Review

How Accurately Can You Suspect Endometrial Carcinoma in PMB?

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Abstract

Endometrial carcinoma is the second commonest gynaecological carcinoma worldwide, which is more frequently present as postmenopausal bleeding in early stages. Evaluation of endometrial thickness by 2D and 3D transvaginal ultrasonography, saline infusion sonography, MRI, blind and hysteroscopic guided endometrial biopsy are the investigations available to evaluate postmenopausal bleeding. Many studies has been conducted to assess and compare the accuracy of each investigation and found to have differences in sensitivity, specificity and predictive values on diagnosing endometrial malignancies. Therefore, systematic analysis of symptoms, risk factors and supportive investigations will give a better prediction of endometrial carcinoma in women presenting with postmenopausal bleeding.

Key words

postmenopausal bleeding, endometrial carcinoma, sensitivity, specificity, predictive value

Introduction

Endometrial carcinoma is the second most common female genital tract malignancy worldwide, but it is the commonest gynaecological malignancy in western countries as they are having well establish cervical screening programmes for cervical carcinoma, which is the number one gynaecological cancer among other countries[(1)]. In Sri Lanka, endometrial Carcinoma is the eighth commonest carcinoma among females, where cervical and ovarian carcinoma are the leading genital tract malignancies[(2,3)]. Most of the endometrial cancers are diagnosed in early stages, as most of them are presented as post-menopausal bleeding (90%), even though only 10% -15% of post-menopausal bleeding is associated with endometrial carcinoma [(4,5,6,7)]. According to the data from year 2018, deaths due to endometrial carcinoma is 1% of all deaths due to malignancies in Sri Lanka[(3)].

Pathology

The most common (80%) histological type of endometrial carcinoma is endometrioid adenocarcinoma (type 1), and they are associated with nulliparity, obesity, insulin resistance, and hyper estrogenic environment. They are graded from 1-3 according to the degree of differentiation and nuclear features. Type 2 tumours include serous, squamous, undifferentiated carcinomas, carcinosarcomas and endometrial stromal sarcomas. They are less common, more aggressive and have a poor prognosis. They are associated with old age and not associated with the risk factors for type 1 cancers. Type 1 tumours usually have a background of endometrial hyperplasia and found to have about 50% of severe atypical endometrial hyperplasia. Endometrial carcinomas are usually primary and very rarely can be secondaries from breast, ovary, lung, gastric, colorectal carcinomas and melanomas.

Endometrial carcinoma spreads locally into the myometrium, to the cervix and vagina (haematogenous spread as well can be seen in the vagina as drop lesions). Deeper myometrial invasion can penetrate the serosa and involves the parametrial tissues. Endometrial carcinoma spread through the lymphatics to the external iliac, internal iliac, obturator and para-aortic lymph nodes and this spread is directly proportional to the degree of myometrial involvement. Trans-tubal spread is also possible to the peritoneum and to the ovaries. Lungs are the commonest site of haematogenous metastasis and, type 2 endometrial carcinomas have the highest tendency to spread even with a minimum myometrial invasion.

Screening and Diagnosis

Routine mass screening of the population is not practical due to very low prevalence of endometrial carcinoma and its precursor lesions (complex hyperplasia of the endometrium). Therefore, proper assessment of symptomatic females, specially associated with risk factors, is the mainstay of the diagnosis.

The commonest cause for postmenopausal bleeding is atrophic endometritis or vaginitis, accounting for 60-80% of all cases[30]. Exogenous Estrogen contribute in 15-25%, endometrial hyperplasia in 5-10% and cervical or endometrial polyps in 2-12% for postmenopausal bleeding. Bleeding may arise from extra genital arears such as urethra, bladder and rectum. The possibility of cervical carcinoma is always should be kept in mind on investigating for postmenopausal bleeding, especially in Sri Lanka, as a third world country. Even the risk is 10-15%, 75% of endometrial carcinomas occur in postmenopausal period and 90% of them present as postmenopausal bleeding, making them to seek medical advice in early stage of the disease.

