MANAGEMENT OF POSTMENOPAUSAL BLEEDING

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ABSTRACT
Aim: To describe the appropriate management of women with postmenopausal bleeding (PMB).
Study Design: Descriptive study in one year (Jan – Dec, 2012).
Method: All patients with postmenopausal bleeding in one year were investigated and managed. Basic investigation was trans-vaginal sonography. Those with endometrial thickness more than 4 mm were further investigated by dilatation and curettage, then management strategy was planned according to the cause.
Result: A total of 23 patients were presented with postmenopausal bleeding (endometrial thickness > 4 mm) during one year. Among them 11 case were having first episode and the remaining had recurrent bleeding. Endometrial hyperplasia (simple) was the common pathology (52%), in whom surgical management (hysterectomy) was performed in 60% cases. Three cases (13%) were managed with MIRENA (levonorgestrel releasing intrauterine system). Two case were diagnosed as endometrial carcinoma. Both of them were having advanced stage and were referred to Shaukat Khanum Hospital Lahore.
Conclusion: Trans-vaginal sonography can reliably assess thickness and morphology of endometrium, thus risk group can be identified. Endometrial hyperplasia is the major cause of PMB. Dilatation and curettage, can provide sufficient diagnostic accuracy. Hysterectomy remained the main management of PMB patients.
Key words: Endometrial sampling, endometrial thickness, postmenopausal bleeding, transvaginal ultrasonography.

INTRODUCTION
Postmenopausal bleeding (PMB), defined as uterine bleeding occurring after at least 1 year of menopausal amenorrhoea, is a common clinical condition with an incidence of 10% immediately after menopause. Patient with PMB have a 10 – 15% chance of having endometrial carcinoma. Therefore, the clinical approach to PMB requires prompt and effective evaluation to exclude cancer in the genital tract or pre-cancerous lesions of the endometrium. However, vaginal atrophy, and benign focal lesions such as endometrial polyps and hyperplasia are estimated to be responsible for it in about 40% of cases.
Endometrial cancer is the most common gynaecological malignancy. Risk factors include obesity, unopposed estrogens, polycystic ovary syndrome, and nulliparity. Ninety percent of women with endometrial carcinoma present with vaginal bleeding. Unlike ovarian cancer, endometrial cancer often presents at an early stage when there is a possibility of curative treatment by hysterectomy; early, accurate and timely diagnosis is therefore important.

PMB is usually attributed to an intrauterine source, but may arise from the vulva, vagina, cervix, fallopian tubes, or it may be related to ovarian pathology. Haematometra may also result from cervical stenosis. The bleeding may originate from extra-genital sites as the urethra or bladder, and the rectum or bowel.

METHODS AND PATIENTS
This was descriptive study, conducted in gynae department of the teaching hospital of Gomal Medical College Dera Ismail Khan.
A total of 41 patients presented with PMB in one year (during the study period).
All patients were subjected to screening by trans-vaginal sonography. Eight patients (%) had endometrial thickness less than 4 mm so they were given just reassurance and no further invasive investigation was carried out. Patient with bleeding from urethra and rectum were also excluded from study.
Twenty three patients, who had endometrial thickness more than 4 mm were subjected to dilatation
and curettage, and specimen was sent to Shaukat Khanum Cancer Hospital through their collection centers.

The patients were evaluated clinically and then in the light of histopathological report management strategies were planned for individual patients.

Two patients, who turned out to be the carcinoma endometrium, were in advanced stage and they electively opted for Shaukat Khanum Hospital and we referred them without further investigation.

All patients were educated about strategic follow-up plan. This follow-up plan also include those who were only on reassurance and no management was done. This will give further information with ongoing visits.

RESULTS
The main cause for postmenopausal bleeding was endometrial hyperplasia (52.1%). Only one patient was reported atypical and others histopathology was simple hyperplasia. Endometrial polyp was found in 26% cases, sub mucosal fibroids 13% and only two patients were diagnosed as carcinoma endometrium.

Regarding management option, 60% had hysterectomy with bilateral salpingo oophorectomy. Three patients with simple hyperplasia were managed with MIRENA, (intrauterine systems) (IUS). Total patients with endometrial polyp were 26%, four among them (17%), underwent simple polypectomy, while two patients with polyp had recurrent PMB, event after polypectomy, so ultimately hysterectomy was

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<th>Table 2: Management Options for PMB.</th>
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performed.

Commonest medical disorder found was hypertension (69%), only 7 patients have associated diabetes mellitus, among them one patient of carcinoma endometrium was diabetic and another one was having hypertension. Asthma was present in 2 cases.

