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REVIEW ARTICLE

The role of hysteroscopy in diagnosis and management of endometrial cancer

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Abstract Endometrial sampling for histopathology examination is essential to diagnose endometrial cancer. There are many ways to obtain the specimen including endometrial biopsy or hysteroscopy. Hysteroscopy provides an accurate evaluation of the endometrial cavity and allows directed sampling of suspected lesion. However, there have been concerns that endometrial cells could be flushed into the fallopian tubes and the peritoneal cavity. We performed a literature search using the key words "endometrial cancer," "endometrial sampling," "dilation and curettage" (D&C), "hysteroscopy," and "cancer cells dissemination" and conducted the search in the Medline, EMBASE, and the Cochrane of Database of systematic reviews. Endometrial cell dissemination could occur after hysteroscopy as well as after endometrial biopsy and D&C. Hysteroscopic distension media and intrauterine pressure play a role in endometrial cell dissemination. Hysteroscopy is an additional tool in the diagnosis of endometrial cancer. However, its use in the initial workup is still controversial. In order to minimize the small risk of cancer dissemination, hysteroscopy should be performed with an intrauterine pressure of less than 80 mmHg, and the duration of the procedure should be as short as possible.

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Endometrial cancer is the most common gynecologic malignancy. Fortunately, about 90% of women will present with abnormal uterine bleeding leading to an early diagnosis [1]. Women with this symptom especially those in perimenopausal age should undergo endometrial sampling, and it could be achieved with either endometrial biopsy, dilation and curettage (D&C), or hysteroscopy. Although, hysteroscopy provides an accurate evaluation of the endometrial cavity and allows directed sampling of suspected lesion, there have been concerns that endometrial cells could be flushed into the fallopian tubes and the peritoneal cavity. In those with endometrial cancer, the procedure might disseminate cancer cells into the peritoneal cavity [2].

The purpose of our review is to evaluate the uses and clinical indications of hysteroscopy in the investigation and the management of women with possible endometrial cancer.

Diagnosis of endometrial cancer

Endometrial sampling for histopathology examination is essential to diagnose endometrial cancer. There are many ways to obtain the specimen.

Endometrial biopsy

Endometrial biopsy (EB) is the simplest method to obtain endometrial tissue. It has high sensitivity and specificity, low complication rate, and economical. In a meta-analysis of 39 studies involving 7,914 women, the authors found

that tissue sampling with a disposable endometrial biopsy Pipelle in postmenopausal and premenopausal women is associated with detection rates of endometrial cancer of 99.6% and 91%, respectively. Using the same tool, the sensitivity to detect endometrial hyperplasia is 81%. However, this technique fails to obtain adequate tissue in 5% of cases [3]. Endometrial biopsy is not without risk of endometrial cell dissemination. Table 1 shows results of endometrial sampling with Pipelle and subsequent positive peritoneal cytology [4–6].

Most patients can be diagnosed with simple endometrial biopsy. However, focal endometrial pathology or a lesion on a polyp could be missed by endometrial biopsy. Accordingly, negative endometrial biopsy in women with persistent abnormal uterine bleeding should be further investigated.

Transvaginal ultrasound

Transvaginal ultrasound (TVUS) examination is mandatory in the investigation of a possible intrauterine pathology. An intrauterine lesion can be further delineated with the use of sonohysterography. In a meta-analysis of 35 studies including 5,892 women and using a 5-mm threshold to define abnormal endometrial thickening, 96% (95% confidence interval (CI), 94–98%) of women with endometrial cancer and 92% (95% CI, 90–93%) of those with other endometrial lesions including cancer, polyp, or atypical hyperplasia had an abnormal result. For a postmenopausal woman with vaginal bleeding, her probability of cancer is 1% following a normal TVUS result [7].

Thin endometrium in symptomatic women should still be followed by invasive diagnostic testing. Endometrial thickness measurement in symptomatic women does not exclude the need for invasive diagnostic testing, because 4% of the endometrial cancers would still be missed with a false-positive rate as high as 50% [8].

