Introduction

Between 80 and 95% of patients with endometrial cancer present vaginal bleeding as the first symptom (1). For many years, dilatation and curettage (D&C) has been the method of choice for diagnosing endometrial pathology in women with abnormal uterine bleeding. Based on the classic study conducted by Word et al., it is known that D&C fails to diagnose one in every ten lesions of the endometrial cavity (2). In 60% of the D&C procedures, less than half of the uterine cavity is curetted, even by experienced surgeons, which can make the diagnosis difficult, especially in cases of focal uterine lesions. Several publications have reported that the accuracy of D&C is limited, citing false negative rates as high as 10%. Now there is a trend toward minimally invasive investigations using outpatient endometrial biopsy, ultrasound scan, and hysteroscopy (3).

Within this context, diagnostic hysteroscopy has been increasingly used in gynecologic practice.

History

A comprehensive historical review by Lindemann in 1973 describes the primitive instruments used by Bozzoni (1773-1809) to examine the interior of the vagina, and by Pantaleoni (1869) who used an early cystoscope to examine the interior of the uterus (4).

At the end of the 19th century and in the first quarter of the 20th century there was slow progress in technology, and only a few papers were published. These were mainly concerned with developing the optical systems of the telescopes, methods for washing the uterine cavity free of blood, and techniques for providing adequate illumination.

Technical Aspects

Hysteroscopy is the direct visualization of the uterine cavity using a fibreoptic endoscope and a cold light source. A hysteroscope consists of an outer sheath which contains a valve through which the fluid or gas used to distend the uterine cavity is circulated. Operating hysteroscopes have side channels for the introduction of probes, scissors, diathermy instruments, and biopsy forceps. In order to obtain a clear view, the uterine cavity must be distended by either gas or fluid directed into the uterus through a side channel in the hysteroscope sheath at a pressure of 50–150 mmHg to allow complete visualization of the fundus and ostial areas. Although a great deal of progress has been made in diagnostic hysteroscopy, doubts remain about the preferential medium for distension of the endometrial cavity. It seems that there is no ‘gold standard’ distension medium.

The gas universally used for diagnostic hysteroscopy is carbon dioxide. Distension of the uterine cavity with CO₂ has disadvantages such as bleeding of the endometrial walls after simple contact with the hysteroscope, creation of gas bubbles and the application of the cervical seal to prevent escape of gas from the cervix (5).

Liquid media used for this purpose include high-viscosity fluids such as 32% dextran 70 or low-viscosity fluids such as 5% dextrose, Ringer’s or normal saline solution. A good view is provided by 20-30 ml of 32% dextran (Hyskon). Hyskon is an innocuous viscous fluid of high molecular weight with good optical qualities. The simplest and cheapest methods of uterine distension is to insufflate a solution of 5% dextrose in water or normal saline (NaCl).

Normal saline presents fewer problems concerning the vagal reaction, in comparison with CO₂, resulting in less discomfort for the women under examination (6).

Hamou has developed the microhysteroscope, which offers a simple outpatient procedure with the ability to observe the uterine cavity and endocervical canal at different magnifications. This ranges from a panoramic view to high magnification of the endometrium by direct contact of the lens. The telescope has a diameter of 3.7 mm with a 5 mm sheath. This means that dilatation of the cervix is either not required or required to a minor degree, and is thus more suitable for an outpatient procedure. The procedure is usually performed under general or local anesthesia to avoid pain and a vagal reaction. However, ambulatory procedures without anesthesia have become common given the obvious advantages to the patients and the cost effectiveness. For scopes with diameters less than 5 mm, it is possible to perform a diagnostic hysteroscopy without premedication or anesthesia (7). Depending on the availability of each type of procedure, biopsies can be performed using either image guidance techniques, such as hysteroscopy with direct viewing of the uterine cavity, or various random sample collection methods, such as Pipelle endometrial sampling, Vabra catheter aspiration, Novak curettage or traditional uterine curettage.
Complications

The main complications, other than failure to observe the uterine cavity because of bleeding or air bubbles, are perforation of the uterus, infection, and cervical laceration.

In the study of Clark et al., eight cases of potentially serious complications (1 pelvic infection, 4 uterine perforations, 1 bladder perforation, 1 precipitation of a hypocalcemic crisis, and 1 anginal episode) were reported out of 25,409 successful procedures (8).

There are two disadvantages in diagnosing carcinoma and staging endometrial carcinoma with hysteroscope:

- First, the depth of invasion into the myometrium cannot be assessed;
- Second, there is the possibility of spread of malignant cells into the peritoneum by the fluid used to distend the uterine cavity.

