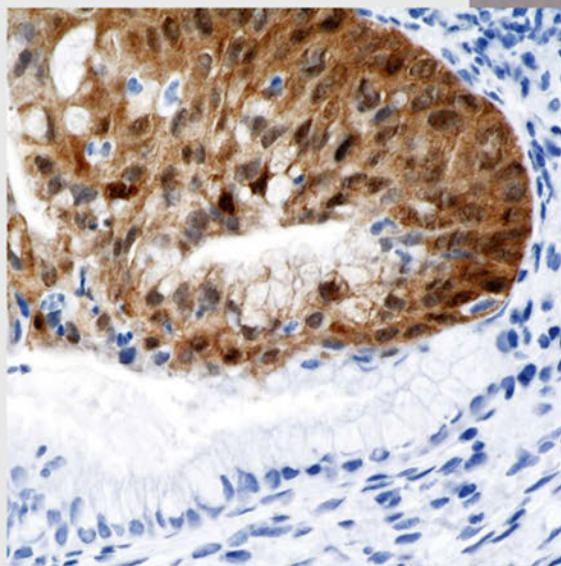


Burghardt's Colposcopy and Cervical Pathology

Textbook and Atlas

Frank Girardi
Olaf Reich
Karl Tamussino

4th Edition



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Preface to the Fourth Edition

The 15 years between the publication of the third and fourth editions of this textbook and atlas have seen huge advances in our understanding of the pathogenesis of cervical neoplasia and specifically the role of human papillomavirus (HPV) infection. In 2008 Harald zur Hausen was awarded the Nobel Prize for Medicine for his work in elucidating the role of HPV in cervical cancer. The development and increasing application of HPV vaccines promises to further push back the scourge of cervical cancer, in developed countries and in the developing world. This understanding of the genesis of cervical neoplasia is leading to major changes in strategies for prevention, early detection, and treatment of this disease. The fourth edition of this textbook and atlas has been reworked accordingly.

Also, we have added new chapters on the vagina and the anus. This is in recognition of the common etiology of many of these lesions and of the fact that physicians should be alert to coexisting problems at sites in the vicinity.

This edition also incorporates the changes in colposcopic terminology agreed on at the 14th World Congress of the International Federation for Colposcopy and Cervical Pathology (IFCPC) in Rio de Janeiro in 2011 and the 2014 WHO *Classification of Tumours of Female Reproductive Organs*.

After Professor Erich Burghardt's death in 2006 we have incorporated his name into the title of the book. We are privileged to have worked with him and to build on his work. Our goal is to carry on his commitment to an atlas of the highest quality while incorporating the advances in the field and to provide a book that comprehensively addresses the fascinating dynamics of the cervix and the underlying histology and histopathology.

We thank Thieme Publishers and the Thieme Publishing Group for their ongoing support and commitment to the painstaking production of highest quality books and atlases.

We thank our families and particularly our spouses Ursula, Christine, Caroline, and Ulrike for their patience, understanding, and support.

*Frank Girardi, MD
Olaf Reich, MD
Karl Tamussino, MD
Hellmuth Pickel, MD*

*Graz, Austria
October 2014*

Preface to the First Edition

Routine colposcopy was instituted at the Graz Frauenklinik by my teacher Ernst Navratil in 1947. This date coincided with the introduction of cytologic diagnosis. In 1950, we acquired a modern surgical pathology laboratory devoted primarily to the study of early cervical cancer. Emphasis was placed on the examination of serial sections of ring biopsies and later of conization specimens. From the beginning of 1954 I had the opportunity to be at the forefront of these developments. Following a year of combined clinical and laboratory duties, I was appointed to the colposcopy outpatient clinic. Within two years I performed approximately 20,000 examinations. This experience was particularly valuable, as I also had the opportunity to interpret all the cytology smears and biopsies that I took. I also examined the serial sections from ring biopsies and conization specimens, not only for the first two years, but also for the following decades.

