Original Article

Abnormal Uterine Bleeding in Peri-Menopausal Age: Diagnostic Options and Accuracy

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Abstract :

Objectives: Various diagnostic techniques have been evolved over the periods to determine the etiology of abnormal uterine bleeding in peri-menopausal women, but their accuracy has not been compared properly. In this study diagnostic accuracy of trans-vaginal sonography (TVS), saline infusion sonography (SIS) and dilatation & curettage (D & C) were compared with hysteroscopic guided biopsy to determine the etiology. **Methods:** In this study, 252 patients had to undergo trans-vaginal sonography and saline infusion sonography in the same sitting followed by hysteroscopic-guided biopsy and dilatation and curettage. All the materials were sent for histopathological examination. **Results:** In determining uterine pathology, positive likelihood ratio (PLR) of TVS, SIS and D & C are 2.81, 7.5 and 3.81 respectively considering hysteroscopy as standard. **Conclusion:** Sensitivity of SIS as a test for detecting pathology in abnormal uterine bleeding (AUB) is high and can be easily performed on out patient basis. D&C has a very low sensitivity and is unacceptable as a screening test for the same conditions.

Key Words: abnormal uterine bleeding, peri-menopause, diagnostic accuracy.

Introduction:

Abnormal uterine bleeding (AUB) in peri-menopausal age group is a common but ill-defined entity which needs proper evaluation. Goldstein et al¹ has defined AUB as "Patients having either metrorrhagia defined as vaginal bleeding separated from expected menses or menorrhagia defined as patients' subjective complaints of either increased duration or increased volume of flow or both". In general, women present themselves to the

gynaecologists whenever there is a departure from their personal menstrual experiences. Variations from the normal cyclical pattern in the peri-menopausal age may be due to physiological hormonal changes on one hand or may be due to neoplastic changes either benign or malignant, on the other hand. Therefore, accurate diagnosis of the causative factor of AUB in this age group is of utmost importance so that appropriate management can be established. Tests have evolved over the years starting from blind dilatation & curettage (D&C), to latest immunohistochemical markers². Relative accuracy of these tests varies and gynecologists all over the world up till now have not reached a consensus on what test to advise first. In this prospective study, diagnostic accuracy of Transvaginal Sonography (TVS), Saline Infusion Sonography (SIS) and Dilatation & Curettage (D&C), were compared in detecting uterine pathology in women

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with AUB. Hysteroscopy guided biopsy was taken as the standard in this study. Hysterectomy and histopathological examination of the entire uterus would provide a more accurate diagnosis but this procedure is neither desirable nor ethical to perform in all perimenopausal patients with AUB.

Methods:

From September 2005 to January 2008, 274 patients of rural Bengal, belonging to the age group 40 to 50 years attending the gynecology out patient department with abnormal uterine bleeding (AUB) of at least three months duration, were included in this prospective study.

Exclusion criteria:

1. Uterus >12weeks size. 2. Hormone therapy within last 6 months. 3. Previous abnormal endometrial biopsy. 4. Positive pregnancy test. 5. Cervical pathology on speculum examination. 6. Abnormal cervical Pap smear. 7. History / evidence suggestive of active pelvic infection.

After thorough history taking, clinical examination and exclusion of cervical malignancy by vaginal speculum & cervical Pap smear examination, informed written consent was taken from every eligible patient. Transvaginal ultrasonography was done followed by SIS in the same sitting. Endometrial cavity was examined from internal Os to fundus in both sagittal and coronal planes. On the following day, hysteroscopy guided

targeted biopsy followed by D & C was done by different gynecologists. Each operator was unaware about the findings of the previous operators. All the tissue samples were examined by competent pathologists and the findings were recorded as follows:

Transvaginal Sonography & Saline Infusion Sonography (Philips, image point-7.5 MHz endocavitary probe):

Endometrial thickness – Thickest part between the basal layers of both anterior and posterior uterine walls. Texture differentiation - Homogenous, heterogeneous and cystic.

Polyp - Intrauterine local overgrowth, hyper echoic relative to myometrium but echogenicity similar to endometrium, connected to endometrial wall by a stalk or forms an acute angle with the underlying endometrium.

Fibroid- Heterogeneous echo texture, hypo echoic relative to myometrium with a broad base or forms an obtuse or right angle with the endometrial wall.

Abnormal / pathological TVS or SIS – double layered endometrial thickness ≥ 5 mm or presence of polyp / fibroid.

