THE RISK OF HYSTEROSCOPY IN SERIOUS ENDOMETRIAL DISEASES

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ABSTRACT

Objective:
The aim of this review article is to compare varied studies on the role of hysteroscopy in serious endometrial diseases (i.e atypical endometrial hyperplasia and endometrial carncer). Specifically to determine it's accuracy compared to other modalities, the risk of microscopic spread, limitations and identify evolving trends.

Methods:
Search engines used were High Wire Press, Springerlink, Medscape -Pubmed, Google, Yahoo

Results:
Hysteroscopy has a high diagnostic accuracy for endometrial cancer but only moderate for hyperplasia. Imaging modalities of transvaginal sonography and sonohysterography also aid in the management. Studies of Obermair, Hirai, Biewanga et al agree that there is microscopic tumor dissemination when hysteroscopy is used but this does not affect clinical course and prognosis. On the other hand, Bradley et al concluded that aside from microscopic spread , hysteroscopy also upstages endometrial cancer as a result of the high pressure used to distend the uterine cavity and the distension liquid. Studies regarding pre-op assessment of cervical involvement depict that hysteroscopy, although invaluable, failed to adequately predict in endometrial carcinoma . Hysteroscopy has also been used to inject tracers for sentinel lymph node (SLN) detection in endometrial cancer patients.

Conclusion:
When diagnostic procedures such as fractional curettage, hysteroscopy with guided biopsy are compared the accuracy rates were quite similar. Numerous studies have opposing views on the danger of peritoneal or intravascular dissemination of tumorous cells. Studies show that cervical involvement cannot be predicted nor detected properly. Innovations in the diagnostic aspect of serious endometrial diseases through hysteroscopy is still evolving .

KEYWORDS
Hysteroscopy, Endometrial carcinoma, Endometrial Hyperplasia

INTRODUCTION

Endometrial cancer is the most frequently occurring female genital cancer. In developed countries it is the most common gynecologic cancer, however in the developing countries it is less common than cervical cancer. Women have been identified as high risk when risk factors of unopposed estrogen, chronic ovulation, use of drugs (i.e. tamoxifen, oral contraceptive pills) and co morbid diseases are present.

Mortality is higher in black women than in white women with a mortality ratio of 7.1 deaths per 100,000 persons in the former group and only 3.9 deaths per 100,000 persons in the latter group (1) But stage for stage, African-American women have a less favorable prognosis.

Although the incidence of disease has remained stable, the death rate has increased over 100% over the last two decades. Precursor lesions of complex hyperplasia with atypia are associated with an endometrial carcinoma in over 40% of cases (2).

Because of these facts, serious endometrial diseases such as atypical hyperplasia and endometrial carcinoma pose a morbid threat to women especially those at high risk. Desormeaux in 1865 produced the first hysteroscope and was used later by Panteleoni to view the cavity of a 60 year old woman. He was able to identify an endometrial polyp within the uterus which he isolated and cauterized with silver nitrate(3). Over the years, strides of technical improvements followed and changed the course of management of serious endometrial diseases.
The continuing trend of minimal access surgery, specifically hysteroscopy, poses a significant impact on serious endometrial diseases particulary hyperplasia with atypia and endometrial cancer. Numerous studies have debated, analyzed, criticized and praised the various concerns as to it's role, accuracy, risk of microscopic spread, limitations and forthcoming innovations.
This review article attempts to probe and dissect diverse studies regarding hysteroscopy both diagnostic and operative , in the field of serious endometrial diseases.

MATERIALS AND METHODS

A systematic review was conducted using the search engines such as High Wire Press, Springerlink, Google, Pubmed – Medscape using the keywords, " Hysteroscopy", "Endometrial Hyperplasia", and "Endometrial Carcinoma". Twenty- seven articles and abstracts were reviewed and 19 were selected for data collection.

DISCUSSION

Endometrial Hyperplasia with Atypia

Atypical hyperplasia can be triggered by increased demand for that tissue or organ; chronic inflammatory response; hormonal dysfunction; or neoplasia. Or it may be triggered by no obvious cause at all. Even if the atypical hyperplasia is not cancerous, it will increase your chances for getting cancer later. Most atypical hyperplasia are

triggered by a normal hyperplasia. For instance, amenorrhea or ologomenorrhea may result in thickening of the uterine endometrium, a hyperplasia. The increased production of cells makes it more likely that some will mutate into a cancer. In the endometrium, this indicates endometrial cancer. The longer endometriosis is left untreated, the more likely it will develop into cancer.