While accumulating knowledge and experience, I participated in the historic evolution of colposcopy, witnessing its hesitant beginning and later, especially during the last ten years, its story international course. The breakthrough was due, no doubt, to better international communication and exchange of ideas. Although textbooks as recently as 1960 have rejected colposcopy as “cumbersome and troublesome,” its value is now undisputed. Controversies are centered merely on the indications for the colposcopic examination. While in Europe and South America colposcopy is accepted as an essential part of every gynecologic examination, in English-speaking countries its use is selective. This is due to the propagation of colposcopy not as a basic diagnostic modality, but as one which enables the taking of a directed target biopsy and consequently the avoidance of conization, a measure which is primarily cost-saving. During the last few years, colposcopy has found further application in the evaluation of vaginal adenosis and that of the seemingly more frequent condylomatous lesions. Colposcopy has thus become regarded as a special diagnostic tool; this was never intended. Typically, history repeated itself; as discussed later, some current concepts of morphogenesis of cervical carcinoma are mainly based on colposcopy, as envisaged by Hinselmann.

With colposcopy well established, every effort should be made to reinstate the method's original role and to reconcile it with the other means of diagnosis, in particular that of histology. This is the aim of this book. With the careful correlation of the colposcopic and histologic findings, it will be shown how easy it is to resolve seemingly difficult problems. The enormous scope for colposcopic research will also be demonstrated. The fact that cervical lesions

arise not only in histologically but also colposcopically recognizable and assessable fields with constant distributions leads us to discuss topics that are ignored or poorly discussed in the present colposcopic literature. It is hoped that in addition to its instructive value, this book will provide the stimulus for further study.

The future prospects for colposcopy have become clear during the last few years. Originally it was intended to devote a chapter to “functional colposcopy” to be written by Otto Baader. This undertaking was interrupted by the untimely death of this eminent colposcopist. He left, however, many photographs that he partly took with his unique equipment during a study leave at our clinic.

This book could not have been written without the assistance of my colleagues, all of whom I thank warmly. First of these is Dr. Hubert Schreithofer. He undertook the task of documenting colpophotographically every lesion on the cervix prior to conization, as well as a number of benign lesions. Most of the colpophotographs reproduced here have come from this collection. The fascinating job of correlating colposcopic and histologic findings in conization specimens was given to Dr. Wolf Dieter Schneeweiss. His schematic representation of the complex colposcopic and histologic findings is entirely original (Chapter 15). In the selection of the microphotographs, I had the valuable assistance of University Dozent Dr. Jürgen Hellmuth Pickel. And not the least, I would like to extend my special gratitude to the translator, Dr. Andrew Östör, who undertook this task with great expertise. He was confronted not only by the challenge of translating the German text into the best possible English, but also with the production of a text with scientific appeal to the English-speaking reader. It is thus more proper to refer to him as a collaborator, rather than merely a translator. Dr. Östör was also the first critical reader of the text. His observations and advice have also been incorporated into the German version. This collaboration between author and translator can only be regarded as unique.

Last but not least, my thanks go to all the staff of Georg Thieme Verlag, who are responsible for the realization of this book. They have troubled themselves to produce the best possible result.

*Erich Burghardt
Graz, Austria
January 1984*

Preface by the Translator to the First Edition

I entered the field of gynecologic pathology in 1973 when the English version of Burghardt's classic monograph "Early Histological Diagnosis of Cervical Cancer" (Thieme, Stuttgart and Saunders, Philadelphia 1973) was published. I first met Erich Burghardt in 1977 in Graz during a study tour and I spent several months in his department in 1979–1980. Our collaboration produced a recent article (Burghardt, E., A. G. Östör: Site and origin of squamous cervical cancer: a histomorphologic study, *Obstet. Gynec.*).

The idea of translating this book arose in October 1982 when Professor Burghardt was a guest lecturer in Sydney. It may be asked why, not being a professional translator, I undertook this arduous task. I believe this book makes a fundamental contribution to the practice of colposcopy and to its histopathologic basis. Colposcopy, introduced by Hinselmann some 50 years ago, has been largely ignored by English-speaking medical communities until recently. However, their new concepts have resulted in some unwarranted and unwelcome trends in the practice of colposcopy. This book will restore the balance.

It will be shown that the role of colposcopy is not to predict the histologic diagnosis, but to delineate the extent of the lesion on the cervix and to select the best area for biopsy. The colposcope cannot replace the microscope for two major reasons. First, invasion, or at least microinvasion, cannot always be excluded by cytology and colposcopy. And second, the same colposcopic picture may be produced by different histologic changes, each of which may have different biologic significance. This fact, however, will be appreciated only if one performs colposcopy in the Burghardt way *routinely* on *all* patients. Through such a routine, it soon becomes clear that the well-known patterns of punctation, mosaic, and keratosis are frequently expressions of a completely benign but specific epithelial change, characterized microscopically by hyperkeratosis, parakeratosis, acanthosis, and elongated stromal papillae, alone or in combination which in German is designated "abnormes Epithel." Because the strictly translated term "abnormal epithelium" does not distinguish between the benign and the premalignant, no equivalent term has found its way into the English colposcopic and pathologic literature, which dismiss it merely as "metaplastic." Furthermore, English-speaking colposcopists do not recognize the significance of this type of epithelium because selection of patients ensures that there is no opportunity to study colposcopically the cervixes of women with normal smears, in whom such epithelium is frequent.