Hysteroscopy guided biopsy: (rigid 30-degree hysteroscope and diagnostic sheath of 5mm diameter, Storz Endoscopy)

Hyperplasia - Thick hyper-vascular friable mucosa, mammilated or polypoid in appearance, further classified as simple or atypical by the pathologists.

Table 1:
Findings of diagnostic procedures (n=252)

	TVS	SIS	D&C	H- BIOPSY*
Normal	90	100	142	98
Endometritis			8	12
Simple hyperplasia			59	34
Homogenous hyperplasia	68	50		
Heterogeneous hyperplasia	14	12		
Cystic hyperplasia	27	25		
Cystic adenomatous hyperplasia			18	18
Atypical hyperplasia			10	13
Polyp	18	23	6	31
Fibroid	35	42	9	46

*H- Biopsy: Hysteroscopy guided biopsy

Polyp - Soft intra-cavitary formation, which was easily mobilized and covered by mucosa with endometrial gland and no distended vascular network.

Fibroid - Firm intra-cavitary formation with thin endometrial lining and superficial large blood vessels.

Endometritis - Irregular proliferation of glands and the presence of chronic inflammatory cells e.g. plasma cells, macrophages, and lymphocyte in the endometrial stroma.

Dilatation & Curettage:

Polyp- soft mobile intracavitary mass with narrow base and hyperplastic endometrium.

Fibroid- firm immobile mass with broad base distorting the shape of endometrial cavity.

Abnormal/ pathological D & C - presence of hyperplasia, polyp or fibroid.

Results and analysis:

Complete data was available on 252 patients and the findings have been shown in Table 1. Four patients refused to undergo any invasive procedure, three patients did not allow hysteroscopy and D & C report showed inadequate sample in nine patients. Ovarian neoplasm was detected in six patients during investigation. These 22 patients were excluded from the result analysis. Mean age of the study population was 46.2 years. 88.5% of the patients were multipara and 92% had history of normal delivery.

Comparison between different diagnostic tests were done following the predefined criteria of normal and abnormal findings as one to one correlation between imaging study and histopathology was not always possible. We have also compared the tests in terms of detectable gross pathology viz. fibroid and polyp. 64.7 % of the study population was pathological on TVS, while the corresponding figures for SIS, D & C and hysteroscopy- guided biopsy were 60.1 %, 43.5 % and 61.1 % respectively. TVS, SIS, D & C and hysteroscopy guided biopsy detected polyp and fibroid in 7.2% & 14%, 9.3% & 16.6%, 2.6% & 3.6% and 12% & 18.1% women respectively (Table 2).

Considering the findings of hysteroscopy guided biopsy as reference, sensitivity, specificity and likelihood ratio for the different methods were calculated. Likelihood ratio (LHR) represents the ratio of the likelihood of a positive (or negative) test result with pathology to the likelihood of the same test result in those without pathology³. In the present study, TVS had a sensitivity of 86.4 % and positive likelihood ratio (PLR) of 2.81, while SIS had a much higher sensitivity and PLR of 90.6 % and 7.5 respectively. D & C had a very low sensitivity albeit a high specificity of 61 % and 84 % respectively and a PLR of 3.81. Specificity of D & C was high as it was more likely to miss a pathology in its presence than diagnose one in its absence. Sensitivity, specificity and likelihood ratios for detection of polyp, fibroid and abnormal uterine pathology by each test are outlined in Table 3.

Table 2:
Distributions of test results (n = 252)

Test	Normal	Abnormal			
		Polyp	Fibroid	AUP	TOTAL
TVS	90 (35.7)	18 (7.1%)	35 (13.9%)	109 (43.2%)	162 (64.3%)
SIS	100 (39.7%)	23 (9.3%)	42 (16.6%)	87 (34.2%)	152 (60.1%)
D & C	142 (56.5%)	06 (2.6%)	09 (3.6%)	95 (37.3%)	110 (43.5%)
H. Biopsy	98 (38.9%)	31 (12.4%)	46 (18.1%)	77 (30.6%)	154 (61.1%)

AUP: Abnormal uterine pathology;

TVS: Transvaginal sonography;

SIS: Saline infusion sonography;

D & C: Dilatation and curettage;

H - Biopsy: Hysteroscopy guided biopsy.

Table 3:
Accuracy of diagnostic options

Test		Polyp	L.R.	Fibroid	L.R.	AUP	L.R.
TVS	Sensitivity	25	+5.2	65.7	+25.3	86.4	+2.81
	Specificity	95.2	-0.78	97.4	-0.35	69.3	-0.2
SIS	Sensitivity	58.3	+24.3	85.7	+65.9	90.6	+7.5
	Specificity	97.6	-0.42	98.7	-0.14	88	-0.1
D & C	Sensitivity	16.6	+27.6	17.1	+26.6	61	+3.81
	Specificity	99.4	-0.84	99.4	-0.83	84	-0.46

L. R: Likelihood ratio;

AUP: Abnormal uterine pathology.