Obtaining a comprehensive history including risk factors with proper clinical examination of the lower genital tract, including assessment of the cervix, vagina and perineum in combination with the investigations, will provide a good predictive value than the predictive values of individual component[28,29]. The pre-test probability of endometrial carcinoma is reduced from 10-15 % up to 1% post-test with negative results. But it varies with the coexisting risk factors and advancing age, where there is 1% risk if the age is <50 years and 25% if the age is > 80years. The risk is 18% in obese, 21% in diabetic and 29% in obese & diabetic in combination[6].

Surgery is the mainstay of management of endometrial carcinoma including, obtaining peritoneal washing for cytology, extra fascial total hysterectomy, bilateral salphingo-oophorectomy, with or without pelvic and para-aortic lymph node dissection which will provide surgico-pathological staging of the disease. Post-operative adjuvant radiotherapy (external beam or brachy-therapy) would be decided depending on the grade, type and the degree of myometrial invasion of the tumour. Still there are some controversies of the management of endometrial carcinoma, where many studies been focused currently on adjuvant chemotherapy, chemoradiation when compared to radiotherapy alone.

The overall 5 year survival of all stages of the endometrial carcinoma is 80% and it varies with the grade and myometrial invasion. Survival in stage I disease is approximately 85-90%, and it reduces up to 70-75% in stage II, 45% in stage III and <30% in stage IV, which reflect the importance of early detection of the disease.

Trans Vaginal Sonography (TVS)

Multiple logistic regression analysis showed that time since menopause and endometrial thickness were statistically significant predictors of endometrial carcinoma[8].

Transvaginal ultrasonography is a known less invasive investigation which is freely available and

has a very good patient acceptancy. Usually it is sufficient for an initial evaluation of postmenopausal bleeding if the ultrasound images reveal a thin endometrial echo (less than or equal to 4 mm). The patient can be reassured, given that an endometrial thickness of 4 mm or less has a greater than 99% negative predictive value for endometrial cancer[9]. Some studies show 100% sensitivity when using 4mm thickness of the endometrium as the cutoff value, therefore none of the patients found to have endometrial cancer after the ultrasonography became negative[10].

According to systematic analysis done by Gupta JK et al. only 4 studies from 21, which used 5mm as the cutoff endometrial thickness, had high quality criteria. Using the pooled estimates only from these four studies, a positive test result raised the probability of carcinoma from 14% to 31.3%, while a negative test reduced it to 2.5%[11]. This shows when the thickness of both endometrial layers at < or = to 5 mm, the negative result will rule out endometrial pathology very well, but it should be always corelated with the associated risk factors and recurrence of postmenopausal bleeding. But positive results will not always give an accurate diagnosis of endometrial carcinoma.

The most cited meta-analysis by Smith-Bindman et al. included 5892 women from 35 prospective studies that compared endometrial thickness measured by TVS to presence or absence of endometrial carcinoma on histology[12]. At 5 mm cut-off, the overall summary mean weighted estimates of the sensitivity for detecting endometrial cancer was 96% for a 39% false-positive rate. This would reduce a pre-test probability of 10% for endometrial cancer to a post-test probability of 1%. Therefore, expectant management (without the need for tissue sampling) is recommended for these women.

There is only one study that looked at follow-up of women with PMB and an endometrial thickness of < or = 4 mm[13]. It showed that none of the women with the expectant management developed cancer over 1 year of follow-up. But endometrial malignancy was missed by TVS in 1 patient among 163 patient (0.6%) who was diagnosed by cervical cytological examination. If the endometrial thickness is > 4mm, the presence of fluid in endometrial cavity is a good marker in diagnosing pathological changes in the endometrium. Curcic´ et al. concluded that, if the endometrial thickness is < 4mm no further evaluation is indicated if the clinical picture supports[24].