Neither the term "abnormally differentiating epithelium" suggested in the aforementioned monograph (Burghardt 1973) nor the appellation "abnormally maturing epithelium" used in our article (Burghardt and Östör 1983) overcome the problem associated with the word "abnormal." The designation "acanthotic epithelium" employed in this book was proposed by Professor Richard Kempson of Stanford University, California, during an animated conversation between him, the author, and the translator. This

term is again not ideal, as acanthotic epithelium, while always acanthotic, frequently also shows parakeratosis or keratinization. However, it avoids premalignant connotation and is established in dermatology.

Acanthotic epithelium provides the key to the understanding of the discrepancy between colposcopic and histologic diagnosis, and obviates the hypothesis of premalignant colposcopic changes predating those of histology (Stafl, A., R.F. Mattingly: Angiogenesis of cervical neoplasia. *Obstet. Gynec.*).

The importance of conization is also stressed. This procedure has attracted notoriety during the last two decades because of indiscriminate use and alleged complications. In English-speaking countries it has been largely superseded by so-called conservative, superficial ablative methods. It will be seen, however, that if carried out for the correct indications and by competent physicians, the complication rate is acceptable. Furthermore, only a cone biopsy (properly processed and examined) provides full assessment of all the histopathologic changes in the cervix. All other therapeutic measures destroy the tissues. The drawback of target biopsies as opposed to cone biopsy is that "tis but a part we see, and not a whole" (Alexander Pope).

This book is the culmination of a lifetime devoted to the study of preinvasive and early invasive carcinoma of the cervix. Professor Burghardt has succeeded in bridging the ever-increasing gap between the laboratory and the bedside, having had rigorous training in all the disciplines required for this purpose: cytology, surgical pathology, colposcopy, and gynecology. It is little appreciated that it was he who first attributed diagnostic importance to aceto-white epithelium (Burghardt, E.: Über die atypische Umwandlungszone. *Geburtsh. u. Frauenheilk.*).

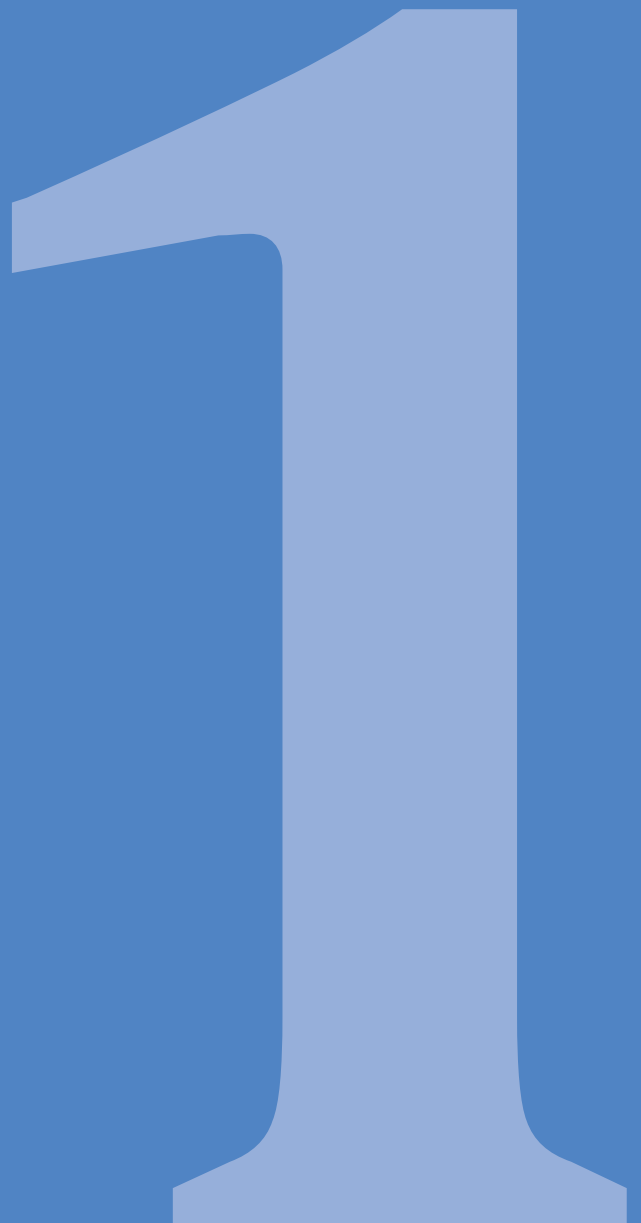
I am indebted to Dr. Ruth Davoren, cytopathologist at the Royal Women's Hospital, Melbourne, and Dr. Vernon Hollyock, the doyen of colposcopists in this city, both of whom have read the translation and made numerous valuable suggestions. My mother, Mrs. Magdalena Östör, has helped with the German language, and to her I am grateful. The final responsibility of course is mine, and I hope I have avoided the pitfalls epitomized by the French savant who compared translations with women: "Lorsqu'elles sont belles, elles ne sont pas fideles." My thanks, also, to Mrs. Kathleen Cassidy, whose expertise on the word processor made my task so much easier. Finally, I would like to express my gratitude to my wife Elizabeth and children Andrew, Jr., and Charlotte, who have kept their patience while I have often lost mine during the work's long gestation.

