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# Office hysteroscopy and endometrial/cervical cancer: an update on their potential close relationship

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**Summary.** *Aim:* To provide an insight on the applicability, efficiency and accuracy of office hysteroscopy (OH) in the diagnosis and potential treatment of endometrial (EC) and cervical cancer (CC) and their respective premalignant states. *Materials and methods:* A literature update on the efficiency of OH in EC and CC, through a search strategy specially created for PubMed. *Results:* Endometrial hyperplasia and EC can be accurately and efficiently diagnosed with OH, which can guide endometrial sampling, while the subsequent histopathological examination can provide an accurate diagnosis. The role of OH in the diagnosis of cervical intraepithelial neoplasia and CC is less well-known and remains supplementary to traditional modes. Regarding the treatment of both gynecological cancers and their premalignant states, there are no data to support the utility of the technique. *Conclusions:* Modern technological advances have led to the development of sophisticated hysteroscopes and respective techniques, OH being an advanced approach in the visualization of the female genital tract with fine imaging along with specialized software utilities for advanced processing. Prospective cohort studies could add to its value and resolve discrepancies arising from previous conflicting views as to the specificity and sensitivity of the technique, while with advanced clinical training, OH might in the near future become established as a first-line diagnostic procedure for the management of pre-malignant and malignant lesions.

**Key words:** office hysteroscopy, cancer, endometrium, cervix, hyperplasia, accuracy

**«Isteroscopia ambulatoriale e cancro dell'endometrio/cervicale: un aggiornamento sulla loro potenziale correlazione»**

**Riassunto.** *Obiettivo:* Fornire una panoramica sull'applicabilità, efficienza e accuratezza della isterectomia ambulatoriale (IA) nella diagnosi e nel potenziale trattamento del cancro dell'endometrio (CE) e del cancro cervicale (CC), nonchè dei loro rispettivi stati premaligni. *Materiali e metodi:* Un aggiornamento della letteratura sull'efficienza di IA nel CE e CC, attraverso una strategia di ricerca creata appositamente per PubMed. *Risultati:* L'Iperplasia endometriale ed il Carcinoma Endometriale possono essere diagnosticati con accuratezza con l'Isteroscopia Ambulatoriale. Grazie ad essa si può individuare con precisione l'area da biopsiare e grazie alla diagnosi istopatologica l'accuratezza diagnostica sarà massima. Il ruolo della IA nella diagnosi di neoplasia intraepiteliale cervicale e CC è meno noto e rimane complementare alle tradizionali modalità. Per quanto riguarda il trattamento sia di tumori ginecologici che dei loro stati premaligni, non ci sono dati per sostenere l'utilità di questa tecnica. *Conclusioni:* I moderni progressi tecnologici hanno favorito l'evoluzione

di sofisticati isteroscopi e delle rispettive tecniche, rendendo così la IA un approccio avanzato nella visualizzazione del tratto genitale femminile, grazie ad immagini precise correlate a software specializzati nell'elaborazione grafica avanzata. Studi prospettici di coorte potrebbero ulteriormente valorizzare la metodica per quanto concerne la risoluzione di discrepanze derivanti da precedenti opinioni contrastanti sulla specificità e sensibilità della tecnica, mentre, nel prossimo futuro, un'avanzata formazione clinica potrebbe definire la IA come la procedura diagnostica primaria per la gestione delle lesioni pre-maligne e maligne dell'utero.

**Parole chiave:** isterectomia ambulatoriale, cancro, endometrio, cervice, iperplasia, precisione

## 1. Introduction

Endometrial cancer (EC) is the most frequent gynecological cancer in developed countries, being the sixth most common malignancy in females worldwide, with 88,000 and 52,000 new cases diagnosed annually in the European Union and the United States of America respectively (1, 2). It mainly affects postmenopausal women, the median age at diagnosis being 63 years old. The vast majority of them are diagnosed at an early stage [Stage I, International Federation of Gynecology and Obstetrics (FIGO)], and this is associated with greater efficacy of treatment, potentially less invasive treatment and a better outcome (3).

Cervical cancer (CC) also remains a major global health problem, though its incidence, while rapidly decreasing in developed countries, remains high in the rest of the world. Every year 275,000 deaths are recorded worldwide and 25,000 deaths due to CC were recorded in Europe in 2008 (1). Affecting a younger group of patients and with nearly 85% of the cases being human papillomavirus (HPV)-related, CC is detectable via a smear Pap test (2).

Office hysteroscopy (OH) is a safe and accurate modern ambulatory procedure; in its currently developed form it integrates both diagnostic and operative capabilities, while providing the additional benefit of histological confirmation and keeping patient discomfort to a minimum. The indications and limitations of the technique have been previously reported (4-6) though the former are rising steadily nowadays. The delay in its more widespread use has been attributed to inadequate counseling, the expense of the equipment and lack of training in handling it (7). Just recently, an easier manner of performance and protocols for training residents and inexperienced doctors have been described (8). The technique's advantage over conventional methods lies in the capacity for direct visual assessment of the cervical canal and uterine cavity and, at the same time, the possibility of surgical intervention ("see and treat" technique), such as biopsy and removal of suspicious tissue (9). Importantly, in terms of diagnostic accuracy, patient satisfaction and complications OH has shown similar results to traditional hysteroscopy using anesthesia (10-12).

The aim of this review is to provide insight into the applicability and efficiency of OH in the diagnosis and potential treatment of EC and CC and their respective premalignant states. In addition, we address a series of critical issues bound up with improving the technique and involving integrating future technological advances and adjusting some practical parameters.

## 2. Current aspects in the diagnosis and treatment of endometrial and cervical cancer

EC is an adenocarcinoma in approximately 80% of cases, the remaining 20% being of the adenosquamous or squamous type and carcinosarcomas. The main risk factors for EC are considered to be age > 50 years, increased estrogen blood levels, tamoxifen adjuvant therapy, adiposity, hypertension, type 2 diabetes mellitus (t2DM) and genetic predisposition (13, 14).

Abnormal uterine bleeding (AUB) is the most common and earliest symptom of the disease and is reported in almost 90% of women affected (15).

Concerning diagnosis, transvaginal ultrasound (TVUS) measurement of endometrial thickness is the first step to be performed in all postmenopausal women: a cut-off value of 3-4 mm is highly sensitive for exclusion of EC (16). If AUB persists, or in endometrial thickness >4 mm, further evaluation of the endometrial cavity via endometrial sampling is mandatory (17). The conventional approach is dilatation and curettage (D&C), which is characterized by low sensitivity, as the endometrial biopsy is blind. One significant drawback is the increased risk of false-negative results (approximately 15%), possibly attributable to faulty technique or inadequacy of the histological sample (18). Endometrial sampling is considered to be an ideal method of diagnosing EC and is also performed in an outpatient setting without anesthesia. Where outpatient sampling is unsuccessful or endometrial pathology is suspected, OH with biopsy under direct visualization has been reported as the optimal method for exploring the endometrial cavity (19-21).