Sonographic examination of endometrium is not always accurate as there can be inter and intra examiner variation. Level of experience, skill of the examiner and some patient factors are unfavorable for the procedure. Transvaginal ultrasonography is also not always reproducible. Therefore, in all the cases where ultrasonography is not possible, considering the risk factors and continuation of per vaginal bleeding, an alternative method should be advised.

Saline Infusion Sonogram (SIS)

Saline infusion sonogram is done by infusing saline into the uterine cavity using a catheter through the cervix before performing trans vaginal ultrasonogram. This will separate two endometrial lining and allows to measure endometrial thickness more accurately and visualize intracavitary lesions such as polyps and fibroids.

The meta-analysis done by de Kroon et al. on the accuracy of SIS on analyzing the endometrium in patients with abnormal uterine bleeding, concluded that its ability in evaluating uterine cavity in pre and postmenopausal women[17]. But it was more feasible on premenopausal women than post menopausal women (success rate 95% and 86% respectively). The pooled sensitivity and pooled specificity of SIS in uterine cavity evaluation were 95% and 88% respectively, the likelihood ratios were 8.23 and 0.06 respectively and the post-test probabilities were 0.91 and 0.07 respec-

tively. But this method can be little discomforting among postmenopausal women than conventional TVS reducing patient's acceptance and technical failure can also be encountered.

Gel instillation sonography is a feasible, accurate alternative for SIS in the evaluation of women with abnormal bleeding, and has fewer technical failures[18].

Endometrial Sampling

Dilatation and curettage was used in the past to obtain endometrial sampling as a blind procedure. But this method is now outdated, as it is considered as a minor surgical procedure which required the patient to get admitted and to undergo general or regional anaesthesia, while there are novel methods that has been developed for endometrial sampling as outpatient procedure. Complications due to anaesthesia, uterine perforation and bleeding are the main possible complication of dilatation and curettage. A Clinical trial conducted by Sanam et al. revealed that dilatation and curettage has 100% sensitivity, specificity, positive and negative predictive values and accuracy, where the values with Pipelles sampling was comparable with the results which is a very cheap, easy and reliable method with high patient acceptancy[25].

The Pipelles device consists of a disposable plastic outer tube measuring 3mm in diameter, within it, is a closely fitting rod. When the rod is withdrawn, it creates a vacuum that sucks in a section of endometrium, sufficient to give a histological report. Because of its smaller diameter it is very easier to insert through the cervix without needing any anaesthesia and cervical grasping. A meta-analysis done by Dijkhuizen et al. shows Pipelle device and the Vabra device (an endometrial aspiration device) has shown a very good detection rates on diagnosing endometrial carcinoma 99.6% and 97.1% respectively[19]. Pipelle was the most sensitive device with the sensitivity of 81% and the specificity of both methods was >98%. But insertion of the device may be difficult in postmenopausal women as the cervix gets narrowed and it is not an infrequent thing that the histology report mentions as insufficient sampling.

6% out of 66 patients with insufficient sampling were diagnosed to have endometrial carcinoma or atypical hyperplasia subsequently by a prospective study performed by Van Doorn et al[20]. This finding implies that women with an insufficient sample and an endometrial thickness of 5mm should not be reassured. The patient can be reassured with inadequate sample if the hysteroscopic and sonographic findings are also reassuring only, according to the controlled regression analysis by Bakour et al[21].

Hysteroscopy

Hysteroscopy provides a direct visualization of the endometrial cavity compared to traditional blind procedures. It allows to take selective endometrial sampling only from the suspicious lesions, and therefore having a very low likelihood ratio of endometrial carcinoma when there is a negative hysteroscopy[22]. Study conducted by Epstein E et al. on the accuracy of TVS, SIS and Hysteroscopy on diagnosing endometrial pathology revealed that hysteroscopy is always superior to other two methods with regard to differentiating between malignant and benign lesions (sensitivity 84%, 44%, and 60%; false-positive rate 15%, 6% and 10%, respectively)[16]. Therefore, outpatient hysteroscopy and biopsy are still the methods of choice[17].