Andrew G. Östör
Melbourne, Australia

January 1984

Chapter 1

History of Colposcopy



1 History of Colposcopy

During much of the 20th century, cervical cancer was a scourge. In large parts of the world this remains the case, the disease often striking women younger than 40. In 1908, Friedrich Schauta in Vienna ended his monograph on radical vaginal hysterectomy for cervical cancer on the note that “the early detection of uterine cancer is the greatest challenge facing future generations of academic teachers and practicing physicians.”¹ In the same year, Howard Kelly in Baltimore wrote that “the only avenue open with certainty to progress today lies in the direction of discovering our cases of cancer at an earlier stage in the disease.”² Physicians battling this disease appreciated the importance of early detection, but did not know how to get there.

In 1924, a German gynecologist working on a chapter on uterine cancer for Veit and Stoeckel's *Handbook of Gynecology*³ was struck by the inadequacy of palpation and unaided visual examination for the early diagnosis of cervical cancer. Hans Hinselmann (1884-1959) thought this could be improved with magnification, a strong light source, and binocular vision. He built and described the first colposcope in 1925⁴ and coined the term “colposcopy.”⁵ At a time when 4-cm cervical cancers were considered early, the colposcope could visualize considerably smaller lesions, even in a grossly normal cervix. Hinselmann described the acetic acid test to evaluate columnar epithelium, the normal transformation zone, and atypical changes in the transformation zone. The acetic acid test was used in conjunction with the iodine test, described by Walter Schiller (1887-1960) in 1929.^{6,7,8} Hinselmann described punctation, leukoplakia, and diverse mosaic patterns. He called these colposcopic findings matrix areas and considered them potentially malignant. Later in the 20th century, Hinselmann was associated with the crimes of the Nazi regime when it emerged that specimens obtained without consent from inmates in Auschwitz were sent to his laboratory in Hamburg.^{9,10} We, the authors of this book, feel that Hinselmann's work in the development of colposcopy before the war needs to be acknowledged, but we have not cited later publications.

Colposcopy initially failed to gain wide recognition. Early instruments were cumbersome. Also, colposcopy consisting only of magnification, without application of acetic acid or iodine, was unsatisfactory. In addition, colposcopists repeatedly attempted to establish pseudohistologic nomenclatures for colposcopic findings, failing to appreciate that histologic nomenclature requires microscopic findings. This, at times, resulted in more confusion than clarity.⁷

Colposcopy was used first in Germany, Switzerland, and Austria (Anderes 1936, Wespi 1938, Mestwerdt 1939, Treite 1942) and South America.^{11, 12,13} In the early 1930s, Alfredo Jakob from Buenos Aires promoted its use in Argentina and Brazil (Jürgens 1933, Jakob 1939, Rieper 1941).