Discussion:

Peri-menopause includes the period beginning with the first clinical, biological and endocrinological features of the approaching menopause and ending twelve months after the last menstrual period. Accurate diagnosis of the cause of AUB in perimenopausal age group is critical. An ideal diagnostic test should be non or minimally invasive, easy to perform, easily acceptable to the patients, low cost and of high sensitivity and specificity. Unfortunately none of the diagnostic tests evolved so far, has fulfilled all the required criteria. Pipple's endometrial sampling and Vabra aspirator initially gained popularity as they were easy to perform, but they lack specificity for focal pathology with unacceptable false negative rates⁴. D & C also is being gradually discarded as a modern day procedure because of its low diagnostic reliability and unacceptable complications⁵. Meta-analysis has demonstrated that sonographic measurement of endometrial thickness is an acceptable test for prediction of endometrial pathology, but it has its limitation in correctly diagnosing the type of endometrial pathology⁶. Minimum endometrial thickness considered to be abnormal was accepted as 5 mm in the present study as it is well proved that the risk of endometrial malignancy in patients with post-menopausal bleeding and with an endometrial thickness ≤ 4 mm is less than 1%⁷.

Imaging studies for AUB are commonly done but no previous study has tried to define the ability of SIS or TVS in detecting different endometrial pathologies in comparison to a standard procedure like hysteroscopy-guided biopsy. Performing a hysterectomy and histopathological examination of the resected uterus

would be an ideal reference standard but as this is not always possible in perimenopausal patients on ethical ground and at the same time is unacceptable to the patients, we have selected hysteroscopic biopsy as the reference standard for comparing the other tests viz. TVS, SIS and D&C.

Vercellini et al⁸ evaluated the role of transvaginal ultrasonography and diagnostic hysteroscopy in pre-menopausal menorrhagic patients irrespective of their age. In the 40 to 50 years age group of their study population, hysteroscopy was able to diagnose polyp and fibroid in 23.5 % and 14 % of the women respectively and was negative in 53.8% of the cases. In the present study, the corresponding figures were 12.4%, 18.1% and 38.9% respectively. However, it should be remembered that their patient population was 'pre-menopausal menorrhagic' while our patients were 'peri-menopausal with AUB'. Similarly, in their study, 39% of the overall patients were normal in TVS and sensitivity & specificity of TVS was 96% and 86% respectively; whereas, the comparative figures are 35.7 %, 86% and 69% respectively in our study. The incidence of polyp in patients with AUB in Allameh et al⁹ series was 38 % and that of Laifer-Narin et al¹⁰ was 42 %. Both were surprisingly high in comparison to our findings and are probably due to difference in patient selection. Goldstein et al¹ have done SIS followed by D&C and / or hysteroscopy only in those cases with abnormal TVS finding which do not allow a proper comparison between the tests.

Not a single incidence of endometrial malignancy has been found in the present study. Apparently it seems to be astonishing but if we consider the demographic

pattern of the participating women, most of whom are coming from the low socio-economic class where obesity and hypertension are rare, 'hormone replacement therapy' unheard of and 88.5% were multipara, then it will appear as a logical phenomenon. So was the result of the study by Allameh et al⁹.

The criteria that distinguish a definitely useful clinical test from one that is of doubtful value has been shifted from the older concept of sensitivity and specificity to the newer and more powerful concept of 'Likelihood Ratios' (LRs). The LRs indicate by how much a given test would raise or lower the probability of having pathology. Therefore, a high 'positive LR' and a low 'negative LR' reflect the diagnostic performance of the test. A positive LR of >10 and a negative LR of <0.1 reflect the high diagnostic accuracy of the test. Positive LR values of 5–10 and negative LR values of 0.1–0.2 reflect a test's moderate accuracy and similar values between 1–5 and 0.2–1 respectively would be poor¹¹.

In the present study, with a positive LR value of 7.5 and a negative LR value of 0.1, SIS has turned out to be a moderately good test for detecting uterine pathology as well as for screening purposes that need further evaluation. Both TVS and D&C have low positive LR values (2.81 & 3.81 respectively) and are unacceptable as diagnostic test for uterine pathology. TVS has slightly higher false positive rate (Type-II error) while D&C has high false negative rate (Type-I error). With a low negative LR value (0.2), TVS may be considered as a screening test only, in which aspect also D&C (negative LR value of 0.46) is an unaccepted one. In detecting anatomical abnormalities like polyp or fibroid, none of the imaging studies appeared to be superior to hysteroscopy.

