MASTER CLASS

Cystoscopy

BY CHARLES E. MILLER, M.D.

As a physician on the teaching faculty of two different residency programs in metropolitan Chicago—and as one whose surgical practice is limited to minimally invasive techniques—I see residents rotating through my service routinely performing cystoscopy in conjunction with total laparoscopic hysterectomy, resection of deep endometriosis over the pelvic sidewall or bladder, placement of a sling for the treatment of stress urinary incontinence, or evaluation of the bladder for interstitial cystitis.

Unfortunately, less than a generation ago, most trainees in our field had virtually no exposure to cystoscopy. Generally, as in my own case, gynecologists interested in gaining cystoscopy skills had to be mentored by a friendly urologist.

With this in mind, I have enlisted Dr. G. Willy Davila to present cystoscopy for this Master Class in gynecologic surgery.

Dr. Davila not only chairs the department of gynecology at the Cleveland Clinic in Weston, Fla., he also heads the clinic's section of urogynecology and reconstructive pelvic surgery.

Dr. Davila serves on the editorial boards of the Journal of Female Urinary Incontinence, Revista Latinoamericana de Uroginecologia y Disfunciones Pelvianas, and the International Urogynecology Journal. He is a prolific writer and has edited three books on the specialty subject matter of urogynecology. ■

DR. MILLER, a reproductive endocrinologist in private practice in Schaumburg, Ill., and Naperville, Ill., is the medical editor of this column.

A Gynecologist's Procedure

BY G. WILLY DAVILA, M.D.

Cystoscopy is a procedure that increasingly is part of the gynecologist's armamentarium, both in the office and in the operating room.

Urology has long claimed the procedure as one that belongs within its realm of care, but for hundreds of years, gynecologic surgeons have used the cystoscope to examine the bladder. In doing so, they have not only evaluated fistulas and other occurrences, but have also authored many of the medical literature's notable papers on cystoscopy.

Gynecologists have also used the instrumentation to examine the urethra as well as the bladder. Dr. J.R. Robertson, an ob.gyn., is in fact the father of the urethroscope, which consists of an external sheath and a 0-degree lens.

In recent years, gynecologists have become more involved in evaluating problems such as bladder and pelvic pain, including interstitial cystitis, as well as recurrent urinary tract infection and overactive bladder symptoms.

Moreover, they have been performing increasing numbers of pelvic reconstruction procedures—and they have increasingly turned to cystoscopy, both to aid them in office diagnosis and to ensure surgical safety.

The evaluation of hematuria is still mainly within the realm of urologists.

Gynecologists' use of cystoscopy has become less controversial over the past decade as the lines between urology and gynecology have blurred, with gynecologists addressing more traditionally urologic issues and performing more procedures that were previously considered urologic, and vice versa.

Many gynecologists are using hysteroscopy to evaluate fibroids, abnormal uterine bleeding, and other symptoms, and for them, learning cystoscopy is an especially natural fit.

Even without the hysteroscopy backdrop, embracing cystoscopy with proper training is a natural and logical evolution for the specialty. In fact, an American College of Obstetricians and Gynecologists' Committee Opinion, issued in July, stated that cystoscopy is an important diagnostic and therapeutic tool, and that practicing gynecologists, especially gynecologic surgeons, should become comfortable with the routine performance of the procedure.

