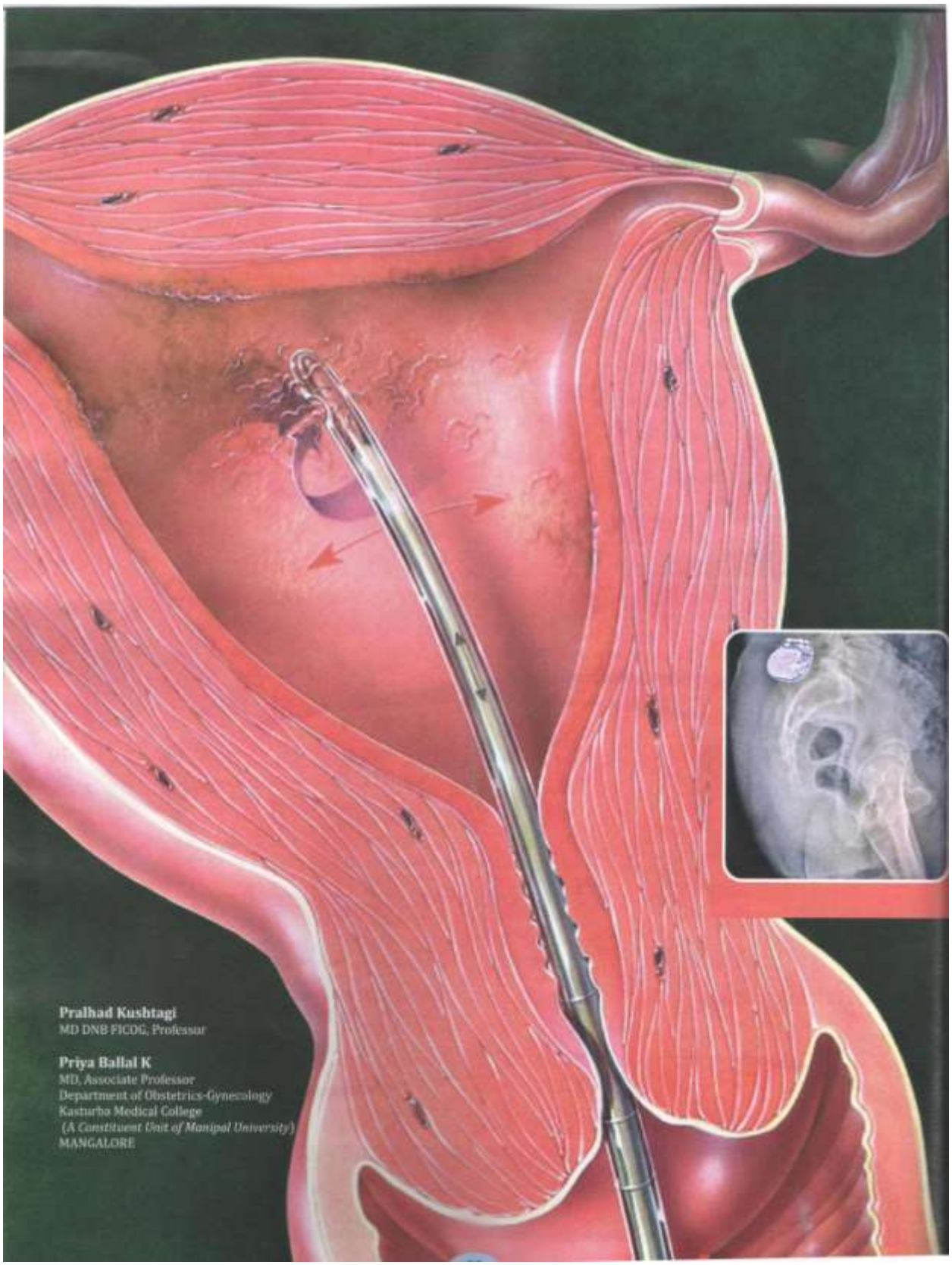

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Screening for Endometrial Cancer – Present Status

Summary
Incidence of endometrial cancer is increasing in parallel with the longer life expectancy, increasing obesity and falling fertility rates. Screening of asymptomatic postmenopausal women has not shown significant advantage and studies have not addressed to the survival benefit. Postmenopausal bleeding is the leading symptom requiring attention. Transvaginal sonographic measurement of endometrial thickness may help in triaging the women requiring endometrial biopsy for diagnosis. Women at high risk should be monitored even before menopause and those with hereditary nonpolyposis colorectal cancer mutations need surveillance from as early as 35 years. Education of patients and physicians about the significance of postmenopausal bleeding is the greatest screening tool available.