The limitation of ultrasound is that it cannot differentiate between endometrial hyperplasia and malignancy. Tissue biopsy is still needed.

Table 1 Endometrial sampling with Pipelle and subsequent positive peritoneal cytology

Authors	No. of patients	Positive peritoneal cytology	Duration of follow-up (months)	Recurrence
Gu et al. [4]	173	16 (9.2%).	16–83	NA
Ben-Arie et al. [5]	99	0	25	15.20%
Bradley et al. [6]	204	14 (6.9%)	NA	NA

Sonohysterography

Saline infusion sonohysterography (SIS) provides a detailed imaging of both the uterine wall and cavity. It is widely used to assess polyps, submucous myomas, or synechiae [9–11]. In tamoxifen-treated asymptomatic postmenopausal women with breast cancer, SIS is a useful diagnostic tool for evaluating endometrial pathologies [12, 13]. However, due to the use of solution to distend the uterine cavity, this technique is also associated with a possibility of disseminating endometrial cells into the peritoneal cavity [14].

Dilation and curettage

Office endometrial biopsy has generally replaced diagnostic D&C, but D&C is still needed for women who cannot tolerate office biopsy due to anxiety or cervical stenosis. On the other hand, it is a blind procedure, and not the entire endometrium could be sampled. In fact, D&C missed up to 60% of the endometrium [15].

D&C has been associated with dissemination of endometrial cancer into the peritoneal cavity (Table 2). Instead of the act of D&C, it is possible that the disease itself is responsible for the positive peritoneal cytology. The direct relation between positive peritoneal cytology or metastasis and D&C is unclear [4, 5, 16–20].

Hysteroscopy

Hysteroscopy plays a role in the diagnosis of patients with possible endometrial cancer in whom endometrial sampling is unsatisfactory or in those who require a dilation and curettage (D&C). Similar to endometrial biopsy and D&C, hysteroscopy is associated with dissemination of endometrial cells into the peritoneal cavity. However, the degree of dissemination is comparable to that of other diagnostic tests including D&C [5].

Table 2 Dilation and curettage (D&C) and subsequent positive peritoneal cytology

Authors	No. of patients	Positive peritoneal cytology	Duration of follow-up (months)	Recurrence
Gu et al. [4]	111	11 (9.9%).	16–83	NA
Ben-Arie et al. [5]	193	1 (0.52%)	25	4.70%
Selvaggi et al. [16]	52	9 (17%)	NA	NA
Takac et al. [17]	122	2 (1.6%)	NA	NA
Kudela et al. [18]	61	8 (13.6%)	60	NA
Wang et al. [19]	63	27 (43%)	NA	NA
Gucer et al. [20]	55	1 (1.8%)	29	Local recurrence

Unlike D&C, hysteroscopy is a more precise technique to evaluate endometrial pathology. For diagnostic purposes, office or outpatient hysteroscopy is sufficient. It is usually performed under local anesthesia. The uterus is distended using either CO_2 gas or liquid solution. The use of solution provides a clear visualization of the uterine cavity. In contrast, CO_2 gas and blood will produce bubbles that impair visualization.

Revel et al. found that hysteroscopy using 32% Dextran 70 as a distending medium is associated with the presence of endometrial cells in the peritoneal cavity. Similar to that with D&C and endometrial biopsy, it is unclear whether their presence was related to hysteroscopy [21]. In general, the prevalence of positive peritoneal cytology in women with endometrial cancer is 12% to 15% [22, 23].

In a study including 181 women with suspected endometrial cancer, 119 women underwent endometrial biopsy and 69 others underwent hysteroscopy and directed biopsy. They found the sensitivity (96%) and specificity (100%) of hysteroscopy to diagnose endometrial cancer were higher than that of endometrial biopsy [24].

Yazbec et al. conducted a meta-analysis of five studies including 756 cases. Among those with a positive peritoneal cytology, 38 women had undergone a previous hysteroscopy examination and 41 others had not (OR= 1.64; 95% CI 0.96–2.80) [25]. Their study showed that hysteroscopy examination does not increase the risk of tumor cell dissemination into the abdominal cavity.