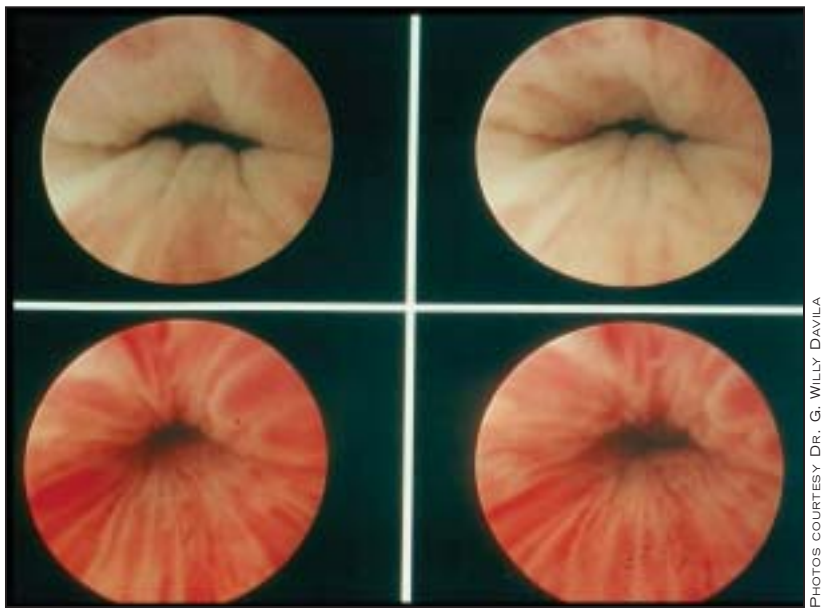
Office Cystoscopy

Cystoscopy is but one of several diagnostic tools and methods available for evaluating a number of indications, but it is proving to be a useful one. It can readily be performed in the office without the need for sedation.

The equipment needed to perform office cystoscopy includes a good light source; an endoscopic video system; a suitable hookup for a sterile water bag and related tubing; a cystoscope—preferably a narrow-angle scope (0-12.5 degrees)—to examine the urethra; and a wider-angle scope (70 degrees) to examine the bladder itself.

The urethra should be visualized first, with attention given to its anatomy, tone, and vasculature. It will look pink and spongy in a patient who is well estrogenized but pale and flat in someone who is atrophic. In a patient who has had a previous sling, the urethra should be evaluated for evidence of erosion.

Openings in the urethral wall that suggest diverticula, evidence of infection, and any other abnormalities can be identified. In women with stress incontinence, the severity of sphincteric deficiency can be evaluated by assessing urethral tone; someone with intrinsic sphincteric deficiency will have a patulous urethra and bladder neck.



PHOTOS COURTESY DR. G. WILLY DAVILA

Urethral changes reflecting different levels of estrogenation: Atrophic looks pale and flat (top), normal looks pink and spongy (bottom).

We can also then evaluate mobility of the bladder neck—an area at which fronds, polyps, and cysts are normal variants—and the appearance of the trigone, or the posterior wall of the bladder right above the bladder neck.

Cystoscopy enables us to visualize various degrees of inflammation and to detect chronic trigonitis, an inflammatory condition that can present in women who have symptoms of recurrent urinary tract infection but negative urine cultures. Confirmation of the condition can usually be achieved with vaginal palpation of the trigone.

In visualizing the ureters, which is the next step in the office evaluation, our goal is to thoroughly evaluate the anatomy of the lower urinary tract. We can then examine the rest of the bladder, looking for evidence of obvious abnormalities like stones, tumors, diverticula, and inflammation. A 70-degree scope allows visualization of the entire bladder wall, including the lateral walls where a sling/suture erosion could occur.

Bladder trabeculations are in a patient with overactive bladder.

We can also look for trabeculations, which are thick ridges observed in the middle of the bladder wall. Such patterns are sometimes a result of normal aging but they are also often found in patients with detrusor overactivity. Diverticula of the bladder can also be visualized; such abnormalities can be responsible for urinary retention.

Bladder tumors can take on various appearances, from flat white areas to cauliflowerlike papillary lesions. Although some cancers are obvious, other low-grade cancers can be extremely subtle in appearance. Persistent hematuria, especially in a smoker, should prompt us to perform a careful cystoscopy to look for tumors. If there is any question of malignancy, a biopsy can be performed in the office or upon referral to a urologist.

In women with bladder pain, we should look out for inflammatory changes, including glomerulations, which can suggest interstitial cystitis.

We also have the option of performing cystoscopy under anesthesia for patients with bladder pain. This process enables us to hydrodistend the bladder—the bladder is filled with fluid to capacity, emptied, and refilled—for an examination both of bladder capacity and of abnormalities like bleeding from glomerulations, while eliminating the pain component. A bladder that holds less than 400 mL of fluid under anesthesia is a bladder that is chronically scarred.

Bladder biopsies can be performed at the time of hydrodistention. Unfortunately, there is no consensus on indications for biopsy or on criteria for diagnosing interstitial cystitis (indeed, much about interstitial cystitis is controversial), but I believe that the scope can be an important diagnostic tool.

There also often is a therapeutic benefit to performing a cystoscopy and hydrodistention under anesthesia: Many patients remain relatively free of pain for 6 months or longer after the procedure. The urethral pain and dysuria that sometimes occur with cystoscopy can be treated with a preprocedure intraurethral injection of lidocaine jelly or oral phenazopyridine (Pyridium). Prophylactic oral antibiotics should be given routinely either right before or right after the procedure.