Endometrial Carcinoma

1. History and Clinical Manifestations

The most common symptom is postmenopausal bleeding. Because bleeding usually occurs from the endometrium, pelvic examination findings may be entirely normal, with no gross evidence of disease on the cervix and with a normal-sized uterus. Cancer can be present upon cervical evaluation and, less frequently, in the upper vagina or periurethrally. In current practice, occult cervical involvement is very unusual, as is clinically evident metastasis, such as in the vagina.

The risk of developing endometrial cancer increases with age. The overall incidence of this cancer is 10.2 cases per 100,000 in women aged 19 to 39 years. The incidence more than doubles from 2.8 cases per 100,000 in those aged 30 to 34 years to 6.1 cases per 100,000 in those aged 35 to 39 years. In women aged 40 to 49 years, the incidence of endometrial carcinoma is 36.5 cases per 100,000.

2. Causes and Risk Factors

Factors generally believed to place women at high risk include increasing age, unopposed estrogen therapy, late menopause, tamoxifen therapy, nulliparity, infertility or failure to ovulate, obesity, and morbid diseases such as obesity, hypertension, diabetes and HPNCC (3).

a. unopposed estrogen therapy in women with an intact uterus increase the risk of endometrial cancer 2 to 10 fold

b. late menopause defined as menopause occurring after age 55 increases the risk two-fold.

c. The relative risk of endometrial cancer in women taking tamoxifen ranged from 1.0 to 7.5.

d. Nulliparity confers an approximately two-fold risk compared with parity of one or more.

e. Chronic anovulation in polycystic ovarian syndrome appears to increase the risk

f. Obesity defined as body weight over 200 pounds or a body mass index more than 27 incerases the risk two to four fold.

g. Diabetes confers about a two-fold relative risk.

HPNCC about 5% of all endometrial cancers occur in women with this risk factor. The accepted definition based on a 1991 meeting of the international Collaborative Group includes: (1) at least three relatives with histologically verified colorectal cancer, with one afirst degree relative of the other two; the diagnosis of familial adenomatous polyposis should be excluded. (2) at least two successive generations should be affected. (3) at least one case of colorectal cancer should be diagnosed before age 50 years. Added to the definition from the 1996 meeting: (4) pedigrees with a colon cancer

case before the age of 40 years and (5) pedigrees with a higher incidence of tumors associated with HPNCC (4).

The American Cancer Society recommends that at the time of menopause, all women should be informed about the risks and symptoms of endometrial cancer, and strongly encouraged to report any unexpected bleeding or spotting to their doctors. For women with or at high risk for hereditary non-polyposis colon cancer (HNPCC), annual screening should be offered for endometrial cancer with endometrial biopsy beginning at age 35 (5).

Pathological diagnosis is obviously the criterion standard for evaluation of the endometrial cavity. A high index of suspicion must be maintained if a diagnosis of endometrial cancer is considered.
The most common histopathologic subtype is endometrioid adenocarcinoma. A squamous component, either benign (adenocanthoma) or malignant (adenosquamous), does not affect prognosis, but the grade of the adeno component does affect prognosis. Papillary serous and clear cell histotypes confer a poor prognosis but, fortunately, are uncommon compared with adenocarcinoma. Secretory carcinomas are the least frequently occurring cancers and are associated with a good prognosis.

3.Staging

* The International Federation of Gynecology and Obstetrics (FIGO) staging system for carcinoma of corpus uteri is as follows:

Stage IA - Tumor limited to endometrium
Stage IB - Invasion to less than one half the myometrium
Stage IC - Invasion to more than one half the myometrium
Stage IIA - Endocervical glandular involvement only
Stage IIB - Cervical stromal invasion
Stage IIIA - Tumor invades serosa and/or adnexa and/or positive peritoneal cytology
Stage IIIB - Vaginal metastasis
Stage IIIC - Metastases to pelvic and/or para-aortic lymph nodes
Stage IVA - Tumor invasion of bladder and/or bowel mucosa
Stage IVB - Distant metastases including intra-abdominal and/or inguinal lymph nodes