Distension media

Several investigators believe that the type of distension media plays a role in endometrial cell dissemination [2, 4–6, 16–20, 26–35] (Tables 3 and 4). Lo et al. compared hysteroscopy with CO_2 gas and with normal saline (NS) in the investigation of endometrial cancer. Among 120 patients with endometrial cancer who had undergone a previous hysteroscopy, positive peritoneal cytology was found in eight patients (6.7%); seven were in the NS group (14%), and one was in the CO_2 group (1.4%). All eight patients with positive cytology received no additional treatment and were disease-free at 12 to 34 months of follow-up. Positive cytology was significantly more common after hysteroscopy using NS than CO_2 gas (14.0% vs. 1.4%, odds ratio (OR)= 11.2, 95% confidence interval=1.3–94.5, P=0.009) [26].

Table 3 Hysteroscopy using CO_2 gas and subsequent positive peritoneal cytology

Authors	No. of patients	Positive peritoneal cytology	Duration of follow-up (months)	Recurrence
Lo et al. [26]	70	1 (0.5%)	12–34	None
Neis et al. [27]	118	1 (0.8%)	NA	NA
Nagele et al. [28]	30	8 (26.7%)	NA	NA

Neis et al. performed hysteroscopy with CO2 gas in 154 women with endometrial cancer and found only one patient with positive endometrial cells in the peritoneal cavity. This particular patient had cancer dissemination to the fallopian tube. They followed the patient for 5 years and found that the disease remained stable [27]. Negele et al. compared hysteroscopy with CO_2 gas or NS in non-oncologic patients. They found tubal reflux of endometrial cells in 23.3% of patients (7/30) in the CO_2 group and in 26.7% (8/20) in NS group, respectively. There was no significant difference between NS group and CO_2 group [28].

Zerbe et al. evaluated 158 patients with adenocarcinoma grade 1 and myometrial invasion of less than 50%. They found a statistical difference in the frequency of positive peritoneal cytology in women who had undergone a previous hysteroscopy with NS vs. those who had not (OR=2.6, 95% CI 1.02–6.63, P=0.05) [29].

Although it appears that hysteroscopy using NS is associated with endometrial cell dissemination into the peritoneal cavity, other factors including the intrauterine pressure used to distend the uterine cavity might play a role.

Intrauterine pressure

Data from hysterosalpingographic studies demonstrated that intrauterine pressure of 100 mmHg was needed before spillage of fluid into the peritoneal cavity occurred. Baker et al. could not find spillage with intrauterine pressure of <70 mmHg [36]. Similarly with hysteroscopy, one requires a high intrauterine pressure before encountering spillage of endometrial cells into the peritoneal cavity [37–39]. In a study of 43 women with endometrial carcinoma diagnosed with the assistance of hysteroscopy using intrauterine pressure of 80 mmHg, no patient had positive peritoneal washings (95% CI 0–8.2%). The 5-year disease-specific survival rate was 91.8%, and the 5-year recurrence-free survival rate was 85.4% [33].

Solima et al. performed hysteroscopy with NS in 40 women with stage I and II endometrial cancer with an intrauterine pressure of ≤40 mmHg. After visualization of the uterine cavity, they injected a radiotracer (technetium (Tc) 99 m) into the tumor and blue dye subendometrially. Peritoneal cytology was positive in two cases [31]. In another study using hysteroscopy with CO_2 gas with intrauterine pressure of 80 mmHg, the authors did not encounter any peritoneal dissemination of endometrial cells [40].