Intraoperative Cystoscopy

With more advanced incontinence and prolapse surgeries being performed by both urologists and gynecol-

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ogists, it has become ever more important to use intraoperative cystoscopy to ensure that the bladder and ureters remain undamaged and unobstructed. In fact, we have reached a point where cystoscopy should be performed routinely for most advanced pelvic reconstructive procedures, whether the procedures are done vaginally or abdominally.

It is absolutely imperative that cystoscopy be performed with every retropubic sling that uses the tension-free vaginal tape (TVT) procedure.

With transobturator tape (TOT), its necessity is more debatable because needles don't pass as close to the bladder. Surgeons who have comfortably and successfully performed a significant number of TOT procedures can probably forego cystoscopy.

There is one exception, however: cases in which TOT is performed before the prolapse is repaired. In this case, cystoscopy remains imperative.

Intraoperative cystoscopy has a fringe benefit as well, in that it sometimes leads to the identification of pathology—bladder stones, for instance—that went undiagnosed during the preoperative work-up.

Cystoscopy can also be used to guide the placement of suprapubic catheters intraoperatively, although its most significant purpose is to document ureteral patency. When examining for patency, most surgeons inject indigo carmine intravenously and examine the bladder approximately 10 minutes later to document flow of the dye through both ureteral openings.

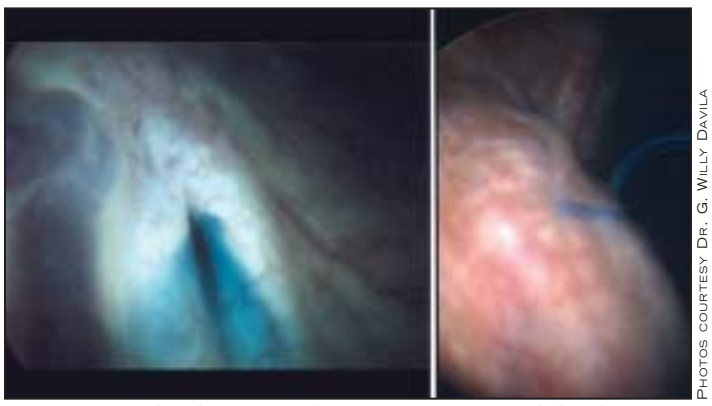
Tension-free vaginal tape mesh is shown in the urethra.

Instruments and Training

A urethroscope with a 0-degree lens allows appropriate examination of the urethra; however, a 70-degree lens is preferable for examination of the bladder because it enables visualization of the entire circumference of the bladder in more detail.

Some surgeons are using flexible cystoscopes—the optics of flexible cystoscopy have improved significantly in recent years—but the 70-degree rigid scope is sufficient in the vast majority of procedures.

Gynecologists who perform trans- or periurethral bulking agent injections for intrinsic sphincteric deficiency must be comfortable with using a 0-degree scope in the office. In this process, which typically is done under cystoscopic guidance, a needle is placed either through the cystoscope or lateral to the urethra, and the agent—collagen (Contigen), silicone (Macroplastique), carbon beads (Durasphere), or another agent—is injected to add bulk around the urethral lumen and to increase urethral resistance.



PHOTOS COURTESY DR. G. WILLY DAVILA

Ureteral opening is shown via cystoscopy, after injection of indigo carmine dye to document ureteral integrity.

For many gynecologists, cystoscopy is a natural progression from hysteroscopy. The two procedures are very similar when used for diagnostic purposes. Others are starting to perform cystoscopy even without the background in hysteroscopy, however.

In any case, the main issue we face is the need for training. We must learn how to use the instrumentation and advance the scope safely, without causing bladder trauma or perforation; how to approach various indications; and how to judge abnormal and normal aspects of the images obtained.

Although there are no courses including certification at this time, ACOG and others do offer various training courses designed to allow ob.gyns. to develop an expertise in cystoscopy. ■

Trastuzumab May Aid in Some HER2-Negative Breast Cancers

BY JANE SALODOF MACNEIL
Senior Editor

CHICAGO — Provocative findings from two studies presented at the annual meeting of the American Society of Clinical Oncology suggest that some patients with HER2-negative breast cancer may benefit from trastuzumab.

A retrospective analysis of the phase III Cancer and Leukemia Group B (CALGB) 9840 trial revealed that human epidermal growth factor 2 (HER2)–negative metastatic breast cancer patients with multiple copies of the chromosome carrying HER2 had significantly better response rates (63% vs. 26%) when they were treated with trastuzumab (Herceptin) in addition to paclitaxel.