The possible intraperitoneal spread of endometrial tissue through tubal reflux when using a distention medium during hysteroscopy has been a major concern.

There is evidence from observational studies that distension of the uterine cavity could be associated with transtubal leakage of endometrial cells and tissue reflux into the peritoneal cavity, thereby changing the course and prognosis of the malignant disease (9-11).

These results are controversial in view of different pressure and method of distention. Abnormal endometrial cells reflux into the peritoneal cavity after diagnostic hysteroscopy which has been reported in about 16% of cases might increase the risk of recurrence (12).

The most important factor associated with transtubal spreading of endometrial cells during hysteroscopy procedure appears to be the intrauterine pressure used. Bettocchi et al. have suggested that intrauterine pressure of 150 mmHg has a higher risk for cell dissemination (13).

Baker and Adamson have demonstrated that no spread of endometrial cell occurs at intrauterine pressure equal or below 70 mmHg (14).

A temporary tubal clamp using bulldog clamps to block the reflux of endometrial tissue is possible to perform during hysteroscopy through laparoscope.

Operative Hysteroscopy Intravascular Absorption (OHIA)

Operative hysteroscopy has the potential for volume and electrolyte disturbances. The absorbed volume of fluids employed for uterine distention depends on the extent of intrauterine transection of vascular beds, the intrauterine distention pressures, the volume of media used, and the duration of the procedure. The biochemical composition of the instilled fluids determines the physiologic alterations. The earliest signs of this syndrome are confusion and bradycardia with systolic and diastolic hypertension. It may be advantageous to use regional anesthesia because awake patients are likely to display precursor symptoms that portend impending brain or cardiac dysfunction and injury. For patients subjected to general anesthesia, delayed diagnosis of the syndrome of operative hysteroscopy intravascular absorption (OHIA) can occur. An instillate solution that contains ethanol 1% as a biologic marker can be used to estimate fluid absorption by measuring the end-tidal ethanol content.

Although treatment regimens for hyponatremia, hypoosmolemia, and circulatory overload are well established, anesthetic management should emphasize the prevention of the OHIA syndrome and its attendant morbidity and possible mortality (15,16).

Accuracy of Hysteroscopy in the Diagnosis of Endometrial Cancer

The uterine cavity can be thoroughly visualized and an endometrial biopsy specimen can be taken under hysteroscopic view in the patients with recurrent uterine bleeding due to a small carcinoma which has escaped diagnosis by curettage. During hysteroscopy biopsy forceps are used for focal endometrial lesions, whereas curettes are preferred for diffuse lesions.

An endometrial carcinoma can be detected in 7%–11% of postmenopausal patients and 2%-3% of premenopausal patients submitted to hysteroscopy (8,17,18).

There is a continuing debate about the value of hysteroscopy in diagnosis of serious endometrial diseases, such as cancer and hyperplasia (Figure 1,2).

This is because individual studies on histopathologic validation of endoscopic visual interpretation are small, leading to imprecise and heterogeneous estimates of accuracy.

The accuracy of hysteroscopic diagnosis may vary according to menopausal status and clinical setting (19,20).

A positive hysteroscopy result increases the probability of cancer to 71.8%, whereas a negative hysteroscopy result reduces the probability of cancer to 0.6% (8). In the same study the failure rate was found for an ambulatory procedure 4.2% compared with 3.4% for an inpatient procedure.
Failed hysteroscopies in the outpatient setting resulted from technical problems (cervical stenosis, anatomic factors, structural abnormalities) or patient factors (pain, intolerance) more often than in inpatient setting (79% v 9%). By contrast, inadequate visualization obscured by bleeding or debris was more common in the inpatient setting as a reason for failure (3% v 0.7%).

Endometrial evaluation among postmenopausal women is a topic of discussion in the literature (21). The question is at what time, based on ultrasound measurements of endometrial thickness and the patient’s history of vaginal bleeding, endometrial sample collection is indicated. Various authors have reported mean thicknesses of carcinomas ranging from 18.2 mm to 23.05 mm (22,23).

There is a trend towards investigating intracavitary uterine lesions only in patients with postmenopausal bleeding when the endometrial thickness, as measured by ultrasound, is > 4 mm. Other authors have recommended systematic collection of biopsies from symptomatic patients regardless of endometrial thickness, because of reports of cancer in patients presenting ultrasound-measured endometrial thickness ≤ 5 mm (24,25).

In the cases when the hysteroscopic appearance is normal, histological sample collection is not essential, but Deckardt et al. found 10 cases of undetected endometrial carcinoma among 1,286 patients who underwent hysteroscopy without biopsy, and in these cases the diagnosis was made by subsequent dilatation and curettage (26). This study analyzed perimenopausal and postmenopausal patients together. Since functional endometrium is the pattern found around the time of the menopause, endometrial lesions possibly more often remain unrecognized than in the atrophic postmenopausal endometrium.