* Cases of carcinoma of the corpus should be classified (or graded) according to the degree of histologic differentiation. The histopathology and degree of differentiation is as follows:

o Class G1 - Nonsquamous or nonmorular solid growth pattern of 5% or less
o Class G2 - Nonsquamous or nonmorular solid growth pattern of 6-50%
o Class G3 - Nonsquamous or nonmorular solid growth pattern of more than 50%

FIGO in 1988, whose Gynecologic Oncology Committee was responsible for the staging of gynecological cancer, recommended that corpus cancer be staged surgically. Clinical evaluation was used for staging previously, and multiple studies noted the inaccuracy of clinical staging compared with surgical pathological findings. Therefore, once the diagnosis of endometrial cancer has been made, routine presurgical evaluation is performed to assess operability.

As surgico-pathologic findings is most essential in the prognosis in serious endometrial diseases such as atypical hyperplasia and endometrial cancer it is also imperative to do proper pre-operative diagnostic work up to optimize treatment.

Accuracy and Comparison of Hysteroscopy with other Modalities
Diagnostic procedures include imaging and histopathologic studies. Saline-infusion sonohysterography bolsters the diagnostic power of transvaginal ultrasonography. This technique entails ultrasound visualization after 5 to 10 mL of sterile saline has been instilled in the endometrial cavity. Its sensitivity and specificity for endometrial cancer are comparable with the high sensitivity and specificity of diagnostic hysteroscopy. When HSG was compared to hysteroscopy a study concluded that saline infusion hysterosonography has a higher failure rate, but a lower pain score, than hysteroscopy, and could reduce discomfort for patients (6) .

Fractional curettage was historically the definitive diagnostic tool to help out endometrial cancer in current practice endometrial biopsy as an office procedure is quick, well tolerated and quite sensitive (1). However both are limited in its ability to access the tubal cornua of the uterus.

Hysteroscopy with biopsy provides more information than dilatation and curettage alone and rivals the combination of saline-infusion sonohysterography and endometrial biopsy in its ability to diagnose polyps, submucous fibroids, and other sources of abnormal uterine bleeding(7).

In the absence of ideal noninvasive preoperative testing, surgical staging remains the most accurate method of determining the extent of disease. There has been an increase in surgical staging and a decrease in postoperative adjuvant pelvic radiation therapy over the past two decades. Women with a family history of hereditary nonpolyposis colorectal colon cancer are at increased risk for endometrial cancer. Conservative treatment to allow for childbearing is possible in select situations. Women with endometrial cancer should be managed by physicians experienced in the treatment of this disease(2).
The routine use of outpatient diagnostic hysteroscopy in addition to endometrial biopsy in all women with abnormal uterine bleeding has been discouraged by researchers from the UK. They suggest that the procedure should only be performed in selected patients.
Dr. Christine Bain (Aberdeen Royal Infirmary, Scotland, UK) and co-workers randomly assigned 370 premenopausal women with abnormal uterine bleeding to receive either outpatient hysteroscopy and endometrial biopsy, or endometrial biopsy alone (8). There were few positive findings of lesions in either group.

The researchers found that outpatient hysteroscopy was an acceptable procedure, and, overall, patients who received hysteroscopy were significantly happier with the procedure than the other patients. Bain et al suggest that being able to visualize the uterine cavity could have made hysteroscopy seem a more reassuring procedure. However, there were no significant differences in clinical management in the two groups, with similar rates of, for example, medication, endometrial ablation, and hysterectomy.

According to the researchers these results should temper the widespread implementation of outpatient hysteroscopy for abnormal uterine bleeding in premenopausal women. They suggest that selective hysteroscopy or an ultrasonographic method of investigation could be more appropriate in s uch women, and call for further research into such possibilities(8).