CC is histologically divided into squamous cell carcinomas (approximately 80%) and various types of adenocarcinoma or mixed adenosquamous carcinoma. Apart from HPV infection, further risk factors for CC include smoking, a history of multiple sexually-transmitted diseases, chronic immunosuppression, a large number of sexual partners, young age at coitus onset and multiple parity (22). Clinically, CC is most often asymptomatic, making early diagnosis very rare. Diagnosis is often made at advanced stages, especially in developing and underdeveloped countries, where national screening programs are limited; in such cases abnormal vaginal bleeding may indicate that there has already been erosion of the cervix or vagina. Diagnosis and staging of the disease beyond stage I remains clinical, according to the recently revised classification by FIGO (23) and the American Joint Committee on Cancer (AJCC) (24). Primary treatment at early stages of CC, stage IIa2 or less, is either surgery or radiotherapy. Alternatively in earlier stages such as Ia, conisation or radical trachelectomy may be performed when fertility-sparing surgery is a priority.

## 3. Office hysteroscopy and endometrial cancer

*Patient selection and methods*

OH is considered as a valuable tool in combination with endometrial sampling in selecting high-risk populations for EC, as reported with the respective indications in Table 1a. The office procedure is preferably performed during the follicular phase of the menstrual cycle (day 7-10). A Ringer's lactate or normal saline 0.9% solution is used as a distension medium. Ideally, it should be preceded by a bimanual vaginal examination along with TVUS, in order to assess the position and size of the uterus and detect any major uterine abnormalities or adnexal pathology that could interfere with the application of the method and, subsequently, with the interpretation of the results. Special pre-operative interventions such as use of a combined oral contraceptive pill (41) and antibiotics are not justified. Regarding vaginal misoprostol prior to hysteroscopy, a recent meta-analysis suggests the use of this regimen only in premenopausal patients (42).

*Diagnosis of pre-malignant and malignant lesions*

Hysteroscopic findings in cases of endometrial hyperplasia (EH) are characterized by a great morphologic variety, whereas in EC these findings are more specific and recurrent. The hysteroscopic appearance of the endometrium in cases of low-risk EH resembles that of the normal glandular endometrium. The thickness of the mucosal lining can be indirectly evaluated by pressing the endometrial surface using the edge of the diagnostic hysteroscope or a blunt instrument (such as closed scissors, closed clamp etc.): this permits direct assessment of the rigidity, elasticity and vascularisation of the surface and, in turn, suggests the thickness. Commonly in these patients the endometrial gland ostia appear widened with cystic configurations about 1 mm in diameter. These formations should be differentiated from the appearance of the normal endothelium and the hysteroscopic appearance of cystic atrophy (43). Other less characteristic criteria include: increased endometrial thickness, intense endometrial vascularization (cystic dilatation, lack of homogeneity, polypoid morphology, necrotic

**Table 1a.** Indications for OH in the diagnosis of pre-malignant and malignant conditions of the endometrium.

| | Populations at risk of EH/EC | Special considerations |
|---|---|---|
| a | Age > 40 years with pre- or postmenopausal AUB (25) | OH not justified for detection of EC or EH based on cut-off values of ET (26)<br>First choice method of investigation in women with post-menopausal AUB (27)<br>First choice of method (TVUS or OH) controversial in women with pre-menopausal AUB (28, 29) |
| b | Unopposed estrogen therapy (30, 31) | Effective in distinguishing between benign and malignant pathology (32)<br>Slightly higher incidence of false positive findings (33)<br>Annual assessment justified (34) |
| c | Tamoxifen-treated postmenopausal women (35) | Investigation with OH should be initiated after 3 years of treatment or AUB presentation (36)<br>OH superior to TVUS in investigating the endometrium and detecting cystic formation and polyp presence (37) |
| d | Family history of endometrial and breast cancer, obesity, t2DM, hypertension and specific lifestyle factors (e.g. high-fat diet) (38) | Evaluation of endometrium justified in presence of AUB or not (39) |
| e | History of chronic anovulation and/or polycystic ovary syndrome (PCOS) (38) | Evaluation of endometrium justified in presence of AUB or not (39) |
| f | Hereditary nonpolyposis colorectal cancer (HNPCC) (14, 38) | Evaluation of endometrium justified in presence of AUB or not (39)<br>Annual assessment with OH and endometrial sampling by age 35 (38) |
| g | Early menarch and/or late menopause (40) | Evaluation of endometrium justified in presence of AUB or not (39) |

OH: office hysteroscopy, EC: endometrial cancer, AUB: abnormal uterine bleeding, TVUS: transvaginal ultrasound scan, ET: endometrial thickness, t2DM: type 2 diabetes mellitus

areas and anarchy in the arrangement of the glandular ostia). In cases of high-risk EH, hysteroscopic findings are also extremely varied and, once again, not significantly different from a normal endothelial appearance. Vascularization is more prominent and visible and polypoid formations are more often present. The mucosa presents a "cerebroid" pattern due to its extreme vascularization and abnormal development (44). Note that whether it concerns low-risk or high-risk cases of EH, endometrial sampling is mandatory. In cases of EC, the hysteroscopic appearance of the endometrium tends to be evaluated early on (45). Diagnosis of EC is rarely missed, due to the conspicuous and clear appearance of the abnormal endometrium. Adenocarcinoma, in its pre-invasive stage appears irregular and presents multiple lobular regions which are usually necrotic and bleed, while vascularization is abnormal with no growth pattern (46). Although EC staging is achieved either during surgery or through imaging techniques, there are reports arguing the usefulness of OH in the preoperative staging of EC (45, 47) and especially its role in detecting cervical involvement (48-50).

In this context, OH makes it easily possible to visualize the location of the polyp base, excluding or confirming cervical invasion; likewise, direct biopsies can bolster a confirmed diagnosis.

*Treatment of pre-malignant and malignant lesions*

Pre-malignant endometrial lesions are considered to include EH, endometrial intraepithelial neoplasia (EIN) and gestational trophoblastic diseases. The rationale of treating such lesions through OH lies in the

fact that they are situated on the upper layer of the endometrium and concern young patients who wish to preserve their fertility. Strict selection criteria of patients and specialized counseling are compulsory (51). This group of patients should have no contraindications for medical therapy, be well informed of and compliant with follow up and accept the risk of cancer progression following uterus preservation (52). The invasion depth should be previously validated via high quality imaging techniques, such as magnetic resonance imaging (53, 54), although the sensitivity of this in certain cases is less than optimal.