Keywords: Endometrial cancer; screening; endometrial thickness; transvaginal sonography; endometrial biopsy; biomarkers

The global burden of new cancer cases was estimated to double by the year 2020 with 70% occurring in the developing world.[1] Endometrial carcinoma (EC) is one of the most common gynecological malignancies in developed countries and is emerging as a significant cause for cancer related mortality in women from other parts of the world. Incidence of EC is reported to be increasing by an average of 1.1%.[2] The changing demographic profile with increasing incidence of obesity and the falling fertility rates could be the contributing factors for this. Obesity is reaching epidemic proportions and India is no exemption with 5% of country's population getting morbidly obese.[3] The total fertility rate too is showing a steady decline. The life time relative risk of developing EC increases from 3 in overweight woman to 10 in the morbidly obese.[4] With the increasing life expectancy all over the world more so among women, the occurrence of EC is likely to assume a significant public health problem.[5]

In this light, endeavour of the authors is to review the feasibility of screening for EC from among the landscape of methods, devices and markers made available and debated in the literature.

Who are likely to develop EC?

Women who develop EC are usually in their 6th decade of life and are nulliparous, have late onset of menopause or are subfertile. There seems to be a direct association between the metabolic syndrome and individual factors, except for cholesterol, suggesting that it is not obesity alone that confers the risk.[6] Unopposed estrogen stimulation on endometrium in women with estrogen producing ovarian tumors, recurrent anovulation as in Polycystic Ovarian Disease, are other risk factors for the disease. Women with family history of endometrial cancer appear to be at increased risk and especially those with Lynch syndrome (Hereditary Non-poplyposis Colon Cancer, HNPCC) have a 22-50% lifetime risk of developing endometrial cancer. These women were also found to develop EC at a younger age than those without family history. Breast cancer patients on Tamoxifen are reported to have increased incidence of EC, but when confounding factors are corrected, the risk of does not appear to be increased in them.[7]

Episodes of vaginal bleeding in menopausal women are the earliest symptom and bring them to the physician early in disease. But, it is only 20 % of women who present with post-menopausal bleeding have EC.[8] When EC occurs in premenstrual women, changes in menstrual pattern are subtle indicators and clinician needs to have high index of suspicion to diagnose early in the at-risk groups.

Is it possible to screen for EC?

When the risk factors are known (Box 1) and that too when precursor lesions for EC with their risk propensity is documented, (Box 2) it should be an easy

Box 1
Factors and the Life-time Risk of development of Endometrial Cancer[4]

Factor	Relative Risk (%)
Nulliparity	2-3
Late menopause	2.4
Obesity	
• Overweight	3
• Obese	10
Diabetes Mellitus	2-8
Unopposed Estrogen	4-8
Atypical Endometrial Hyperplasia	8-29
Tamoxifen user	2-3
HNPCC	20
• Germline mutations in mismatch repair genes: MLH1, MSH2, MSH6	40-60

Risk of Endometrial Cancer in precursor lesions 4

Type of Endometrial Hyperplasia	Progression to Cancer (%)
Simple - Cystic without Atypia	1
Complex – Adenomatous without Atypia	3
Atypical	
• Simple Cystic with Atypia	8
• Complex, Adenomatous with Atypia	29

- Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia: a long term study of "untreated" hyperplasia in 170 patients. Cancer 1985; 56: 403-412.

task to plan the preventive strategy. Endometrial hyperplasia under the influence of unopposed estrogen stimulation may develop nuclear atypia leading to EC. The exfoliated endometrial cells provide an opportunity to exploit and repeat the success of Pap smear that has reduced significantly the mortality from cancer cervix. The endometrium is accessible to be aspirated, curetted, visualised and biopsied; it can also be imaged. These are the means and the tools that have been studied to explore their application in screening for the disease.

Endometrial cells on Pap smear

It is reported that endometrial cells are identified on cervical smear. Presence of benign appearing endometrial cells is noted in 10-25% of asymptomatic women with EC giving rise to optimism for the relevance in screening. [6, 11] Studies of cervical smears showing endometrial cells have revealed 67% sensitivity and 78% specificity for EC and that for endocervical smear/ aspiration the sensitivity of 80% and 75% specificity. [12] The positive predictive value obtained for presence of endometrial cells on smear was 15% and that with atypical cells on cytology was 50%. In smear positive postmenopausal women detection of abnormal endometrial histology or EC is markedly variable from 0.8-12%. [13-15] These observations have made Pap smear a less than ideal method of screening for EC. Despite the changes made in Bethesda system for reporting endometrial cells in smear, the detection rates for EC have not significantly increased, [16] but have only resulted in increase in proportion of endometrial biopsies.