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<th>S. No.</th>
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<td>1.</td>
<td>Diabetes Mellitus</td>
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<td>2.</td>
<td>Hypertension</td>
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<td>3.</td>
<td>Asthma</td>
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DISCUSSION
Patient specifications and the risk of endometrial cancer is the main concern of PMB. The pre-test probability of endometrial cancer of women with PMB is about 10%, but various clinical specifications may alter this proportion, which rises from 1% in women aged < 50 years to almost 25% in women aged > 80% years. The incidence of cancer is higher in women with PMB and obesity (18%) or with PMB and diabetes the incidence may be as high as 29%.5

Since it was introduced in the 1980s, trans-vaginal sonography (TVS) has become widely used in the evaluation of woman with PMB. Before TVS, women with PMB underwent dilatation and curettage. The relatively non-invasive nature of the TVS makes it more acceptable, especially to older women. The likelihood of important pathology (cancer) being present increases with increasing thickness of endometrium (Figure 1).6

TVS can reliably assess thickness of the endometrium and can thus identify a group of women with PMB who have a thin endometrium (≤ 4 mm) and are therefore unlikely to have endometrial cancer.
cer (Figure 2). Endometrial sampling is therefore not recommended below this cut-off value.6–9

To date, four meta-analysis have been published; each has used different methods to determine the accuracy of TVS in diagnosing endometrial abnormalities in women with PMB.

The most sited meta-analyses by Smith-Bindman et al.3 included 5892 women from 35 prospective studies that compared endometrial thickness measured at TVS to presence or absence of endometrial carcinoma on histology. There is only one study that looked at follow-up of women with PMB and an endometrial thickness of < 4 mm.10 It showed that none of the women with the expectant management developed cancer over 1 year of follow-up.

The comprehensive systematic review of Gupta et al.7 included only best quality studies (only four studies were included). For an endometrial thickness of ≤ 5 mm, the review concludes that, using the evidence from the best quality studies, a negative result at ≤ 5 mm cut off rules out endometrial pathology with a high degree of certainty.

In their meta-analysis, Tabor et al.8 included only studies from which they were able to extract the original data from the authors. The median endometrial thickness was calculated per study / centre then pooled data for endometrial thickness were used with a sensitivity of 96% and specificity of 50% and 4% false – negative rate. In their opinion, endometrial thickness measurement does not reduce the need of invasive diagnostic testing. Timmermans et al.11 conducted meta-analytic strategies whereby 79 primary investigators were conducted to obtain the individual patient data of their reported studies of which 13 could provide data. Data on 2896 individuals, of whom 259 had cancer, were analyzed. It was conclude that previous meta-analyses on endometrial thickness measurement have probably overestimated its diagnostic accuracy in the detection of carcinoma.

Meaningful assessment of the endometrial (thickness and morphology) by ultrasonography is not possible in all patients. In such cases or if bleeding persists despite negative initial evaluation, alternative methods are indicated.9

Saline infusions sonography (SIS) involves the infusions of saline into the uterine cavity during ultrasound to separate the two walls of the endometrium, which allows their thickness to be measured. It also allows the evaluation of intra-cavity lesions such as fibroids or polyps. Meta – analyses, de Kroon et al.12 concluded that SIS is accurate in the evaluation of the uterine cavity in pre- and postmenopausal women. Therefore outpatient biopsy and hysteroscopy are still the methods of choice.

Patients with an increased endometrial thickness should undergo further invasive testing. Dilatation and curettage is now considered to be an outdated practice and is replaced by less invasive outpatient evaluation using endometrial biopsy devices and outpatient hysteroscopy – guided biopsies.

In the next meta – analyses of Dijkhuizen et al.13 different endometrial biopsies devises were compared. In postmenopausal women endometrial sampling with both the Pipelle device (Pipelle de Cornier, Paris, France) and the Vebra device (Berkeley Med Devices, Inv; Richmond, CA, USA) were very sensitive techniques for the detection of endometrial carcinoma, with detection rates of 99.6% and 97.1% respectively but we still rely upon conventional curettage because of minimum facilities in our district and the amount of tissue obtained by office sampling is sometimes insufficient for histological diagnosis. In those cases the clinician is an doubt whether or not to proceed with more invasive testing or to rely on the negative biopsy in a prospective study performed by Van Doorn et al. finding implies that women with insufficient and endometrial thickness of > 5 mm should not be reassured.14

It would appear from the controlled regression analyses by Bakour et al.15 that clinicians can be confident in reassuring women with an insufficient sample on outpatient endometrial biopsy, provided that the hysteroscopic and sonographic endometrial assessment is consistent with endometrial atrophy. This means that it is reasonable to reassure and discharge women with an insufficient endometrial sample with negative scan (≤ 4 mm) without the need to expose them to hysteroscopy and curettage. The need for reinvestigation on recurrence of symptoms should be borne in mind; for example, a small polyp in an atrophic endometrium may not be detected be-
cause the endometrial sampling does not yield enough cells. Compared with traditional methods such as curettage, hysteroscopy offers the possibility of visualizing macroscopically focal abnormalities and taking directed biopsies. Outpatient hysteroscopy allows direct visualization of the uterine cavity, which is particularly useful for excluding endometrial polyps or fibroids. With the development of smaller diameter hysteroscopic symptoms and the introduction of a ‘vaginoscopic’ approach, patient acceptance has improved and hysteroscopy nowadays can be performed in an outpatient setting without anesthesia. Inpatient hysteroscopy is required only if the outpatient assessment is either inadequate or impossible to perform.