Regarding premalignant lesions, mini-resectoscope (used with no general anaesthesia) is a potentially efficient treatment option (55, 56). In cases of stage IA EC, such treatment could also be offered. Conservative resectoscopic treatment under general anesthesia after administration of medroxy-progesterone acetate or followed by administration of megestrol acetate (160 mg) or a levonorgestrel-medicated intrauterine device (52 mg) for 6 and 12 months respectively, has been described with satisfactory follow-up results (57-59). Moreover, resectoscopic surgery did not appear to adversely affect the 5-year survival and the long-term prognosis in 14 women with EC (60). In contrast, a recent systematic review of 45 studies including 391 patients reported the rate of recurrence to be as high as 25% after 24 months of follow-up (61). Interestingly, recurrence rates remain high during long term observation even after complete remission of the disease (62).

It seems that operative OH has the potential for being used with safety in premalignant lesions and early stage EC in properly selected patients, additionally offering a unique advantage through its periodical repetition during the follow up of the patients.

## 4. Office hysteroscopy and cervical cancer

*Patient selection and Methods*

The value of OH in the diagnosis of CC has been extensively studied and currently there is no robust evidence on its efficacy in this setting, either in its own right or in comparison with colposcopy. Currently, colposcopy has been established as the gold standard procedure for diagnosing premalignant lesions and CC at an early stage, due to its ability to carry out biopsies on an outpatient basis and at low cost.

OH provides an excellent view of the cervical canal, so it could play a role in the evaluation of selected individuals at risk of developing CC (Table 1b). Microhysteroscopy combined with computerized analysis of hysteroscopic images has been proposed for the assessment and treatment of precancerous and malignant lesions (67). Nevertheless, a major concern still regards evaluation of the endocervical canal, especially near the internal cervical os; moreover, it is often impossible for the clinician to identify and examine the inner third of the cervical canal in the event of stenosis or symphysis (68).

Both patient preparation methods have been described above for EC. However, since the area of interest is the cervical canal, the clinician should exercise patience with cervical dilatation and allow the distention medium to act slowly on the internal and external os. The use of prostaglandins are only suggested in premenopausal women (42). It remains uncertain whether mechanical dilatation of the canal might alter the pragmatic image of a potential malignant area.

**Table 1b.** Indications for OH in the diagnosis of pre-malignant and malignant conditions of the cervix.

| | Populations at risk of CC | Special considerations |
|---|---|---|
| a | Abnormal cytology in Pap-smear (LGSIL or HGSIL) (63) | Endocervicoscopy provides better visualization of the endocervix |
| b | Negative or unsatisfacory colposcopy (64) | Performed in the office setting |
| c | Follow up of diagnosed and/or treated women with CIN (65) | Guided biopsies mandatory in case of abnormal findings (66) |

CC: cervical cancer, LGSIL: low-grade squamous intraepithelial lesion, HGSIL: high-grade squamous intraepithelial lesion, CIN: cervical intraepithelial neoplasia

*Diagnosis of pre-malignant and malignant lesions*

Pre-malignant lesions of the cervix include conditions such as squamous cells or glandular, dysplasia or atypia of the cervix and endometrial pathologies involving the cervix. Hysteroscopy affords better visualization of polyps in the intrauterine cavity and cervical canal than any other imaging technique (10, 69-71). Thus, identification of the origin of a polyp (originating from the cervix or the endometrium) and biopsy sampling from the base of the polyp appear to be more advantageous than fractional curettage. Recently, endocervicoscopy aroses as a supplementary technique in the diagnosis of CIN, offering the advantage of giving the precise localization of a precancerous cervical lesion and therefore the possibility of more conservative and effective excision in an office setting (66). Regarding diagnosis of malignant lesions of the cervix, OH could be useful in certain conditions, such as the diagnosis of adenocarcinoma and particularly differentiating it from other pathology of endometrial origin. Although OH in combination with targeted biopsies has proven useful in preoperative assessment of cervical invasion in EC (48-50), currently it is not routinely recommended for the diagnosis and staging of either EC or CC (23, 24). For this, lack of any visual landmark separating the internal cervical os from the uterus, and distortion of the normal anatomy by a tumor are appreciable etiological factors. Likewise, in a significant number of case, the cervix is invaded submucosally, so that invasion cannot be detected during OH. In such cases, further imaging options, such as TVUS and cervical focused MRI, or OH guided biopsies and endocervicoscopy along with the application of acetic acid could further assist the diagnosis (66).

Thus, we propose that OH be used only as a diagnostic method supplementary to colposcopy for clarification of suspicious cervical lesions.

*Treatment of pre-malignant and malignant lesions*

Treatment of such lesions can be proposed in selected patient categories after proper consultation, especially for those who wish to preserve their fertility (24). Radical abdominal trachelectomy for early-stage CC has been reported as a safe option associated with successful obstetrical outcomes (72). Mini-resectoscope is a promising alternative (55). Thus, in cases of stage IA1 CC in young patients OH combined with mini-resectoscope and proper cervical conization (73) could theoretically reassure the endocervical margins and be justified. Superficial tissue sampling or tissue excision of suspected areas could support a diagnosis. However, deeper granular lesions cannot be detected. It is important to evaluate the uterus and cervix presurgically (74) for nodal involvement and the presence of metastatic disease (75), using high accuracy imaging techniques, in order to provide every patient with the option of fertility preservation (24).

In contrast, in cases of higher stages than IB1, no fertility sparing surgery should be offered, and of course OH has no place. Similarly, in cases of local recurrence after radiation therapy in the cervix, OH has been technically questioned, as cervical and vaginal stenosis and fibrosis are usually present and heavy cervical bleeding during the procedure is common.

## 5. Safety of OH in pre-malignant and malignant lesions

In the diagnosis of suspected pre-malignant or malignant lesions the technique may be validated by an endometrial biopsy performed upon its completion. This is feasible by mechanical (biopsy forceps and scissors) or electrical (Versapoint, unipolar or bipolar resectoscopes) means.