A systematic quantitative review involving 65 primary studies and 26346 women was conducted from 1984 to 2001 showed that hysteroscopy has a high diagnostic accuracy for endometrial cancer but only moderate for hyperplasia(9). A positive hysteroscopy result increased the probability of cancer to 71.8% (95% CI, 67%-76.6%) whereas a negative hysteroscopy result reduced the probability of cancer to 0.6% (95% CI, 0.5% - 0.8%)This study also cited the heterogeniety among the studies hence ingerences were based on the overall pooled result for the hysteroscopic diagnosis of cancer. Using endometrial histologic findings as a reference, the high likelihood ratio of 60.9 (95%CI, 51.2-72.5) for a positive test result on hysteroscopy increased most pretest probabilities over any threshold for advanced management. In contrast, the LR of 0.15 (95% CI,0.13-0.18) for a negative test result is not low enough to negate further diagnostic investigation thereby reducing the use of hysteroscopy in isolation for exclusion of diagnosis. Hysteroscopy has thus high accuracy and thereby clinically useful in diagnosing endometrial cancer in women with abnormal uterine bleeding. The researchers also noted that the accuracy of hysteroscopy tended to be higher among postmenopausal women, and in an outpatient setting(9).

Hysteroscopic Findings in Endometrial Hyperplasia and Carcinoma

The question as to identifying malignancy hysteroscopically lies at hand. An important limitation about office hysteroscopy usage is the lack of studies correlating the visual aspects of the lesion and the histology. In a recent case control study by Zola et al they analyzed the hysteroscopic appearance of benign and malignant endometrial lesions in order to identify patterns estimating malignancy risk.

The researchers concluded that hysteroscopic features associated with malignancy were: papillary aspect, size larger than a half of the uterine cavity, irregular and ulcerated surface, mixed color, vascularization diffuse with anarchical or little branced aspect, and disagreement between the main vascular axe and the direction of the growth(10).

Retrospectively, the same hysteroscopic findings combined with histopathologic reports were used as reference standard in correlating transvaginal sonography and hysterosonography in postmenopausal women with breast cancer taking tamoxifen(11).

TVS is usually the first imaging tool in evaluating women taking tamoxifen therapy however when there is nonspecific thickening of the central endometrial complex

hysterosonography can help in triage for hysteroscopic versus non directed endometrial biopsy.
Sonographically, well- defined thickening with or without cysts are seen. By HSG, endometrial thickening in endometrial hyperplasia is diffuse and smooth. However, assymetrical or focal thickening with surface irregularity has also been described. At hysteroscopy, this is usually thicker than the typical glistening, mucoid, pink-gray appearance of normal proliferative endometrium. Histopathologic examination shows architecturally complex, closed packed endometrial glands that when cytologic atypia is involved is diagnosed as endometrial hyperplasia with atypia.
At TVS, they are either diffusely or partially echogenic and endometrial thickening may be well-defined. However, this thickening is poorly defined due to the underlying adenomyosis and therefore is not a helpful diagnostic feature for the diagnosis of carcinoma. At hysterosonography, an irregular inhomogenous mass or irregular, focally thickened endometrium is highly suggestive of the disease. The potential sign of endometrial carcinoma is the lack of distensibility. At hysteroscopy, the disease shows polypoid, either sessile or pedunculated and is composed of irregularly heaped up tissue that often has a granular surface. It appears opaque, dry pale yellow or white, and friable. Areas of necrosis or the accumulation of lipid-filled cells of stromal origin between the neoplastic glands appear as dark yellow areas. When the tumor is poorly differentiated hemorrhage, ulcerations and abnormal vascular patterns may be seen. At histopathologic study, the glands exhibit fused confluent pattern, cribriform architecture and nuclear atypia.
However, TVS may not depict the true endometrial thickness owing to adenomyosis or endometrial cystic atrophy in these women on tamoxifen therapy. Hysterosonography although relatively easy to perform and usually well tolerated the failure rate may reach as high as 37% owing to cervical stenosis, severe pain or both. Hence, hysteroscopy with guided biopsy is essential in the treatment follow up of postmenopausal women taking tamoxifen.

Microscopic spread

The most debatable issue is perhaps the potential risk of microscopic extrauterine spread of endometrial cancer through hysteroscopy. This brings about hesitancy among practitioners in using this modality in diagnosing and thereby utilizing optimal treatment of such a serious disease as cancer.

Concern has often been expressed that the increase in intrauterine pressure during hysteroscopy may lead to dissemination of malignant cells into the abdominal cavity. An increasing number of case reports assume abdominal dissemination of malignant cells during hysteroscopy have actually demonstrated this phenomenon .