The detection rate of EC with different modalities of exfoliated cell collection have not been encouraging **(Table 1)** and addition of aspiration to Pap smear did not reach the acceptable levels. This is

Table 1
Detection Rate of Endometrial Cancer according to the source for exfoliated cells

Source	Detection Rate (%)
Pap smear	50-60%
Endometrial aspiration	70-85%
Pap + Aspiration	85%
Posterior vaginal pool smear	50

despite efforts to improve the yield and interpretation using liquid based cytology or adoption criteria based on composition and architecture of large tissue fragments in smears. Difficulty in interpreting the endometrial cells on the smears is another problem contributing to inaccuracy. Since most cases with significant endometrial pathology were the women with clinical symptoms followed up on finding endometrial cells, and the follow-up of asymptomatic women with endometrial cells has not helped identify significant cases, [17] debate against the usefulness of reporting their presence.

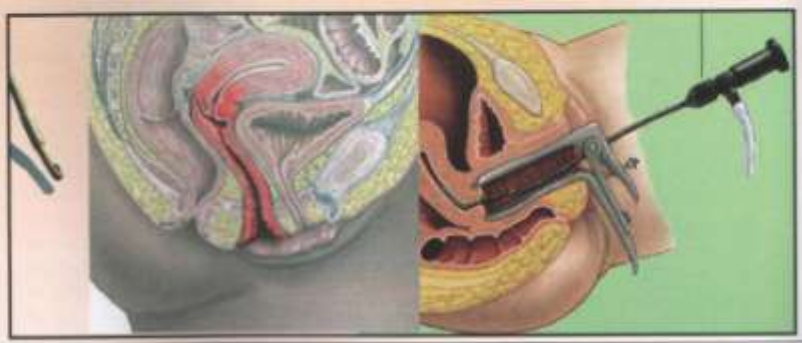
Endometrial Biopsy

Direct uterine sampling with the brush sampler using a liquid-based preparation method for the detection of endometrial cancer and atypical hyperplasia provided 95% sensitivity and 96% specificity. [18] The study being heavily weighted with EC patients (81 of 139 patients), the findings fail to plead for translating them into screening program. In a study of 917 women for cytohistologic correlation, the correlation was possible in only 50% of cases and in 39% of cases biopsies were reported to be insufficient for tissue diagnosis. [19] Whenever blind endometrial curettage was used, in 60% cases less than half the uterine cavity was curetted. [20] Most of the endometrial biopsy studies were on symptomatic women. Inability to provide adequate tissue for diagnosis and the vague criteria used to define adequacy along with the problems of physical discomfort for the procedure and possible complications of hemorrhage, infection and perforation do not make it the procedure worth considering for screening. There are no randomised control trials showing reduction in mortality associated with sampling based screening program and it remains as tool to provide tissue for a diagnostic test.

Hysteroscopy

Hysteroscopic examination and the directed biopsy has provided near 90% of sensitivity and specificity through different studies. Although most were in symptomatic women, the diagnostic accuracy was similar in the studies on asymptomatic women. [21] The subsequent reports have confirmed supremacy of seeing and biopsying, it remains a tool for obtaining tissue for diagnostic test. Inability to replicate the sensitivity in diffuse lesions, unavailability at all health care facilities and invasiveness limit its use. Moreover, hysteroscopy has not been evaluated as a screening tool.

Patients with HNPCC also known as Lynch Syndrome are at an increased risk of developing colon, gastric, endometrial and ovarian cancer. Lynch syndrome mutations are found in 1.8% of endometrial and 2.2% of colorectal



cancers. The cumulative incidence of EC in HNPCC carriers is 20-60% by the age of 70 and the lifetime risk differs based on germ-line mutation. The germ-line mutations found in mismatch repair are for genes MSH2, MSH6, MLH1, and PMS2. MSH1 has the lifetime risk of 25% and that for MSH2 is reported to be 35-40% at 70 years.[22] Identifying gene mutations in these patients could help by subjecting them to screening and early diagnosis. Individuals can be screened by immunohistochemistry testing which stains proteins produced by DNA repair genes in lynch syndrome. Thus individuals who carry these mutations and those with positive family history for these conditions should be subjected to careful screening. Although no studies exist to show the benefit of screening in them, various cancer bodies across the globe recommend yearly screening subjecting them to annual transvaginal sonography and biopsy of the endometrium starting at the 35 years of age.[23]

Biomarkers

Biomarkers have been used in the diagnosis and prognostication of ovarian cancer but very few studies have evaluated the use of markers such as CA 125 in EC due to early presentation of symptoms unlike ovarian cancer. However, higher incidence of endometrial cancer and poor prognosis in late stage disease warrant the need for further research in biomarkers for EC.