One of the major concerns when using OH either in the diagnosis of EC or during investigation of the uterus, is the risk of spreading cancer cells into the peritoneal cavity, a risk which remains controversial according to publications to-date. Prospective studies have argued that there is no increased risk of cancer progression (76, 77). However, a recent meta-analysis of controlled trials concluded that patients diagnosed with EC are at risk of disease upstaging after hysteroscopy (78). In the same setting the role of the type of distension medium and intrauterine pressure employed in suspected EC continue to be debated. The review demonstrated that the risk of dispersion is increased when saline chloride 0.9% is used and when the pressure of the extension media exceeds 100 mmHg (78). There is evidence that such risk diminishes when the

pressure of the media extension applied is lower than 40 mmHg (79). In our view, even though there is an established risk of dispersing cancer cells in the peritoneum, the patient-oriented benefits acquired from this practice are likely to outweigh the risks, although careful assessment of the managing approach, case by case, should precede any medical intervention.

## 6. Accuracy and efficiency of OH in pre-malignant and malignant conditions

The diagnostic accuracy of OH in recognizing endometrial pathology has been widely evaluated. Our search revealed contradictory results regarding the accuracy of the procedure, mainly owing to whether or not it was combined with a biopsy of the suspected endometrial lesion. The studies reporting sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) with regard to OH accuracy are summarized in Table 2a (80-96). In the only meta-analysis found in our literature search, hysteroscopy (ambulatory or not) performed well in the diagnosis of EC, but only moderately in the diagnosis of EH; where it proved proved particularly efficient was in postmenopausal women, especially through the non-touch technique (84). Nevertheless, the majority of investigators conclude that OH is a highly accurate diagnostic tool in discriminating abnormal from normal endometrium in populations at high-risk of EH and/or EC. Interestingly, in women at risk of HNPCC (92) and in tamoxifen-treated patients, OH has been proposed as the preferred diagnostic method for patient follow-up (85, 97).

Regarding hysteroscopy's accuracy in recognizing pre- and malignant lesions of the cervix, little data are available in the literature (Table 2b). Endocervicoscopy has recently emerged as a promising and more accurate alternative to colposcopy for the diagnosis and follow-up of patients treated for CIN. It seems that current hysteroscopes lack the technological efficiency for high-definition imaging of the endometrial cavity and cervical canal, a power that, if gained, could establish the office technique as the first-line diagnostic procedure for evaluation of pre- and malignant lesions in the near future.

To date, a limited number of authors have evaluated the feasibility and efficacy of OH in a general gynecological setting and diagnosis of benign endometrial pathology (8, 99, 100). Thus, the evaluation of both feasibility and efficacy of OH, through careful assessment of the risks over the benefits to the patients, is still in progress.

To conclude, OH is not a validated treatment option for either EC or CC. Operative hysteroscopy is capable of removing only superficial malignant tissue from the endometrium or the endocervical canal. It is currently not used for therapeutic reasons related to malignancy and it cannot be used for staging purposes; note that the only possible case is when cancer cells are removed through hysteroscopy upon an accidental pathologic finding or for diagnostic purposes. Again, OH cannot determine precisely the depth of invasion or the extent of a lesion intruding into the myometrium or the cervical stroma. However, new technological equipment could initiate new approaches in these two cancers' staging and treatment, at least in their early stages.

## 7. A potential dynamic protocol and suggestions for improving the accuracy and effectiveness of OH

Our preliminary suggestions could be summarised as follows:

1. Broad application of the technique on a routine basis by all clinicians, especially the young and inexperienced, is a crucial preliminary step. The improvements to be considered involve some already proposed dynamic protocols and an evaluation checkpoint during training in order to confirm that the requisite skills have been acquired. Wider adoption of OH may extend the mandatory experience of clinicians in diagnosing focal cancer, the presence of premalignant conditions or lesions either inside the cervical canal or in the uterine cavity.

2. Improving gynecologists' education and upgrading their skills in OH techniques through an accredited organization: for example, FIGO could promote further awareness of the advantages of OH and familiarize gynecologists with this approach. In addition, official certification following further education,

**Table 2a.** Studies evaluating accuracy of OH in pre-malignant and malignant conditions of the endometrium (reporting on SE, SP, PPV and NPV).

| Trial | Country | Type of study | Type of intervention | Reference standard | Studied disease | Studied population | SE, SP, PPV, NPV (%) |
|---|---|---|---|---|---|---|---|
| Loverro 1996 (80) | Italy | retrospective | OH with biopsy | endometrial biopsy (H-guided forceps) | EH | 980 women with AUB | SE: 98<br>SP: 95<br>PPV: 63<br>NPV: 99 |
| Widrich 1996 (81) | USA | prospective | OH | endometrial biopsy (Pipelle) | EH | 113 women with AUB or tamoxifen use or other indications | SE: 43<br>SP: 100<br>PPV: 100<br>NPV: 93 |
| Lo 2000 (82) | Hong-Kong | retrospective | OH without biopsy | endometrial biopsy (Pipelle or H-guided forceps) | EC | 1468 women with any endometrial pathology | SE: 58.8<br>SP: N/A<br>PPV: 20.8<br>NPV: N/A |
| Ceci 2002 (83) | Italy | retrospective | OH | hysterectomy specimens | (EH) (EC) | 443 women with any endometrial pathology | SE: (83.3) (95.6)<br>SP: N/A<br>PPV: N/A<br>NPV: N/A |
| Clark 2002 (84) | UK | meta-analysis of prospective and retrospective trials | H or OH | D&C; office biopsy; H-guided forceps | (EC) (ED=EH or EC or both) | 26.346 women with AUB | SE: (86.4) (78)<br>SP: (99.2) (95.8)<br>PPV: N/A<br>NPV: N/A |
| Garutti 2002 (85) | Italy | prospective | OH with biopsy | endometrial biopsy | EH | 66 tamoxifen treated women with ET >4mm | SE: 100<br>SP: 94.1<br>PPV: 100<br>NPV: 97.8 |
| de Wit 2003 (86) | The Netherlands | retrospective | OH | endometrial biopsy | EH and/ or EC | 1045 women with any endometrial pathology | SE: 60.9<br>SP: 94.7<br>PPV: 40<br>NPV: 97.7 |
| Vasile 2003 (87) | Italy | retrospective | OH with biopsy | endometrial biopsy | EH | 145 women with any indication | SE: 89.4<br>SP: 92<br>PPV: 82.4<br>NPV: 95.4 |
| Arslan 2005 (88) | Turkey | prospective | OH with biopsy | endometrial biopsy | EH | 330 women with AUB | SE: 80.6<br>SP: 92.5<br>PPV: 71.4<br>NPV: N/A |
| Garuti 2005 (89) | Italy | retrospective | OH with biopsy | endometrial biopsy | EH | 323 women with any endometrial pathology | SE: 63.7<br>SP: 91.7<br>PPV: 64.7<br>NPV: 91.3 |
| Kelekci 2005 (90) | Turkey | prospective randomized | TVS, SIS, and OH. | hysterectomy specimens | EH | 50 women with or without AUB | SE: 100<br>SP: 78.9<br>PPV: 27.3<br>NPV: 100 |

