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Study the Accuracy of Transvaginal Ultrasound Combined with Endometrial Office Biopsy (Pipelle) as a Predictor of Final Pathology in Patients with Abnormal Uterine Bleeding

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Abstract

Women with abnormal uterine bleeding need examination for diagnosis of different diseases particularly endometrial carcinoma. Office endometrial sampling with pipelle combined with vaginal ultrasonography is easier, cheaper, non invasive. Objectives of the study were to investigate the use of both transvaginal ultrasonography and office endometrial sampling for the diagnosis of endometrial disease in women with vaginal bleeding.

Methods: The 480 women presenting with abnormal uterine bleeding were enrolled in the study. Trans Vaginal ultrasonography was done. Endometrial sampling was done using endometrial biopsy pipelle, as office procedure, in the out patients clinic. The sample was sent for Histopathological Examination (HPE), the accuracy of vaginal ultrasound and pipelle was measured and compared the gold stander pathology of hysterectomy where this was indicated.

Result: We had no procedure failure or complications the study revealed sample adequacy of 98.2%. The inadequate samples were from postmenopausal ladies with atrophic endometrium. Endometrial carcinoma could be picked up all cases. The procedure proved to be simple, acceptable, accurate, and cost effective. The results from this study when compared with other population based studies, showed a higher proportion of successful samplings.

Conclusions: This study showed that by combined use of Trans Vaginal Sonography (TVS) and office endometrial pipelle sampling, sufficient diagnostic information was obtained for women with abnormal uterine bleeding, obviating the need for more invasive diagnostic procedures.

Keywords: Endometrial sampling; Trans vaginal sonography; Vaginal bleeding

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Introduction

Approximately one third of all the gynaecological consultations are related to abnormal vaginal bleeding. This proportion rises to 70% in the premenopausal and postmenopausal years [1]. Endometrial assessment is indicated at the age of 40 years to exclude endometrial hyperplasia or carcinoma as less than 1% endometrial carcinoma occur under 35 years of age [2] and 6% in those 45 or less. Younger women may also need endometrial investigation if abnormal bleeding does not resolve with medical management. It is also indicated in polycystic ovarian disease or if there is unusual endometrial appearance. Endometrial biopsy is important even if hysteroscopy is normal [3].

Endometrial sampling is the gold standard method for evaluation of abnormal uterine bleeding. Pipelle biopsy is performed as an endometrial biopsy method extensively nowadays. It is safe, cheap and non-invasive as well as its complication is too rare, it doesn't need operation room and anesthesia [4].

Pelvic ultrasonography, and in particular Transvaginal Ultrasonography (TVUS), is a method extensively utilized in gynecology and obstetrics. In pregnancy, it is widely utilized to analyze embryonic and fetal anatomy at the first trimester [5] and to evaluate the biometry and morphology of the uterine cervix in more advanced gestations [6], demonstrating to be an excellent predictor

Table 1: Age distribution, type of bleeding, parity.

Age (years)	No. of cases	Percentage
35-40	50	10.40%
41-45	52	10.80%
45-50	187	38.90%
51-55	148	30.80%
>55	43	8.90%
Type of bleeding	**No. of cases**	**Percentage**
Prolonged >7 days or heavy or both at time of menstruation (Menorrhagia)	216	45%
Irregular Intermenstrual bleeding (Metrorrhagia)	7	14%
Postmenopausal bleeding	106	22.08%
Continuous bleeding	5	1.04%
Regular , Frequent and Heavy (Polymenorrhagia)	27	5,06%
Irregular, Heavy (Menometrorrhagia)	119	24.79%
Parity	**No. of cases**	**Percentage**
Nullipara	30	6.25%
Para 1	20	4.16%
Para 2	192	40%
Para 3	168	35%
Para 4	60	12.50%
Grand Multipara	10	2.08%

of preterm delivery [7]. It leaves no doubts about the benefit of evaluating adnexal masses [8], including deep endometriosis and its intestinal involvement-with effectiveness comparable to magnetic resonance imaging [9]. It is the most frequently utilized propedeutic imaging method as a first line of investigation in patients with abnormal uterine bleeding [10].