Clark et al.\textsuperscript{16} conducted a systematic quantitative review looking at the accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia in women with abnormal uterine bleeding. The review concluded that the diagnostic accuracy of hysteroscopy is high for endometrial cancer but only moderate for endometrial diseases defined as cancer and / or hyperplasia.

Diagnostic strategies for postmenopausal bleeding depends upon the true clinical value of a test lies in the information obtained beyond what was already known from the history and examination. In the evaluation of Diagnosis test, Khan et al. built a step-wise four multivariable approach to take into account the clinical context. The first model provides a valid estimate of the combined predictive value of the clinical history variables and tests (ultrasonography or hysteroscopy, or the ultrasonography and hysteroscopy combined). The predictive ability of the addition of both ultrasonography and hysteroscopy is markedly increased.\textsuperscript{19-20}

Similarly, to determine the most cost – effective testing strategy for diagnosing endometrial carcinoma in women with PMB, Clark et al. constructed a decision model the strategy of TVS as initial investigation with a cut – off 5 mm and endometrial biopsy were most cost – effective. Khan et al. proposed to evaluate tests using a multivariable approach and proposed the use of individual patient data meta – analyses.\textsuperscript{21-22}

Individual patient characteristic including age, time since menopause, obesity hypertension and diabetes mellitus are known risk factors of endometrial carcinoma. However, current policy is based not on these risk factors but on endometrial thickness.

TVS has been suggested as screening test. The UK Collaborative Trial for Ovarian Cancer Screening (JKCTOCS), which aims to establish the impact of ovarian cancer screening on ovarian cancer mortality, is the world’s largest collaborative screening trial, involves > 200000 UK women and reports in 2015. Data from the assessment of endometrial thickness and morphology in the course of this trial have provided invaluable information on endometrial thickness in asymptomatic women. These findings concluded that TVS screening for endometrial cancer has high sensitivity in postmenopausal women.\textsuperscript{21-22}

Schmidt et al.\textsuperscript{23} Proposed that hysteroscopy represents an easy, safe and effective methods for the investigation of asymptomatic women with a thickened endometrium (> 6 mm). The commonest pathology was endometrial polyps (74.3%).

Curcic et al.\textsuperscript{24} concluded that the presence of endometrial fluid detected by TVS is a good marker for pathological changes of the endometrium in a postmenopausal women if the endometrial thickness is < 4 mm. If the endometrial is < 4 mm, the presence of endometrial fluid is not an indication for further invasive investigation.

In a multicenter study by Ferrazzi et al.\textsuperscript{25} on 1152 asymptomatic women and 770 women with PMB, only one case (0.1%) of stage 1, grade 1 endometrial carcinoma on a polyp with a mean diameter of 40 mm was observed in asymptomatic women.

The authors concluded that follow-up and / or
treatment of endometrial polyps incidentally diagnosed in asymptomatic postmenopausal patients could be safely restricted to a few select cases based on polyp diameter.

Endometrial polyps are frequent findings in postmenopausal bleeding. A cohort study investigated the efficacy of treatment regarding recurrent bleeding, and found that the recurrent rate of postmenopausal bleeding in women with endometrial thickness > 4 mm was 20%. There was no difference with respect to recurrence rate between patients with polyp removal, patients with a normal hysteroscopy, and patients with office endometrial sampling alone at the initial workup.

In their nested case–control study of endometrial hyperplasia (EH) progression, Lacey et al. summarized the 34-year experience of the included 138 cases, which were diagnosed with EH and then with carcinoma.

Atypical hyperplasia (AH) significantly increased the relative risk of carcinoma (14; 95% CI 5 – 38). This risk justifies discussing the management of these cases by case in the multidisciplinary gynecology oncology meeting where by hysterectomy is generally recommended for women with endometrial hyperplasia, (atypical) because of a high probability of underlying carcinoma. Treatment of endometrial hyperplasia without atypia in postmenopausal women with a levonorgestrel intrauterine device has been suggested to be an effective and safe alternative.

It is concluded that all patients with postmenopausal bleeding should be screened by trans-vaginal sonography. Those with endometrial thickness > 4 mm should have endometrial sampling. Though total number of study group is very minimal for a scientific conclusion, but still in our under developed medical setups, dilation and curettage is a valid investigation.

Patients with PMB, specially recurrent cases, hysterectomy is main management option. Patients with simple hyperplasia can be effectively managed with MIRENA IUS.

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REFERENCES