*(continued)*

**Table 2a (continued).** Studies evaluating accuracy of OH in pre-malignant and malignant conditions of the endometrium (reporting on SE, SP, PPV and NPV).

| Trial | Country | Type of study | Type of intervention | Reference standard | Studied disease | Studied population | SE, SP, PPV, NPV (%) |
|---|---|---|---|---|---|---|---|
| Litta 2005 (19) | Italy | prospective | OH without biopsy | endometrial biopsy (Novak curettage) | EC | 220 women with AUB | SE: 100<br>SP: 49.6<br>PPV: 81.3<br>NPV: 100 |
| Lasmar 2006 (91) | Brazil | retrospective | OH with biopsy | endometrial biopsy | (EH)<br>(EC) | 4054 women with AUB | SE: (56.3) (80)<br>SP: (89.1) (99.5)<br>PPV:( 48.0) (81.5)<br>NPV: (92.0) (99.5) |
| Avila 2008 (50) | Spain | prospective | OH with or without biopsy | endometrial biopsy (OH or Pipelle or Novak curettage) | EC (cervical involvement) | 240 women with EC | SE: 79.5<br>SP: 88.1<br>PPV: 56.4<br>NPV: 95.7 |
| Lecuru 2008 (92) | France | prospective | OH without biopsy | endometrial biopsy (Pipelle) | ED | 62 women at risk of HNPCC | SE: 50<br>SP: 100<br>PPV: 100<br>NPV: 40 |
| Svirsky 2008 (93) | Israel | retrospective | OH with endometrial biopsy | blind endometrial biopsy with Novak curettage | EH | 639 women with any endometrial pathology | SE: 37<br>SP: N/A<br>PPV:N/A<br>NPV: N/A |
| Tripodi 2011 (94) | Italy | prospective | OH with biopsy | endometrial biopsy (Novak curettage and H-guided forceps) | (EH)<br>(EC) | 95 women with AUB | SE: (77.4) (90)<br>SP: N/A<br>PPV: N/A<br>NPV: N/A |
| Shinar 2014 (95) | Israel | retrospective | OH without biopsy | endometrial biopsy (H-guided forceps) | EH | 132 women with abnormal TVS findings | SE: N/A<br>SP: N/A<br>PPV: 14.3<br>NPV: N/A |
| Issat 2014 (96) | Poland | retrospective | OH | biopsy | EC | 494 women | SE: 80<br>SP: 99.4<br>PPV: 66.7<br>NPV: 99.6 |

EH: endometrial hyperplasia, EC: endometrial cancer, ED: endometrial disease, AUB: abnormal uterine bleeding, H: hysteroscopy (with anesthesia), OH: office hysteroscopy (without anesthesia), TVS: transvaginal sonography, SIS: saline infusion sonography, SE: sensitivity, SP: specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value, ET: Endometrial thickness

and training through specified programs and technical modules from acknowledged centers worldwide, should make application of the technique safer for patients.

3. Technological upgrading of the additional equipment beside the hysteroscope e.g. an ultrasound transducer or a different lighting/lens for improved visualization of the canal or the cavity to assist identification of potential lesions. For instance, green filters could enhance identification of pathological vascularization, as an adjunct to colposcopy. Development of high resolution microscopes, along with specialized

**Table 2b.** Studies evaluating accuracy of OH in pre-malignant and malignant conditions of the cervix (reporting on SE, SP, PPV and NPV).

| Trial | Country | Type of study | Type of intervention | Reference standard | Studied disease | Studied population | SE, SP, PPV, NPV (%) |
|---|---|---|---|---|---|---|---|
| Bifulco 2010 (66) | Italy | prospective | endocervicoscopy | surgical specimen of cervical conization | CIN | 95 patients with HGSIL | SE: 79<br>SP: 100 |
| Pityński 1999 (98) | Poland | prospective | micro-colpo-hysteroscopy | colposcopically directed punch biopsy | (LGSIL)<br>(HGSIL)<br>(CC) | 86 women cytologically suspected for SIL | SE: (73) (98) (94)<br>SP: (50) (33) (75)<br>PPV: (85) (95) (99)<br>NPV: (33) (50) (38) |

CIN: cervical intraepithelial neoplasia, CC: cervical cancer, LGSIL: low grade squamous lesion, HGSIL: high grade squamous lesion, SE: sensitivity, SP: specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value

software with "save picture" modality able to compare images acquired from subsequent hysteroscopies and contrast alterations in the cervical/endometrial tissues of the same risk patient, could facilitate more accurate diagnosis of suspect lesions; in addition, though "extreme" technological advances the near future may see early diagnosis of cancer cell proliferation in myometrium and cervical stroma.

4. Modifications toward improving preparation of the cervical canal -e.g. vaginally inserted prostaglandins in order to avoid tissue damage by hysteroscope insertion - could yield clearer images. This might be necessary in those cases where an OH-related dispersion of endometrial cancer cells is expected. Again, preparing the patient with painkillers and light sedatives before OH could improve tolerance of the examination and make the investigation more successful, in particular where immobilization of the patient is required for more stable imaging and instrument insertion is not well-tolerated.

5. Financial aspects are a crucial factor when suggesting a practice enter routine clinical or office investigation. By reducing the cost of the equipment, this technique should be affordable patient-wise and therefore more broadly acceptable by the national health systems and/or individual gynecologists.

6. Further clarification of the efficacy and potential of this technique should be provided by future prospective cohort studies. Randomized controlled trials would provide the highest accuracy, although ethical issues need to be considered in this connection.

## 8. Conclusions

Office hysteroscopy (OH) is a modified and technologically evolved approach tovisualization of the female genital tract; to a large extent it is a safe, accurate, modern diagnostic procedure, providing the additional benefit of sampling and histological confirmation, with minimal discomfort to the patient. Intrauterine investigation in selected high-risk patients for EC appears to be enabled by this intervention, since, when combined with endometrial sampling, it can effectively differentiate between benign and malignant conditions; in cases of premalignant lesions and early stage EC, it seems that there is room for using it with safety. In cases of cervical malignancies, OH appears beneficial as an adjunct to colposcopy for clarification of suspicious cervical lesions. In contrast, OH is not a validated treatment option for either EC or CC.

Although the risk of inducing cancer progression through cancer cell dispersion in the peritoneum is not confirmed, careful case-by-case assessment of the managing approach is imperative.