Patients and Methods

This is a prospective study which has been done at Zagazig university hospital in outpatient gynecological clinic between June 2015 and January 2018, 480 patients were recruited.

Initially, the present study included 490 patients with abnormal uterine bleeding. However, ten women were excluded for refusal in participating in the study.

The 480 women over the age of 35 years, who presented to gynecological clinics with abnormal uterine bleeding (e.g., menorrhagia, post-coital or inter-menstrual bleeding, irregular menstruation or postmenopausal bleeding) between June 2015 and January 2018, were recruited. Intrauterine pathology appears to be age related, with abnormalities rarely seen before 35 years of age 18 (Table 1).

Inclusion criteria

Women with

1. Abnormal uterine bleeding such as heavy menstrual bleeding.
2. Inter-menstrual bleeding.
3. Irregular and heavy bleeding.
4. Regular, frequent and heavy bleeding.
5. Postmenopausal bleeding.

Table 2: Pipelle findings, histopathology findings, transvaginal ultrasonography findings in 480 cases of abnormal uterine bleeding.

Pipelle Pathology	No. of cases	Percentage
Normal	212	44.16%
Endometrial Polyp	57	11.87%
Endometrial Hyperplasia	78	16.25%
Endometrial Polyp and Hyperplasia	42	8.70%
Atrophic endometrium and Polyp	7	1.40%
Endometrial Carcinoma	19	4%
Endometritis	40	8%
Submucous fibroid	25	5.20%
Histopathology	**No. of Cases**	**Percentage**
Normal	148	30.80%
Endometrial Polyp	78	16.25%
Endometrial Hyperplasia	78	16.25%
Endometrial Hyperplasia and Polyp	39	8.10%
Atrophic endometrium and End. Polyp	9	1.80%
Atrophic endometrium	9	2%
Endometrial Carcinoma	19	4%
Endometritis	40	8.30%
Submucous Fibroid	35	7.20%
Adenomyosis	25	5.20%
Ultrasonography	**No. of cases**	**Percentage**
Normal	173	36.04%
Endometrial Polyp	89	18.50%
Endometrial Hyperplasia	103	21.40%
Atrophic endometrium	10	2.08%
Endometrial Carcinoma	51	10.60%
Submucous fibroid	37	7.70%
Adenomyosis	17	3.50%

6. Continuous bleeding related to uterine causes.

Exclusion criteria

1. Pelvic infection.
2. Pregnancy.
3. Drug intake that can lead to vaginal bleeding (anticoagulants, hormonal replacement therapy, hormonal contraceptives).
4. Vaginal, vulval or cervical causes of bleeding.
5. Vaginal bleeding due to endocrine disease such as diabetic mellitus, thyroid diseases, liver and kidney diseases, SLE (Systemic lupus erythematosus).
6. Coagulopathy, thrombocytopenia.

- Systemic and pelvic examinations were done on all the patients. Laboratory tests were done accordingly and non-gynecological cases were excluded.
- Transvaginal ultrasound examination was done using Logiq-5 Sonography Machine from GE for sonographic evaluation with 7.5 MHZ vaginal transducer. Each patient was advised to empty the bladder before examination.

Table 3: Endometrial thickness as measured by Transvaginal ultrasonography (TVS) in correlation to histopathology and patient age.

Histopathological examination	Age in years	Endometrial thickness in mm as measured in TVUS	Number of patients
Endometrial polyp	44-70 (59 ± 7.5)	8-13 (11.66 ± 1.55)	78
Endometrial hyperplasia	46-68 (60.5 ± 5.5)	11-29 (16.77 ± 1.55)	76
Endometrial hyperplasia + polyp	48-71 (56 ± 10.6)	15-31 (15.56 ± 1.88)	39
Atrophic endometrial + polyp	45-65 (50 ± 10.45)	2-6 (4.6 ± 2.1)	9
Atrophic endometrial	47-70 (56 ± 10.44)	1-4 (2.3 ± 1.08)	9
Endometrial carcinoma	51-72 (6o.8 ± 7.3)	7.3-22 (13.8 ± 7.1)	19
Endometritis	47-51 (39.9 ± 10)	6-12 (4.6 ± 2.1)	40
Adenomyosis	44-66 (51 ± 7.5)	9-12 (11.66 ± 1.55)	25
Submucous fibroid	44-56 (49 ± 5.5)	8-12 (11.66 ± 1.55)	35

Table 4: Sensitivity and negative predictive value of Endometrial thickness by TVUS as correlation with malignant findings on histopathological examination.