A study(12) compared the incidence of positive peritoneal washings in patients with endometrial cancer who underwent fluid hysteroscopy plus dilatation and curettage with that in patients who underwent only dilatation and curettage before surgical staging. The results strongly suggested that dissemination of endometrial cancer cells occurred during hysteroscopy.

Another study (13) involved 448 subjects with clinical stage I-II endometrial carcinoma treated by total abdominal hysterectomy or radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic/ para-aortic lymphadenectomy. Peritoneal fluid retained in the cul de sac was completely aspirated. 55 patients had positive cytology of which all except 5 have had hysteroscopy 7 days before the procedure. Thus hysteroscopy appears to be responsible for the transport of malignant endometrial cells into the peritoneal cavity.
Biewenga et al also believe that the malignant cells disseminated through hysteroscopy have little potential for implantation and little influence on clinical course. They found that positive peritoneal cytology carries an adverse effect if the cancer had spread to the peritoneum, adnexa, or lymph nodes, but not if disease was otherwise confined to the uterus (Stage 1). Micrometasis in the peritoneal cavity are probably more easily born during the process of metastases to the adnexa, tubes and ovaries rather than spread from the hysteroscopic procedure (14).

A retrospective study reviewed 256 charts to estimate the effect of preoperative diagnostic hysteroscopy on peritoneal cytology in patients with endometrial cancer provided contradiction as to its effect on staging. Hysteroscopy appears to be associated with an increased rate of malignant cytology after controlling for confounders of stage and grade. Further, there appears to be an association between hysteroscopy and upstaging patients due to cytology alone(15).
On the other hand, another retrospective study (16)compared hysteroscopy and dilatation and curettage or endometrial biopsy(Pipelle) and concluded that both did not increase the risk of microscopic intraperitoneal spread in early stage disease.

Cervical Depiction in Hysteroscopy

Significant prognostic factors are tumor stage, histologic grade and depth of myometrial invasion. The presence and nature of cervical involvement (FIGO stage II) is the most important criteria evaluated by the pathologist to determine prognosis and guide treatment.

Garuti et al in 2001 related hysteroscopic features of endometrioid endometrial adenocarcinoma to stage, grade and overall survival. Hysteroscopy was done on 60 patients with endometrioid adenocarcinoma of the endometrium to relate stage, grade of the disease. Sensitivity and sensitivity in predicting cervical spread was 100 and 87.3% respectively. This group concluded that hysteroscopy had a high accuracy rate in predicting spread(17).
Almog et al conducted a retrospective chart review on all endometrial cancer who had surgical staging procedures in Israel. None of the hysteroscopy procedures revealed any suspicious lesion in the cervical canal. Those who underwent fractional dilatation and curettage had pre-operative evidence of cervical infiltration. Though Fractional D and C has limitations by not being able to clearly differentiate borders between the cervix and uterus and is done without visual detection , it remains a simple and good tool for prediction of cervical involvement(18). It remains to be the best method until a more effective method option becomes available.

Emerging Trends of Hysteroscopy on Endometrial Cancer

Aside from the use of hysteroscopy in diagnosing the presence of serious endometrial diseases a feasibility study of sentinel lymph node detection in endometrial cancer patients was done(19). Hysteroscopic injection of technetium-99m-labelled colloids and blue dye subendometrially around the lesion was followed by direct visualization of blue-dye marked nodes and by a radio-guided surgery. The results seem promising as 17 of 18 hysteroscopic procedures were satisfactory regarding the uterine cavity visualization.

CONCLUSION

When diagnostic procedures such as fractional curettage, hysteroscopy with guided biopsy are compared the accuracy rates were quite similar. Imaging modalities of transvaginal sonography and sonohysterography also aid in the management. Using parameters such as papillary aspect, size, surface irregularity, vascularization and distorted vascular growth hysteroscopy assess the risk of malignancy in endometrial lesions. Despite of these uses, several studies have opposing views on the danger of peritoneal or intravascular dissemination of malignant cells as a result of the high pressure used to distend the uterine cavity and the distension liquid. Studies regarding pre-op assessment of cervical involvement depict that hysteroscopy, although invaluable, failed to adequately predict in endometrial carcinoma. However Hysteroscopy has also been used to inject tracers for sentinel lymph node (SLN) detection in endometrial cancer patients. And so, innovations in the diagnostic aspect of serious endometrial diseases through hysteroscopy is still evolving .

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