In the adjuvant setting, another retrospective analysis showed that a small group of HER2-negative patients in the phase III National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial had significantly better disease-free survival with a relative risk of 0.40 when given trastuzumab after completing treatment for early breast cancer.

Both studies drew considerable attention, with investigators and discussants discouraging attendees from using findings in the clinical setting before they can be verified.

"We emphasize that additional study is needed. At the moment we don't feel that these data should be used clinically," Dr. Peter A. Kaufman concluded in his presentation of the CALGB data.

He stressed that only a small number of patients were analyzed and noted that trastuzumab did not improve progression-free survival or overall survival for the HER2-negative patients with polysomy of chromosome 17.

Dr. Soonmyung Paik of the NSABP called for a randomized clinical trial to test adjuvant trastuzumab in HER2-negative women.

A favorable outcome might lead to expansion of trastuzumab's indication from 20% to about 60% of breast cancer patients, he said.

"The major question raised by this paper is, what now?" Dr. James H. Doroshow said, advising that the NSABP study needs to be confirmed before new standards for HER2 positivity can be developed.

"It is critical that all appropriate adjuvant breast cancer sets be reevaluated, so that a new consensus can be established for HER2 testing," said Dr. Doroshow, director of the National Cancer Institute's division of cancer treatment and diagnosis.

After a lengthy audience discussion in which one physician demanded a reason not to expand use of trastuzumab, Dr. Vered Stearns advocated further investigation of HER2 copy number in available data sets from large clinical trials in the metastatic and adjuvant settings.

"Until additional information is available, HER2 copy number and proteomics are not ready for prime time," said Dr. Stearns of the cancer center at Johns Hopkins University, Baltimore.

Investigators were limited to available tissue blocks in the two retrospective studies of completed trials. They also grappled with disparities between local and central laboratories testing for HER2 positivity, and with standards for making the determination by immunohistochemistry (IHC) and/or fluorescent in situ hybridization (FISH).

The original report from the CALGB 9840 trial indicated that weekly paclitaxel was superior to paclitaxel taken every 3 weeks in metastatic breast cancer. Although more HER2-negative women responded when trastuzumab was added to paclitaxel, the difference was not significant.

For the new report (CALGB 150002), a laboratory correlative science study associated with CALGB 9840, Dr. Kaufman and his associates found that 303 tissue blocks were available from the original 585 patients.

These included samples from 129 patients whom local pathologists and/or central testing had classified as HER2-negative at the time that the data were collected.

'This is the bottom line. We couldn't find any subset that didn't benefit from trastuzumab,' although admittedly the subsets were small.

Within this group, the new investigation determined that 25 patients (19%) had polysomy (defined as 2.2 copies or more per cell) of chromosome 17.

Because the HER2 gene is located on chromosome 17, polysomy is typically associated with increased copies of the HER2 gene as well, according to Dr. Kaufman of the cancer center at the Dartmouth-Hitchcock Medical Center, Lebanon, N.H.

Retesting all the available samples, the investigators classified 192 patients as FISH-negative and identified 38 patients with extra copies of the chromosome. This group included the original 25 HER2-negative patients plus 7 patients who had been classified previously as HER2-positive and 6 whose original HER2 status was unknown.

New central IHC testing of 37 of the 38 cases determined that only 3 (8%) were HER2-positive based on an IHC count of 3+. The remaining 34 (92%) were HER2-negative with IHC counts of 0-2+.

Although trastuzumab significantly increased response in the 38 women, Dr. Kaufman reported that it added no benefit for 103 women who were HER2-negative and did not have polysomy of chromosome 17. An identical proportion (36%) responded to paclitaxel with and without trastuzumab.

Reporting on the reevaluation of the NSABP trial, Dr. Paik noted that the protocol was changed during the trial to require that IHC testing for HER2 be done by qualified laboratories. He said the proportion of patients classified as HER2-negative by IHC and FISH fell from 16.4% before the amendment to 6.8% afterward. Of the trial population, 9.5% (171/1,795) was negative by both measures.

"This is the bottom line. We couldn't find any subset that didn't benefit from trastuzumab," he said, acknowledging the subsets were small.

In patients deemed negative by both IHC and FISH, the relative risk of recurrence was 0.34.

Noting that the parameters of HER2 positivity originated in the metastatic setting, Dr. Paik and his associates concluded that the "current definition of HER2 overexpression/gene amplification based on data from advanced disease may need to be modified for the adjuvant setting." ■