In the English-speaking world colposcopy was first studied in the early 1930s (Emmert 1931, Ries 1932)¹² but spread slowly. A barrier to the spread of colposcopy was the lack of easily reproducible teaching materials such as colpophotographs, which became available in the 1950s. Colpophotography was first described by Creer and Bruner et al in 1936 and Treite in 1941; Galloway published a small atlas in 1938.^{11,12} Satisfactory colpophotographs were facilitated by the advent of zoom lenses and electronic flash. In the following years Ganse, Schmitt, and

Menken contributed many improvements in colpophotography. In France, Bret and Coupez, in Scandinavia, Koller and Kolstad were protagonists.¹² Today, videocolposcopy can easily and vividly demonstrate and document colposcopic images.

Interest in colposcopy renewed in the 1950s in Austria (Navratil, Bajardi and Burghardt in Graz^{14,15,16,17}; Antoine¹⁸ in Vienna), Germany (Ganse, Limburg,¹⁹ Mestwerdt²⁰), Switzerland (Wespi,²¹ Held²²), France (Palmer, Funck- Brentano, De Watteville, Bret, Coupez), Italy (Cattaneo, De Palo), and Spain (Martinez de la Riva).

Colposcopy started in earnest in the United States in the 1960s. For a long time colposcopy in the United States was recognized only to clarify cytologic findings and encountered firm resistance because it was considered a technique that competed with cytology. Scheffey^{23,24} and Schmitt²⁵ were the first American authors to report on the technique. Adolf Štafl, a 1968 emigrant from Czechoslovakia, won an international reputation for cervicography, a kind of colpophotography.²⁶ Others who promoted colposcopy in the United States in the 1960s were Richart,²⁷ Burke,²⁸ Townsend,²⁹ Wilbanks,³⁰ and Scott.³¹ In Australia, colposcopy was introduced in the 1960s by Coppleson, Pixley,³² and Reid.³³ In the United Kingdom, colposcopy was promoted by Jordan³⁴ from Birmingham and Singer³⁵ from Oxford. In Scandinavia, Per Kolstad was a pioneer.³⁶

The International Federation for Cervical Pathology and Colposcopy (IFCPC) was founded at a meeting in Mar del Plata, Argentina, in 1972 through the initiative of the leading colposcopist in the country, Di Paola.¹³ The first president of the IFCPC was Erich Burghardt (1921–2006) from Graz, Austria.³⁷ The IFCPC, which now includes more than 30 national societies, strove to develop and maintain an internationally valid nomenclature for colposcopy and colposcopic findings.

The discipline of cytology, epitomized by the classic monograph of Papanicolaou and Traut,³⁸ revolutionized the early diagnosis of cervical cancer and thereby quashed interest in colposcopy. Cytology rapidly gained acceptance in the Anglo-Saxon world, where it was the only method for detecting early cervical cancer, as well as in Europe. Colposcopy was expected to be entirely replaced by cytology, which was simpler and more practical. That this did not happen is due to studies showing that the techniques should be used to complement one another. The names of Mestwerdt,²⁰ Limburg,¹⁹ Wespi,²¹ Navratil,^{14,15,16,17} and Held²² come to mind. These men championed colposcopy as a method that allowed direct observation of the site of developing cancer, something that cytology alone cannot do. Experience showed that high-quality cytology is the more accurate of the two methods. This is because about 15% of carcinomas develop exclusively in the endocervical canal, out of reach of the colposcope. Detailed studies, especially those from Graz between 1954 and 1960, showed that the best results were achieved by combining the two methods.^{14,15,16,17}

Today, colposcopy is used primarily to evaluate the diverse changes elicited by human papillomavirus (HPV) infection. Many of these changes, with the exception of simple condylomas, correspond to what used to be known as matrix areas.^{4,7}

Colposcopy succeeded because it closed a diagnostic loophole. Cytology detected an abnormality but not its location. Colposcopy can direct a biopsy to a suspicious area and reduce the

number of conizations. Today, in the era of HPV and molecular diagnostics, colposcopy continues to play a central role in the evaluation of women with lesions of the lower genital tract and in the worldwide fight against cervical cancer.

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Chapter 2

Role of Colposcopy

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2 Role of Colposcopy

Colposcopy is a diagnostic procedure to visualize the epithelia of the lower genital tract with magnification and adequate illumination. Application of acetic acid and Lugol's iodine (Schiller test) are useful parts of the examination. The aim of colposcopy is to identify and plan the treatment of premalignant (intraepithelial) diseases of the cervix, vagina, vulva, and perianal region. Worldwide, colposcopy is performed in different settings and for different indications. Training programs were introduced to produce competent colposcopists.¹ Competency in colposcopy avoids overtreatment and promises better patient outcomes.² Colposcopy can be applied in a variety of contexts.