Ca 125 levels are elevated in EC (below cut off levels for ovarian cancer). CA 125 and CA15-3 were studied for their utility in screening. It was concluded that they may in some way be associated with the prognostic factors, but are best useful in monitoring the response to treatment.[24] Use of CA125 may be restricted to diagnosis of advanced stage of EC where its levels are markedly elevated.[25]

Promising value of **Human Epididymis-specific 4-disulfide Core Protein** (HE4) which is expressed in variety of tissues including endometrium was explored and as a single marker was found to be more accurate for the diagnosis and addition of CA125 estimation improved the sensitivity regardless of stage of the disease.[26]

Advances made in clinical proteomics have propelled the scientists into an exciting period of discovery of new cancer biomarkers. Development of multimarker panel for early detection of EC is one such attempt. Overview of various markers in current use, lack of or otherwise of sensitivity and specificity for them and the discussion about the novel biomarkers of the future is recently made by Ueda and colleagues.[27] Some have used panels of two,[28] three[29] and as high as 13 markers[30] on the panel to find out their usefulness in screening and/ or early detection of EC. Analysing the use of five markers in the panel, Yukovetsk Z et al[31] placed **Prolactin** to be superior to other markers like Thyroid Stimulating Hormone, Growth Hormone, Eotaxin and E-selectin. They did not find any advantage with addition of other markers. Prolactin with high sensitivity and specificity of 98% helped to discriminate EC from ovarian and breast cancers.

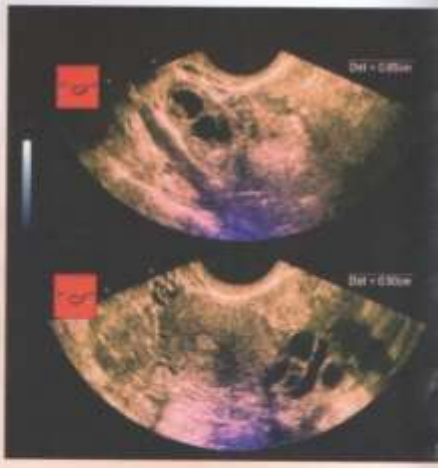
Table 2
Novel Biomarkers and Detection Rate of Endometrial Cancer 27

Biomarker	Rate (%)
CA 125	11-43
CA 72-4	22-32
CA 15-3	24-32
CEA (*Carcino-Embryonic Antigen*)	14-22
IAP (*Immuno Acidic Protein*)	55-76
M-CS F(*Macrophage Colony Stimulating Factor*)	25-73
HE4	46

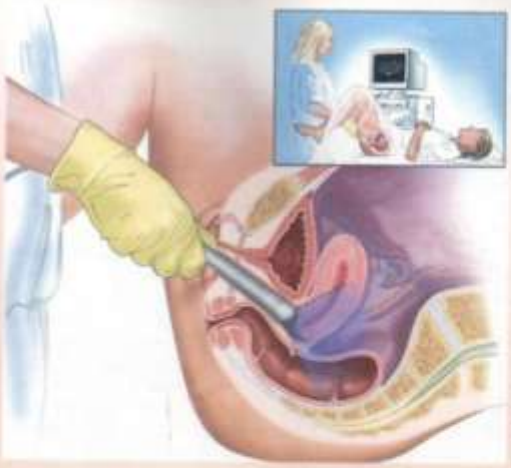
Although there are so many tumor markers that are investigated, none seem to have significant EC detection rate (Table 2) that could catapult them to be considered for screening the population.