Another problem of the radiologists arises when they have to diagnose the exact form of hyperplasia as it can be established by pathological examination only. Hysteroscopy offers the possibility of visualizing macroscopic or focal abnormalities suggestive of endometrial hyperplasia and of taking biopsy under visual control known as 'targeted hysteroscopic biopsy'. But the lack of established hysteroscopic criteria for 'abnormal endometrial hyperplasia' and its overlapping pattern with the normal late secretory endometrium, mainly in pre-menopausal women, is a limitation that still arouses some doubt to the reliability of this procedure¹². Another problem of hysteroscopy is that it needs specialized equipment, skilled operator and general anaesthesia or when performed as an office procedure with local or no anaesthesia, it can cause

significant patient discomfort. Chambers¹³ commented, "The expense and time involved in the use of hysteroscope are not justified for routine evaluation of all the women with abnormal uterine bleeding".

The concluding remark of Vercellini et al⁸ is remarkable in this aspect "Considering the good specificity and negative predictive value, TVS may be suggested as the initial investigation in pre-menopausal patients with menorrhagia. When appropriate, endometrial biopsy may be performed. Hysteroscopy may be limited to cases with a positive or doubtful TVS finding with the aim of defining the lesion, obtaining targeted biopsy and evaluating endoscopic operability correctly". We only like to replace 'TVS' with 'SIS' in 'peri-menopausal patients with AUB' keeping the role of hysteroscopy unaltered as suggested by Vercellini et al⁸.

Conclusion:

From the present study, it is clear that accuracy of SIS as a test for detecting pathology in AUB in peri-menopausal patients is moderately good and suitable for developing countries whereas D&C is unacceptable as a screening test. However, hysteroscopy and guided biopsy if can be performed as office procedure, still is the tool of choice both for screening as well as diagnostic purposes.

Bibliography

1. Goldstein SR, Zeltser I, Horan CK et al. Ultrasonography based triage for perimenopausal patients with abnormal uterine bleeding. *Am J Obstet Gynecol* 1997;177:102-8.
2. Abberton KM, Taylor NH, Healy DL et al. Vascular smooth muscle alpha-actin distribution around endometrial arterioles during the menstrual cycle: increased expression during the perimenopause and lack of correlation with menorrhagia. *Human Reprod* 1996;11:204-11.
3. Irwig L, Tosteson AN, Gatsonis C et al. Guidelines for meta-analysis evaluating diagnostic tests. *Ann Intern Med* 1994;120:667-76.
4. Guido RS, Kanbour-Shakir A, Rulin MC et al. Pipelle endometrial sampling. Sensitivity in the detection of endometrial cancer. *J Reprod Med* 1995;40:553-5.
5. Seamark CJ. The demise of the D&C. *J R Soc Med* 1998;91:76-9.
6. Gupta JK, Chien PF, Voit D et al. Ultrasonographic endometrial thickness for diagnosing endometrial

- pathology in women with postmenopausal bleeding: a meta-analysis. *Acta Obstet Gynecol Scand* 2002;81:799-816.
7. Gull B, Karlsson B, Milsom I et al. Can ultrasound replace dilatation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. *Am J Obstet Gynecol* 2003;188:401-8.
 8. Vercellini P, Cortesi I, Oldani S et al. The role of transvaginal ultrasonography and outpatient diagnostic hysteroscopy in the evaluation of patients with menorrhagia. *Hum Reprod* 1997;12:1768-71.
 9. Allameh T, Mohammadizadeh F. Diagnostic value of hysteroscopy in abnormal uterine bleeding compared to pathology reports. *Iranian J Reprod Med* 2007;5:61-4.
 10. Laifer-Narin SL, Ragavendra N, Lu DS et al. Transvaginal saline hysterosonography: characteristics distinguishing malignant and various benign conditions. *AJR Am J Roentgenol* 1999;172:1513-20.
 11. Jaeschke R, Guyatt GH, Sackett DL. User's guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? *JAMA* 1994;271:703-7.
 12. Rogerson L, Bates J, Weston M et al. A comparison of outpatient hysteroscopy with saline infusion hysterosonography. *BJOG* 2002;109:800-4.
 13. Chambers JT, Chambers SK. Endometrial sampling: When? Where? Why? With what? *Clin Obstet Gynecol* 1992;35:28-39.