Timing of hysteroscopy and definitive surgery

Most studies evaluating the safety of hysteroscopy in women with endometrial cancer are retrospective, and the

Table 4 Hysteroscopy using normal saline and subsequent positive peritoneal cytology

Authors	No. of patients	Positive peritoneal cytology	Intrauterine pressure (mmHg)	Duration of follow-up (months)	Recurrence
Arikan et al. [2]	24	20 (83%)	100–150	NA	NA
Gu et al. [4]	23	3 (13.0%)	NA	16–83	NA
Ben-Arie et al. [5]	100	1 (1%)	100	25	NA
Bradley et al. [6]	52	4 (7.7%)	NA	NA	NA
Selvaggi et al. [16]	39	9 (23%)	150	NA	NA
Takac et al. [17]	24	3 (12.5%)	NA	NA	
Kudela et al. [18]	134	4 (5.3%)	NA	60	NA
Lo et al. [26]	50	7 (14%)	NA	12–34	None
Nagele et al. [28]	30	7 (23%)	NA	NA	NA
Zerbe et al. [29]	64	11 (17.2%)	NA	NA	NA
Leveque et al. [30]	28	7 (37%)	NA	25	None
Solima et al. [31]	40	2 (5%)	40	NA	NA
Obermair et al. [32]	113	10 (8.8%)	NA	NA	NA
Biewenga et al. [33]	50	0 (0%)	NA	60	NA
Duan et al. [34]	121	61(51.2%)	NA	NA	NA
Cuesta et al. [35]	38	8 (21%)	NA	34[a]	None

[a] Adjuvant radiation treatment for those with positive peritoneal cytology; one patient died

time between the hysteroscopy and the definitive surgery varies. In a few studies, these two operations were performed in one setting [31, 40]. In others, there were 2–3 weeks gap between the two procedures [16, 29, 33]. It is unclear whether the presence of endometrial cells in the peritoneal cavity is related directly to the previous hysteroscopy only.

The duration of hysteroscopy may play a role as well. For example, Damiao et al. reported that when the duration of hysteroscopy was 4 min, they did not encounter any positive peritoneal cytology in 72 patients [40]. However, Gutman et al. who performed hysteroscopy in less than 3 min found two of 64 patients with positive peritoneal cytology [41]. Those studies suggest that other factors may play a role.

Clinical implications of hysteroscopy in endometrial cancer

Staging

In addition to directed tissue biopsy, hysteroscopy is useful to assess cervical involvement in endometrial cancer. Traditionally, fractional D&C is the method of choice. However, it has been shown to be inaccurate in detecting cervical invasion by endometrial cancer [42]. Cronji et al. found no difference between fractional D&C and hysteroscopy in the evaluation of cervical involvement [43]. Lo et al. found that hysteroscopy with NS as a distension medium had a higher accuracy in determining tumor spread to the cervix than that with CO_2 (96.8% vs. 88.7%, $P = 0.03$) and NPV (96.4% vs. 88.4%, $P < 0.05$) [44].

Toki et al. evaluated cervical involvement of endometrial cancer using different diagnostic procedures: cervical cytology, endocervical curettage, transvaginal ultrasonography, hysteroscopy, and magnetic resonance imaging. They found that endocervical curettage revealed the high sensitivity (91%), the highest negative predictive value (96%), and the lowest negative likelihood ratio (0.14). Hysteroscopy showed high positive likelihood ratio (8.2) and low negative likelihood ratio (0.20). Magnetic resonance imaging showed the highest positive predictive value (75%) and the highest positive likelihood ratio (12.5). They concluded that MRI was excellent for predicting stromal invasion, whereas hysteroscopy was superior for assessing mucosal involvement [45].

Resection of endometrium as a treatment for endometrial cancer

In order to preserve fertility in women who wish to conceive, hysteroscopic resection of endometrial cancer has been advocated. Traditionally, the treatment was repeated D&C followed by hormonal treatment [46–48]. Mazzon et al. performed hysteroscopic resection of stage I, grade I, endometrioid adenocarcinoma after proper evaluation of depth of invasion and hormonal status. The patient subsequently conceived and delivered. No evidence of disease recurrence was noted [49]. Other similar case reports followed [50, 51]. Whether this method is more effective than hormonal therapy only is unclear.

Conclusion

Hysteroscopy is an additional tool in the diagnosis of endometrial cancer. However, its use in the initial workup is still controversial. In order to minimize the small risk of cancer dissemination, hysteroscopy should be performed with an intrauterine pressure of less than 80 mmHg, and the duration of the procedure should be as short as possible.

Declaration of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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