There are rigid and flexible hysteroscopes that can be used in outpatient procedures. Although flexible hysteroscopy is comparatively less painful, rigid hysteroscopy provides superior optical qualities and higher success rates. A liquid with low viscosity (normal saline) or gas (CO_2) can be used as expansion medium and continuous flow of fluid will distend the vagina and the cervical canal and allows the easy entry into the endometrial

cavity. Introduction of very small diameter hysteroscopes (3mm), and vaginoscopic non-touch method has reduced insertion of speculum and cervical grasp by tenaculum and has increased patient acceptancy and minimized the requirement of anaesthesia, making the office hysteroscopy as a currently popular method. In some instances, patient can develop pain due to cervical and uterine distension, therefore, a low threshold should be kept for local anaesthesia. Sometimes vision may be poor due to bleeding and fluid collection. In-patient hysteroscopy may be required if the outpatient hysteroscopy is inadequate or difficult. The sensitivity, specificity, accuracy and positive and negative predictive values of hysteroscopy are 94.4%, 97.0%, 96.8%, 68% and 99.6%, respectively, on diagnosing endometrial carcinoma or hyperplasia according to a systematic quantitative review conducted by Clark et al[22].

Three-dimensional Ultrasonography

Three-dimensional ultrasonography will provide a 3D view of the endometrium and the uterus, needs good technical skills than conventional 2D ultrasonography and availability is also limited. Studies show that the diagnostic performance of 3D ultrasonography is not superior to 2D ultrasonogram on differentiating benign and malignant endometrial lesions in women present with postmenopausal bleeding.

MRI (Magnetic Resonance Imaging)

MRI images help in differentiating endometrial polyps from endometrial malignancies by morphology and accurate detection of myometrial and cervical invasion. It has a mean sensitivity of 79%, specificity of 89%, accuracy of 86%, positive predictive value of 82%, and negative predictive value of 88% for diagnosis of carcinoma[33]. But MRI is not frequently used as a routine investigation in postmenopausal bleeding, as its limited availability and less cost effectiveness compared to other methods.

Table 1. Sensitivity, specificity, positive and negative predictive values of investigations, frequently used for the evaluation of postmenopausal bleeding in diagnosis of endometrial carcinoma.

Diagnostic test	Sensitivity	Specificity	positive predictive value	Negative predictive value
TVS (ET-4mm as cut off)	100%	61%	39%	100%
TVS (ET-5mm as cut off)[19,32]	88-95%	45-96%	31%	97.5%
SIS	95%	88%	16%	97%
Pipelle biopsy[31]	84-99.6%	98-99%	94%	94%
Novac Curratage	90-100%	100%	100%	98-100%
Hysteroscopic guided biopsy	94%	97%	68%	99.6%
MRI	79%	89%	82%	88%

(TVS - Trans Vaginal Sonogram, ET - Endometrial Thickness, SIS - Saline Infusion Sonography, MRI - Magnetic Resonance Imaging)

Summary and Conclusion

As a summary, when a postmenopausal woman comes with bleeding and having negative cervical smear, normal cervix and vagina on speculum examination, Trans-vaginal ultrasonography and endometrial thickness assessment can be offered as first line investigation. Even if the endometrial thickness is less than 4mm endometrial sampling can be considered if there are associated risk factors, such as, recurrence of bleeding, fluid in the cavity, irregular endometrium and other risk factors for endometrial carcinoma (lack of evidence yet). If the endometrial thickness is >4 mm, blind or hysteroscopic guided endometrial sampling, is recommended depending on the availability of the resources and to be managed according to the pathology. If the histopathology sample comes as insufficient, patient can be reassured provided there are hysteroscopic evidence of endometrial atrophy. If there is no evidence of atrophy or recurrence bleeding even with atrophy, inward hysteroscopy and biopsy is recommended for further evaluation[26]. The sensitivity, specificity, positive and negative predictive values of each investigation is summarized in Table 1.

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