Imaging – Endometrial Thickness (ET) on Transvaginal sonography

There is confusion regarding the cut off of ET to be taken as suggestive of pathology or occurrence of pathology. ET of less than 4 or 5 mm in women with post-menopausal bleeding is less likely to be associated with EC. Literature is replete with studies on ET as marker for EC. Many of them have small numbers studied or are studied in symptomatic women. One of the claimed to be largest observations regarding usefulness of transvaginal ultrasound giving way for its use as a screening test for EC has come from the collaborative trial of ovarian cancer screening in United Kingdom (UKCTOCS). The publication correlated ET and any endometrial abnormality detected during screening with a subsequent diagnosis of EC or atypical endometrial hyperplasia. It screened 48,230 women and 136 were diagnosed to have either EC or atypical endometrial hyperplasia. The optimal cut off for endometrial thickness in women with abnormal histology was 5.15mm, with sensitivity of 80.5% and specificity of 86.2%. But the restriction of analysis to 96 asymptomatic women who developed endometrial cancer, a cut off of 5mm yielded sensitivity of 77.1% and specificity of 85.8%. Using patient risk factors to help stratify the group into quartiles at risk, 39.5% of EC and atypical endometrial hyperplasia were identified in that group using a cut off for ET at 6.75mm. This provided 84.3% sensitivity and specificity of 89.9%.[32] Although valuable information about the usefulness of ET in foreseeing EC is provided, the findings do not by themselves suggest acceptance of ET as a tool to screen postmenopausal women for EC. Including this study, no earlier reports involving evaluation of ET, did not study the effect of screening on survival or death from the disease. None of the studies had protocol driven intervention



as the end point in their design. It is possible that sonologist measuring ET could be biased since it will be difficult to restrain one from enquiring about postmenopausal bleeding. Studies have shown that no difference in survival rates exist among women thus diagnosed through sonography screening and that in those detected through early recognition of symptoms.[9] Therefore, it is too early to accept ET measurements to screen asymptomatic postmenopausal women for EC on routine basis.



Is screening required?

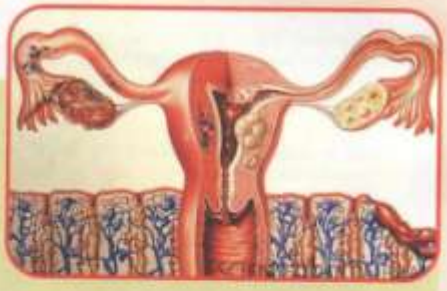
Occurrence of postmenopausal bleeding, more often than not, initiates evaluation leading to diagnosis of EC in the woman. Generally EC presents in early stage and can be treated without extensive surgery. Survival chances are unaffected if detected and treated in early stage. Not all endometrial cancers are a threat to life, since they are slow growing tumours with onset at later years of life. The diagnosis of EC seemed to have made no difference as shown by autopsy incidentally detecting the disease in the elderly.[4] Although described as the benign cancer, high morbidity and mortality in late stages of EC warrant early detection and treatment.

Not all cases with postmenopausal bleeding will harbour EC. Abnormal histology is the cause in only 15-20% cases. Thin endometrium due to estrogen depletion in menopause is the cause of postmenopausal bleeding in 30% of cases. For sometime progesterone challenge was used to assess presence of endogenous estrogen.[10] Withdrawal bleeding warrants further evaluation with endometrial biopsy. Progesterone challenge test is not a widely accepted line of management, but it helps in triaging the patients leading to early diagnosis.

Tamoxifen users are a special group of patients who require a separate consideration. The nonsteroidal antiestrogen agent used widely in adjunctive therapy for breast cancer, pushes these women to be at 2-3 times increased risk for development of EC than that in their age matched controls.[11] Tamoxifen induced subepithelial stromal hypertrophy render poor correlation between sonographic ET measurements and abnormal pathology in asymptomatic tamoxifen users.[12] Ultrasonography with ET as marker will not be effective in increasing the early detection of EC in them. These women should be educated about the risks of EC, encouraged to promptly report any abnormal bleeding or vaginal discharge, and monitored yearly for symptoms.

High index of suspicion is required to make diagnosis early in women who develop EC earlier than the usual age. Women who develop EC when younger are those who are at higher risk of developing EC. (Box 1) Probably in these women screening for EC is justified to make an early diagnosis. Suspicion of EC should be excluded in postmenopausal women with pyometra.

Women with history of familial cancer, HNPCC will benefit for genetic testing for mismatch repair genes so that they can be offered counseling and increased surveillance for EC in addition to other carcinomas. It is recommended that they be subjected to yearly transvaginal sonography and endometrial biopsy from 35 years of age.



Conclusion

Endometrial cancer is slow growing and has late onset. Current levels of evidence do not support routine endometrial cancer screening in the general population. The greatest screening tool available is education of patients and physicians about the significance of postmenopausal bleeding and the need for further appropriate investigations to help arrive at an early diagnosis.

Women with factors assigning higher risk status should be monitored closely for symptoms. Those with positive family history for HNPCC may need surveillance from the age of 35 years.

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