This, added to experience, broad application of the technique, upgraded training and possible modifications in patient preparation to reduce the length of the procedure, could provide a safer environment in intrauterine biopsy sampling. A fall in the cost of the equipment, along with technological advances involving the improvement of hysteroscopes exploiting their fine imaging of both endometrial cavity and cervix, along with specialized software utilities for advanced

processing of the images, could establish the office technique as a highly beneficial and functional module and a first-line diagnostic procedure for the evaluation of pre-malignant and malignant lesions in the near future. Future prospective cohort studies could add to its value, resolving previous conflicting views and results as to the specificity and sensitivity of the technique.

## References


1. Jemal A, Bray F, Center MM, *et al.* Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
2. WHO International Agency for Research on cancer - Globocan. Estimated cancer incidence, mortality and prevalence worldwide in 2012, www.globocan.iarc.fr
3. Siegel R, Ma J, Zou Z, *et al.* Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.
4. Bradley L. Indications and Contraindications for Office Hysteroscopy. In: Bradley L & Falcone T. Hysteroscopy: Office Evaluation and Management of the Uterine Cavity, Elsevier Health Sciences, 2008.
5. Siristatidis C, Chrelias C, Salamalekis G, *et al.* Office hysteroscopy: current trends and potential applications: a critical review. Arch Gynecol Obstet 2010; 282: 383-8.
6. Bettocchi S, Achilarre MT, Ceci O, *et al.* Fertility-enhancing hysteroscopic surgery. Semin Reprod Med 2011; 29: 75-82.
7. Isaacson K. Office hysteroscopy: a valuable but under-utilized technique. Curr Opin Obstet Gynecol 2002; 14: 381-5.
8. Siristatidis CS, Miligkos DS, Klyucharov IV, *et al.* Constructing a protocol for the evaluation of residents' competency with office hysteroscopy. Gynecol Surg 2013; 10: 193-7.
9. Bettocchi S, Selvaggi L. A vaginoscopic approach to reduce the pain of office hysteroscopy. J Am Assoc Gynecol Laparosc 1997; 4: 255-8.
10. De Angelis C, Santoro G, Re ME, *et al.* Office hysteroscopy and compliance: mini-hysteroscopy versus traditional hysteroscopy in a randomized trial. Hum Reprod 2003; 18: 2441-5.
11. Sagiv R, Sadan O, Boaz M, *et al.* A new approach to office hysteroscopy compared with traditional hysteroscopy: a randomized controlled trial. Obstet Gynecol 2006; 108: 387-92.
12. Guida M, Di Spiezio Sardo A, Acunzo G, *et al.* Vaginoscopic versus traditional office hysteroscopy: a randomized controlled study. Hum Reprod 2006; 21: 3253-7.
13. Kitchener HC, Trimble EL. Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup. Endometrial cancer state of the science meeting. Int J Gynecol Cancer 2009; 19: 134-40.
14. Obermair A, Youlden DR, Young JP, *et al.* Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer 2010; 127: 2678-84.
15. Seebacher V, Schmid M, Polterauer S, *et al.* The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. BMC Cancer 2009; 9: 460.
16. Apgar BS, Kaufman AJ, Bettcher C, *et al.* Gynecologic procedures: colposcopy, treatments for cervical intraepithelial neoplasia and endometrial assessment. Am Fam Physician 2013; 87: 836-43.
17. Moodley M, Roberts C. Clinical pathway for the evaluation of postmenopausal bleeding with an emphasis on endometrial cancer detection. J Obstet Gynaecol 2004; 24: 736-41.
18. MacKenzie IZ, Bibby JG. Critical assessment of dilatation and curettage in 1029 women. Lancet 1978; 2(8089): 566-8.
19. Litta P, Merlin F, Saccardi C, *et al.* Role of hysteroscopy with endometrial biopsy to rule out endometrial cancer in postmenopausal women with abnormal uterine bleeding. Maturitas 2005; 50: 117-23.
20. Guruwadayarhalli B, Jones SE, Srinivasan V. Hysteroscopy in the diagnosis of postmenopausal bleeding. Menopause Int 2007; 13: 132-4.
21. Dreisler E, Poulsen LG, Antonsen SL, *et al.* EMAS clinical guide: assessment of the endometrium in peri and postmenopausal women. Maturitas 2013; 75: 181-90.
22. Parkin DM. Tobacco-attributable cancer burden in the UK in 2010. Br J Cancer 2011; 105 Suppl 2: S6-S13.
23. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet 2014; 125: 97-8.
24. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. V 3.2013 Available at http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed March 5, 2014.
25. van Hanegem N, Breijer MC, Khan KS, *et al.* Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. Maturitas 2011; 68: 155-64.
26. Breijer MC, Peeters JA, Opmeer BC, *et al.* Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2012; 40: 621-9.
27. Gredmark T, Kvint S, Havel G, *et al.* Histopathological findings in women with postmenopausal bleeding. Br J Obstet Gynaecol 1995; 102: 133-6.
28. Trevoux R, De BJ, Castanier M, *et al.* Endometrium and plasma hormone profile in the peri-menopause and postmenopause. Maturitas 1986; 8: 309-26.
29. Burbos N, Musonda P, Crocker SG, *et al.* Outcome of investigations for postmenopausal vaginal bleeding in women under the age of 50 years. Gynecol Oncol 2012; 125: 120-3.
30. Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of oestrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321-33.
31. Beral V, Bull D, Reeves G. Million Women Study Col-

laborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet 2005; 365: 1543-51.
32. Okeahialam MG, Jones SE, O'Donovan PJ. Outcome of outpatient micro-hysteroscopy performed for abnormal bleeding while on hormone replacement therapy. J Obstet Gynaecol 2001; 21: 277-9.
33. Elliott J, Connor ME, Lashen H. The value of outpatient hysteroscopy in diagnosing endometrial pathology in postmenopausal women with and without hormone replacement therapy. Acta Obstet Gynecol Scand 2003; 82: 1112-9.
34. Pickar JH, Archer DF. Is bleeding a predictor of endometrial hyperplasia in postmenopausal women receiving hormone replacement therapy? Menopause Study Group (United States, Italy, Netherlands, Switzerland, Belgium, Germany, and Finland). Am J Obstet Gynecol 1997; 177: 1178-83.
35. Bergman L, Beelen ML, Gallee MP, *et al.* Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet 2000; 356: 881-7.
36. Taponeco F, Curcio C, Fasciani A, *et al.* Indication of hysteroscopy in tamoxifen treated breast cancer patients. J Exp Clin Cancer Res 2002; 21: 37-43.
37. Gardner FJ, Konje JC, Brown L, *et al.* Uterine surveillance of asymptomatic postmenopausal women taking tamoxifen. Climacteric 1998; 1: 180-7.
38. Smith RA, Cokkinides V, Brooks D, *et al.* Cancer screening in the United States, 2010: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin 2010; 60: 99-119.
39. ACOG practice bulletin: management of anovulatory bleeding. ACOG Committee on Practice Bulletins—Gynecology. American College of Obstetricians and Gynecologists 2001; 72: 263-71.
40. Foley DV, Masukawa T. Endometrial monitoring of high-risk women. Cancer 1981; 48 (2 Suppl): 511-4.
41. Bifulco G, Di Spiezio Sardo A, De Rosa N, *et al.* The use of an oral contraceptive containing estradiol valerate and dienogest before office operative hysteroscopy: a feasibility study. Gynecol Endocrinol 2012; 28: 949-55.
42. Polyzos NP, Zavos A, Valachis A, *et al.* Misoprostol prior to hysteroscopy in premenopausal and post-menopausal women. A systematic review and meta-analysis. Hum Reprod Update 2012; 18: 393-404.
43. Zola FE, Nogueira AA, de Andrade JM, *et al.* Hysteroscopic appearance of malignant and benign endometrial lesions: a case-control study. Arch Gynecol Obstet 2007; 275: 49-52.
44. Mencaglia L, Valle RF, Perino A, *et al.* Endometrial carcinoma and its precursors: early detection and treatment. Int J Gynaecol Obstet 1990; 31: 107-16.
45. Joelsson I, Levine RU, Moberger G. Hysteroscopy as an adjunct in determining the extent of carcinoma of the endometrium. Am J Obstet Gynecol 1971; 111: 696-702.
46. Sugimoto O. Hysteroscopic diagnosis of endometrial carcinoma. A report of fifty-three cases examined at the Women's Clinic of Kyoto University Hospital. Am J Obstet Gynecol 1975; 121: 105-13.
47. Cronjé HS, Deale CJ. Staging of endometrial cancer by hysteroscopy. S Afr Med J 1988; 73: 716-7.
48. Toki T, Oka K, Nakayama K, *et al.* A comparative study of pre-operative procedures to assess cervical invasion by endometrial carcinoma. Br J Obstet Gynaecol 1998; 105: 512-6.
49. Almog B, Gutman G, Lessing JB, *et al.* Prediction of cervical involvement in endometrial cancer by hysteroscopy. Arch Gynecol Obstet 2007; 275: 45-8.
50. Avila ML, Ruiz R, Cortaberria JR, *et al.* Assessment of cervical involvement in endometrial carcinoma by hysteroscopy and directed biopsy. Int J Gynecol Cancer 2008; 18: 128-31.
51. Letourneau JM, Ebbel EE, Katz PP, *et al.* Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012; 118: 1710-7.
52. Gracia CR, Jeruss JS. Lives in the balance: women with cancer and the right to fertility care. J Clin Oncol 2013; 31: 668-9.
53. Ortashi O, Jain S, Emannuel O, *et al.* Evaluation of the sensitivity, specificity, positive and negative predictive values of preoperative magnetic resonance imaging for staging endometrial cancer. A prospective study of 100 cases at the Dorset Cancer Centre. Eur J Obstet Gynecol Reprod Biol 2008; 137: 232-5.
54. Tong T, Yajia G, Huaying W, *et al.* Application of 1.5T magnatic resonance imaging in endometrial cancer. Arch Gynecol Obstet 2012; 285: 1113-8.
55. Papalampros P, Gambadauro P, Papadopoulos N, *et al.* The mini-resectoscope: a new instrument for office hysteroscopic surgery. Acta Obstet Gynecol Scand 2009; 88: 227-30.
56. Garuti G, Luerti M. Hysteroscopic bipolar surgery: a valuable progress or a technique under investigation? Curr Opin Obstet Gynecol 2009; 21: 329-34.
57. Yasuda M, Terai Y, Sekijima T, *et al.* Successful pregnancy after conservative surgery for stage IA endometrial cancer in a young woman. Fertil Steril 2009; 91: 936.e13-5.
58. Mazzon I, Corrado G, Masciullo V, *et al.* Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. Fertil Steril 2010; 93: 1286-9.
59. Laurelli G, Di Vagno G, Scaffa C, *et al.* Conservative treatment of early endometrial cancer: preliminary results of a pilot study. Gynecol Oncol 2011; 120: 43-6.
60. Vilos GA, Edris F, Al-Mubarak A, *et al.* Hysteroscopic surgery does not adversely affect the long-term prognosis of women with endometrial adenocarcinoma. J Minim Invasive Gynecol 2007; 14: 205-10.
61. Gunderson CC, Fader AN, Carson KA, *et al.* Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 2012; 125: 477-82.
62. Chiva L, Lapuente F, González-Cortijo L, *et al.* Sparing fertility in young patients with endometrial cancer. Gynecol Oncol 2008; 111 (2 Suppl): S101-4.