Identifying endometrial adenocarcinoma is minimal, less than in 0.5% in asymptomatic patients presenting thin endometrium on ultrasound examination. To improve medical care among postmenopausal women, hysteroscopy should be used to obtain endometrial samples only from symptomatic patients (27). Hysteroscopy is highly accurate and clinically useful in diagnosing endometrial cancer in women with abnormal uterine bleeding. Its high accuracy relates to diagnosing cancer rather than excluding it (8).

**Hysteroscopy in Sentinel Node Biopsy in Endometrial Cancer Patients**

The concept of SN (sentinel node) biopsy is based on two basic principles: The existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin, and the functioning of a first lymph node as an effective filter for tumor cells. These nodes (or node) are the SNs and are predictive of the local nodal network. Therefore, in theory, the identification of SNs and their histological status can be used to determine the extent of nodal dissection required. The SN is defined as the first node in the lymphatic system that drains a tumor site. If the SN is not metastatic, then all other nodes should also be disease-free. In endometrial cancer, the sentinel node procedure is increasingly used as an alternative to systematic lymphadenectomy, with the aims of avoiding excess morbidity and improving lymph node staging, while at the same time preserving the control of regional disease.

Endometrial cancer is ideal for lymphatic mapping because the lymphatic drainage is ambiguous and complex (28).

Potential at-risk lymph node basins are found along the obturator, external iliac and aortic vessels. Identification of reliable sentinel nodes would preclude the need for complete lymphadenectomy, which is particularly valuable for morbidly obese patients in whom lymphadenectomy can often be difficult to perform.

Raspagliesi et al. (29) submitted eighteen patients with endometrial adenocarcinoma to hysteroscopic injection of technetium-99m-labeled colloids and blue-dye subendometrially around the lesion followed by lymphoscintigraphic scans. The SNs was detected by direct visualization of blue-dye marked nodes and by a radio-guided surgery (RGS). Seventeen hysteroscopic procedures were satisfactory regarding the visualization of the uterine cavity. The compliance to the procedure was acceptable in 15 cases, with no severe complication. A hysterectomy and bilateral salpingo-oophorectomy were performed in all cases, and pelvic lymphadenectomy in 14 cases. The RGS detected a total of 45 SNs with a mean of 3 SN/patient (range 2 to 4). Blue-dye uptake was observed in 6 (33%) cases. No case presented blue-dye uptake and radioactive-colloid negativity.

Feranec et al. (30) found that 47% patients had radioactive nodes only in the paraaortic area. Synchronic appearance of SLNs in the pelvic and paraaortic areas was detected in 6% cases. Overall, in 44% cases of sentinel lymph node localization in the paraaortic area the SNs were detected at the level above the inferior mesenteric artery. The sensitivity and specificity for SL metastases detection was 100%.

The main problem with the SN procedure is the false-negative rate, i.e. the number of procedures in which the SN is
negative but one or more pelvic non-SNs are positive, divided
by the number of procedures in which any pelvic lymph node
is positive. A false-negative finding understages the patient,
and may result in an incorrect decision regarding the need for
adjuvant therapy.

Administration of technetium-99m-labeled colloids and
blue-dye is carried out with four pericervical injections as
well as with hysteroscopic injection subendometrially around
the lesion followed by lymphoscintigraphic scans and direct
visualization during laparotomy or laparoscopy. If the tracers
are injected into the cervix, this way is not reflecting the
corpus uterine drainage but the cervical pathway (31).

SN detection in endometrial cancer appears to be a
promising method with the potential to reduce unnecessary
surgery radicality and to clarify staging. The utilization
of hysteroscopic application of radiocolloid respects the
anatomical consequences and natural lymphatic drainage
of the endometrium. The combination of pre-operative
lymphoscintigraphy and intra-operative detection using a
handheld gamma probe and sentinel lymph node (SN) detection
is perspective method in the management of the patients
with endometrial cancer.

The enhanced detection of ‘occult’ metastases in the
SNs may reflect the more intensive histological technique
using serial sectioning and immunohistochemistry rather
than the physiological significance of the SN (32). The same
histopathological analysis for SNs and non-SNs should be
performed. The extensive histopathological analysis
should be performed before the potential diffusion of the
SN procedure in endometrial cancer. Standardization of the
handling, sectioning and staining of the SN is necessary as
lymphatic mapping and sentinel lymphadenectomy become
integrated into the care of patients with endometrial cancer.