Cut Off Endometrial thickness (mm)	Numbers of missed cases	Sensitivity (%)	Negative Predictive Value (%)
>2	0	100	100
>3	0	100	100
>4	0	100	100
>5	0	100	100
>6	3	95	96.98
>8	6	91	95.1
>10	7	88	94.3

- Examination techniques include 3 basic maneuvers:

  – Advancement and withdrawal of transducer along long axis of vagina.

  – Angling the transducer tip from side to side and from anterior to posterior.

  – Rotating the transducer along its axis.

- The following criteria were adopted to express the sonographic results:

  – A centrally placed echo dense line within the uterus and a homogeneous endometrial lining with distinct margins to the myometrium were also considered normal.

  – Deformations of the endometrial lining, absence of central hyperechoic line, and the appearance of any structure with or without well-defined margins or variable echogenicity, were considered abnormal.

  – Endometrial thickening (>14 mm for premenopausal women and >5 mm for postmenopausal women) and endometrial atrophy (endometrial thickness <4 mm) [11].

  – Hyperechogenic nodular lesions in the endometrial cavity were considered as polyps, while lesions with mixed echogenicity or hypoechoic lesions altering the contours of the endometrial cavity were considered as submucosal myomas.

  – Findings were considered as suspected for malignancy in cases where the endometrial echo was irregular or with a variable echo texture [12].

- Endometrial sample was performed at gynecology clinic in lithotomy position using flexible pipelle. All pathological examinations of this study were done and reviewed by a single experienced pathologist to reduce the observational bias.

Results

1. Mean age of 45.5 ± 5.36 years.

2. Out of 78 Polyps in Histopathology findings, pipelle picked up 57 cases and TVS picked up 75 cases. TVS falsely diagnosed 3 endometrial polyps as normal study. Out of 78 cases of Hyperplasia, both pipelle and TVS correctly diagnosed all cases. The 39 cases of Hyperplasia and polyp in pipelle correlated with findings of Histopathology (Table 2).

3. Endometrial thickness on TVS in patients with carcinoma endometrium was in the range of 7.3 mm to 22 mm with mean of 13.8 mm ± 7.1 mm. The mean ET of patients with endometrial hyperplasia was 16.77 ± 1.55, with endometrial polyp was between 8 mm to 13 mm, with atrophic endometrium had ET ranging between 1 mm to 4 mm. Patients with Endometritis had ET ranging between 6 mm to 12 mm. Patients with submucous fibroid had ET ranging between 8 mm to 12 mm with range (11.66 ± 1.55). Patients with adenomyosis had ET ranging between 6 mm to 12 mm with range (4.6 ± 2.1) (Table 3).

4. Present study shows that when the ET cutoff was taken as ≤ 5 mm then the negative predictive value was 100% as no malignancy was missed but it dropped to 96%. And 98% when cutoff was ≤ 6 mm in the present study, it was found that TVS, which is a non-invasive process, measures only the endometrial thickness. But endometrial sampling with pipelle which is an invasive process gives Histopathologic findings. In the present study, no abnormal histopathology finding was detected in any subject who had ET ≤ 5 mm. Thus, it was concluded that as no abnormal histopathology finding was found below ET of 5 mm hence patients with ET ≤ 5 mm can be safely followed up and should only be subjected to endometrial sampling if recurrent episodes of postmenopausal bleeding occurs (Table 4). However, for final confirmatory result Histopathological Examination (HPE) is must as measurement of ET by TVS cannot differentiate between benign and malignant HPE findings. That Ultrasound and HPE both are effective for diagnosing pathology when used together.