63. Mogensen ST, Bak M, Dueholm M, *et al.* Cytobrush and endocervical curettage in the diagnosis of dysplasia and malignancy of the uterine cervix. Acta Obstet Gynecol Scand 1997; 76: 69-73.
64. Skjelestad FE, Hagen B, Lie AK, *et al.* Residual and recurrent disease after laser-conization for cervical intraepithelial neoplasia Obstet Gynecol 1997; 90: 428-433.
65. Reich O, Lahousen M, Pickel H, *et al.* Cervical intraepithelial neoplasia III: long term follow-up after cold-knife conization with involved margins. Obstet Gynecol 2002; 99: 193-6.
66. Bifulco G, Piccoli R, Lavitola G, *et al.* Endocervicoscopy: a new technique for the diagnostic work-up of cervical intraepithelial neoplasia allowing a tailored excisional therapy in young fertile women. Fertil Steril 2010; 94: 2726-31.
67. Hamou J. Microhysteroscopy: a new procedure and its original applications in gynecology. J Reprod Med 1981; 26: 375-82.
68. Underwood M, Arbyn M, Parry-Smith W, *et al.* Accuracy of colposcopy-directed punch biopsies: a systematic review and meta-analysis. BJOG 2012; 119: 1293-301.
69. Hickey M, Dwarte D, Fraser IS. Precise measurements of intrauterine vascular structures at hysteroscopy in menorrhagia and during Norplant use. Hum Reprod 1998; 13: 3190-6.
70. Panda JK. One-stop clinic for postmenopausal bleeding. J Reprod Med 2002; 47: 761-6.
71. Bettocchi S, Nappi L, Ceci O, *et al.* The role of office hysteroscopy in menopause. J Am Assoc Gynecol Laparosc 2004; 11: 103-6.
72. Nishio H, Fujii T, Sugiyama J, *et al.* Reproductive and obstetric outcomes after radical abdominal trachelectomy for early-stage cervical cancer in a series of 31 pregnancies. Hum Reprod 2013; 28: 1793-8.
73. Abu-Rustum NR, Sonoda Y. Fertility-sparing surgery in early-stage cervical cancer: indications and applications. J Natl Compr Canc Netw 2010; 8: 1435-8.
74. Park JY, Kim EN, Kim DY, *et al.* Comparison of the validity of magnetic resonance imaging and positron emission tomography/computed tomography in the preoperative evaluation of patients with uterine corpus cancer. Gynecol Oncol 2008; 108: 486-92.
75. Mitchell DG, Snyder B, Coakley F, *et al.* Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. J Clin Oncol 2006; 24: 5687-94.
76. Revel A, Tsafrir A, Anteby SO, *et al.* Does hysteroscopy produce intraperitoneal spread of endometrial cancer cells? Obstet Gynecol Surv 2004; 59: 280-4.
77. Biewenga P, de Blok S, Birnie E. Does diagnostic hysteroscopy in patients with stage I endometrial carcinoma cause positive peritoneal washings? Gynecol Oncol 2004; 93: 194-8.
78. Polyzos NP, Mauri D, Tsioras S, *et al.* Intraperitoneal dissemination of endometrial cancer cells after hysteroscopy: a systematic review and meta-analysis. Int J Gynecol Cancer 2010; 20: 261-7.
79. Solima E, Brusati V, Ditto A, *et al.* Hysteroscopy in endometrial cancer: new methods to evaluate transtubal leakage of saline distension medium. Am J Obstet Gynecol 2008; 198: 214.e1-4.
80. Loverro G, Bettocchi S, Cormio G, *et al.* Diagnostic accuracy of hysteroscopy in endometrial hyperplasia. Maturitas 1996; 25: 187-91.
81. Widrich T, Bradley LD, Mitchinson AR, *et al.* Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium. Am J Obstet Gynecol 1996; 174(4): 1327-34.
82. Lo KW, Yuen PM. The role of outpatient diagnostic hysteroscopy in identifying anatomic pathology and histopathology in the endometrial cavity. J Am Assoc Gynecol Laparosc 2000; 7: 381-5.
83. Ceci O, Bettocchi S, Pellegrino A, *et al.* Comparison of hysteroscopic and hysterectomy findings for assessing the diagnostic accuracy of office hysteroscopy. Fertil Steril 2002; 78: 628-31.
84. Clark TJ, Voit D, Gupta JK, *et al.* Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA 2002; 288: 1610-21.
85. Garuti G, Cellani F, Grossi F, *et al.* Saline infusion sonography and office hysteroscopy to assess endometrial morbidity associated with tamoxifen intake. Gynecol Oncol 2002; 86: 323-9.
86. de Wit AC, Vleugels MP, de Kruif JH. Diagnostic hysteroscopy: a valuable diagnostic tool in the diagnosis of structural intra-cavital pathology and endometrial hyperplasia or carcinoma? Six years of experience with non-clinical diagnostic hysteroscopy. Eur J Obstet Gynecol Reprod Biol 2003; 110: 79-82.
87. Vasile C, Piazza M. Accuracy of office hysteroscopy in the diagnosis of endometrial hyperplasia. Clin Exp Obstet Gynecol 2003; 30: 223-5.
88. Arslan S, Aytan H, Gunyeli I, *et al.* Office hysteroscopic evaluation of endometrium: can we hit the target? Arch Gynecol Obstet 2005; 271: 200-2.
89. Garuti G, Cellani F, Garzia D, *et al.* Accuracy of hysteroscopic diagnosis of endometrial hyperplasia: a retrospective study of 323 patients. J Minim Invasive Gynecol 2005; 12: 247-53.
90. Kelekci S, Kaya E, Alan M, *et al.* Comparison of transvaginal sonography, saline infusion sonography, and office hysteroscopy in reproductive-aged women with or without abnormal uterine bleeding. Fertil Steril 2005; 84: 682-6.
91. Lasmar RB, Barrozo PR, de Oliveira MA, *et al.* Validation of hysteroscopic view in cases of endometrial hyperplasia and cancer in patients with abnormal uterine bleeding. J Minim Invasive Gynecol 2006; 13: 409-12.
92. Lécuru F, Le Frère Belda MA, Bats AS, *et al.* Performance of office hysteroscopy and endometrial biopsy for detect-

ing endometrial disease in women at risk of human non-polyposis colon cancer: a prospective study. Int J Gynecol Cancer 2008; 18: 1326-31.
93. Svirsky R, Smorgick N, Rozowski U, *et al.* Can we rely on blind endometrial biopsy for detection of focal intrauterine pathology? Am J Obstet Gynecol 2008; 199: 115.e1-3.
94. Tripodi A, De Salvo C, Ermio C, *et al.* Importance of office hysteroscopy screening to diagnose endometrial carcinoma in menopausal women. Eur J Gynaecol Oncol 2011; 32: 303-6.
95. Shinar S, Bibi G, Barzilay L, *et al.* The value of diagnostic hysteroscopy before operative hysteroscopy for suspected abnormal intrauterine findings. J Minim Invasive Gynecol 2014; 21: 228-32.
96. Issat T, Beta J, Nowicka MA, *et al.* Accuracy and diagnostic value of outpatient hysteroscopy for malignant and benign disease. Eur J Gynaecol Oncol 2014; 35: 52-5.
97. Ceci O, Bettocchi S, Nappi L, *et al.* Comparison of hysteroscopic and hysterectomy findings to assess the diagnostic accuracy of office hysteroscopy in tamoxifen-treated patients with breast cancer. J Am Assoc Gynecol Laparosc 2003; 10: 392-5.
98. Pityński K, Basta A, Kolawa W, *et al.* The value of microcolpo-hysterectomy in the diagnosis and therapeutic evaluation of squamous intraepithelial lesions. Przegl Lek 1999; 56: 41-4.
99. Gulumser C, Narvekar N, Pathak M, *et al.* See-and-treat outpatient hysteroscopy: an analysis of 1109 examinations. Reprod Biomed Online 2010; 20: 423-9.
100. Siristatidis C, Chrelias C. Feasibility of office hysteroscopy through the "see and treat technique" in private practice: a prospective observational study. Arch Gynecol Obstet 2011; 283: 819-23.

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