**Hysteroscopy in Conservative Management of Early Endometrial Adenocarcinoma**

With advances in the predictability of the prognosis of
endometrial carcinoma by using retrospective analyses of
clinical and surgical-pathological variables, conservative
treatment of early-stage adenocarcinoma in selected young
women who wish to remain fertile can be considered as
permissible alternative. Most researchers will agree that the
indication for fertility-sparing treatment is restricted to
presumed IA stage for a well differentiated endometrial
adenocarcinoma (33,34).

Nevertheless, the diagnostic accuracy of myometrial
invansion by imaging studies is limited. In detecting myometrial
invansion by magnetic resonance imaging, the rate of accuracy
varied between 68% and 82% (35). CT scan failed to identify
myometrial invasion in 39% of patients (36).

A combination of initial vigorous endometrial curettage
and aggressive progestin hormone therapy for 6 months
as a primary treatment modality would have eradicate the
existing tumour nests in the endometrial layer.

The basis of conservative treatment strategy is repeat
hysteroscopy and curettage on two occasions 3 months apart.

These procedures show if the endometrium is free of residual
tumour during the period of aggressive hormone therapy.

Contrary to the conventional method of blunt curettage
in treating endometrial lesions, panoramic visualization of the
exact location of the endometrial carcinoma in the uterine
cavity under the guidance of hysteroscopy provides a better
way to eradicate as much of the tumour foci as possible.
The surgeon is able to confirm the completion of operative
procedures in eliminating the gross residual tumour by
comparative assessment of preoperative and postoperative
hysteroscopies (37).

Hysteroscopy allows for a more precise approach in
panoramically examining the tumour nest in the endometrial
cavity, and the subsequent endometrial response to hormone
therapy.

Laparoscopy using bulldog clamps can be applied to
the isthmic portion of the Fallopian tubes as prevention of
intraperitoneal spread of endometrial tissue from retrograde
regurgitation during hysteroscopy.

The significant implications for the use of endoscopy are
(38-40):

(i) hysteroscopic panoramic visualization of the gross-
appearing endometrial adenocarcinoma, the tumour location
and extent, and the endometrial response to hormone
therapy;

(ii) bilateral tubal blockade, effectively preventing the
retrograde spread of endometrial tissue during hysteroscopy
and then avoiding the possibility of subsequent intraperitoneal
tumour implant.

Response rates and recurrence rates varied (ie, the
response rate for endometrial cancer and atypical hyperplasia
ranged from 57% to 76% and 83% to 92%, respectively, and
the recurrence rate ranged from 11% to 50%). Such variations
are probably due to the differences in drugs used, dosage,
and duration of treatment (41-44).

In the Japan multicenter phase II study (45) at 16
institutions the patients were scheduled to receive 600
mg of medroxyprogesterone acetate (MPA) with 81mg of
aspirin, orally on a daily basis for 26 weeks, followed by
cyclic estrogen-progestin therapy for 6 months. Response
was assessed histologically at 8 and 16 weeks of MPA
treatment. Thickness of the endometrium was measured by
transvaginal ultrasonography at 8 and 16 weeks. At 26 weeks
of MPA treatment, hysteroscopy and endometrial curettage
was performed for the final evaluation. Complete response
(CR) rate was found in 55% of endometrial cancer cases and
82% of atypical hyperplasia cases. The overall CR rate was
67%. Neither therapeutically death nor irreversible toxicities were
observed. During the 3-year follow-up period, 12 pregnancies
and seven normal deliveries were achieved after MPA therapy.
Fourteen recurrences were found in 30 patients (47%)
between 7 and 36 months. This multicenter prospective study
showed fertility-sparing treatment with MPA to be an effective
therapy with the least toxicities for young patients with
atypical hyperplasia and those with grading 1 endometrial cancer
at presumed IA stage. Nevertheless, endometrial cancer lesions
may recur at a considerably high frequency, and patients may develop synchronous malignancy in the ovary or peritoneum, which clearly indicates that a patient’s excessive anticipation of fertility preservation may threaten her life. Patients should be informed of the risks and limitations of this conservative treatment.

Conclusion

Diagnostic hysteroscopy is safe, with a low incidence of serious complications and a small failure rate and is extensively used. When the uterine cavity is adequately visualized, hysteroscopy is highly accurate and thereby clinically useful as well as in the diagnosis of endometrial cancer. Recent advances in instrumentation have allowed hysteroscopy to be performed in an ambulatory setting, further increasing its use. In addition to hysteroscopy, other new diagnostic modalities, namely, transvaginal ultrasonography and endometrial biopsy, have been introduced to replace traditional inpatient dilatation of the cervix and curettage of the endometrium. There remains a considerable debate regarding the best sequence and combination of these tests.

References