2.1 Routine Colposcopy

We believe colposcopic inspection of the cervix should be an integral part of the gynecologic examination. Lesions are better seen when magnified and optimally illuminated. This is true for inflammatory lesions, condylomas, and polyps as well as for pre-invasive and early invasive neoplastic lesions. With practice, the colposcopist can react quickly and accurately detect visible lesions. Many believe colposcopy should not be used as a screening method where the likelihood of finding cancer precursors is low,³ but it is easy to combine colposcopy with routine cytology. The diagnostic accuracy of cytology and colposcopy can then be checked by performing a biopsy of colposcopically suspect findings. We believe this practice is superior to colposcopy restricted to evaluating abnormal smears because it can detect lesions missed by cytology. In contrast to cytology, colposcopy can localize suspicious lesions. If cytology is positive but the ectocervix and the vagina are normal, an endocervical lesion can be predicted. In this way, cytology can select patients for biopsy. Also, it is possible to direct a smear for cytology under colposcopic guidance so that a colposcopic lesion can be scraped directly with an Ayre spatula, or the endocervical canal can be sampled when there are no lesions on the ectocervix. There is also no doubt that the quality of cytology can be improved by the simultaneous use of colposcopy. Lastly, routine colposcopy facilitates an appreciation of the dynamic processes that occur at the cervix in the different phases of life. It is instructive to follow up on given patient over years.

2.2 Colposcopy to Evaluate an Abnormal Pap Smear

In many countries, colposcopy is used primarily to evaluate women with an abnormal Pap smear. In this setting, the goal is to identify and localize lesions suspected on the basis of abnormal cytologic findings. In a meta-analysis, the sensitivity of colposcopy for the detection of high-grade squamous intraepithelial lesion (HSIL) was 96%, with a specificity of 48%.⁴ Colposcopy is no substitute for histologic evaluation,^{5,6,7} and a biopsy should be taken from the area of the most clinically severe abnormality of any lesion.^{8,9}

2.3 Colposcopy to Evaluate Patients Positive for HPV or Other Biomarkers

Testing for high-risk types of human papillomavirus (HPV) is more sensitive for the detection of HSIL than cytology.¹⁰ The association between infection with high-risk types of HPV and HSIL and cervical cancer is so strong that HPV testing has become an important part of the management of women with borderline cytologic abnormalities. Furthermore, the detection of HPV after treatment for HSIL is an accurate predictor of relapse, significantly more sensitive than repeated cytology (see Chapter 3).

The limitation of HPV testing is that women who test positive for high-risk (HR) HPV carry only a only small risk of underlying high-grade squamous intraepithelial lesions (H-SIL) or cancer. Dual staining for p16^{INK4a}/Ki-67 increases specificity and maintained sensitivity for the diagnosis of HSIL or adenocarcinoma in situ (AIS) compared with testing for HR-HPV.^{11,12,13,14} Most experts agree that women positive for both high-risk HPV and p16^{INK4a}/Ki-67 should be referred for colposcopy to verify or rule out a lesion.

Because there is a strong evidence base that HPV testing is advantageous in primary screening of women aged 30 years or older,¹⁰ HPV screening may come to supplant cytologic screening. If this comes to pass, we will likely see a large number of women positive for high-risk HPV referred for colposcopic evaluation of the cervix.

2.4 Colposcopy to Evaluate Abnormal Cytologic Findings during Pregnancy

Colposcopy is safe in pregnancy and is performed with the intention of ruling out invasive cancer (see Chapter 9). Cumulative data suggest that expectant treatment of pregnant women with an abnormal Pap smear (i.e., delaying treatment of preinvasive changes until after pregnancy) is safe.^{15,16,17}

2.5 Colposcopy to Evaluate Lesions before Treatment

Colposcopy is performed before treatment of presumed intraepithelial lesions to exclude overt invasive cancer and define the extent of disease. Also, colposcopy is helpful to plan the extent of conization and reduce the risk of overly aggressive excisions in young patients (see Chapter 11).

2.6 Colposcopy in Screen-and-Treat Approaches in Resource-Poor Settings

In developing countries with high rates of mortality from cervical cancer, new algorithms for cervical screening are being tested.

These algorithms include high-risk HPV testing with consecutive colposcopy of HPV-positive women and immediate treatment if a lesion is detected.¹⁸

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