Discussion

The main goal for endometrial biopsy in women with vaginal bleeding is to detect the nature of the problem, by ruling out or confirm endometrial carcinoma, so that proper management can be done. An ideal diagnostic test should be none or minimally invasive, easy performed, accepted to the patients, low cost, of high sensitivity, and specificity. Less harmful examination methods, such as TVS

Table 5: Sensitivity, Specificity, positive predictive value and negative predictive value of pipelle pathology as correlation with surgical histopathological examination.

Endometrial Histopathology	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Carcinoma	100	100	100	100
Endometrial hyperplasia	100	100	100	100
endometrium polyp	96.5	100	96.5	100
Endometrium hyperplasia + polyp	95.5	100	100	95.8
Atrophic endometrium + polyp	91.5	100	91.5	100
Atrophic endometrium	0	0	0	0
Submucous fibroid	75	100	100	98
Endometritis	57	97	57	97
Adenomyosis	0	0	0	0

combined with endometrial cytology. In this prospective study we had study the accuracy of combined TVS and pipelle biopsy in 480 cases of abnormal uterine bleeding as compared to histopathological study of hysterectomy spacemen as this was indicated in these cases. We had no procedure failure or complications. The study revealed sample adequacies of 98.2%. The inadequate samples were from postmenopausal ladies with atrophic endometrium.

Transvaginal ultrasonography can reliably assess endometrial thickness and uterine cavity morphology. It is a safe, rapid, highly effective, generally painless, and relatively less invasive method. It provides highly magnified images of endometrial contents. Furthermore, it may evaluate other pelvic organs for potential abnormalities [13].

In the present study, the mean ET in endometrial carcinoma group was 13.8 ± 7.1 mm. Similarly, the studies conducted by Van Den Bosch et al., Bengt Karlsson et al., and Aruna. Kekre et al., had higher ETs, 22.5 ± 8.9 mm, 21 ± 11.8 mm and 12.5 ± 5.8 mm, depicting thereby that as the ET rises chances of getting endometrial carcinoma increases [14].

In the present study, it was found that as the endometrial thickness raises the chances of getting abnormal endometrial histological finding including endometrial carcinoma increases. This finding was similar to study of Van Den Bosch et al., Ilan Bruchim et al., Ayman AA Ewies and Russell et al., [15]. Thus, the present study is in strong agreement with the above studies.

Present study shows that when the ET cutoff was taken as ≤ 5 mm then the negative predictive value was 100% as no malignancy was missed but it dropped to 96. The 98% when cutoff was ≤ 6 mm as one case of malignancy was missed (Table 5). This finding was similar to study by Ayman. Ewies and Musonda. [16], Ferrazzi et al. and Epstein et al., in which ET cutoff of ≤ 5 mm had negative predictive value of 100%, 100% and 99.6% respectively [16]. The study by Karlsson et al., Gull et al. and Ferrazzi et al., used 4 mm as the cutoff with negative predictive values of 100%, 100% and 99.8% respectively [17].

In the present study, it was found that TVS, which is a non-invasive process, measures only the endometrial thickness. But endometrial sampling with pipelle which is an invasive process gives Histopathologic findings. In the present study, no abnormal histopathology finding was detected in any subject who had ET ≤ 5 mm. Thus, it was concluded that as no abnormal histopathology finding was found below ET of 5 mm hence patients with ET ≤ 5 mm can be safely followed up and should only be subjected to endometrial sampling if recurrent episodes of postmenopausal bleeding occurs. However, for final confirmatory result HPE is must as measurement of ET by TVS cannot differentiate between benign and malignant HPE findings. The same was inferred by study conducted by Van Den Bosch et al., Tabor et al., Minagawa et al., Tsikouras et al. and Ewies and Musonda [16] concluded that Ultrasound and HPE both are effective for diagnosing pathology when used together [16]. Doorn et al. [18] concluded that in women with postmenopausal bleeding and a non-reassuring transvaginal ultrasound evaluation, a non-diagnostic office endometrial sample does not rule out endometrial cancer and further endometrial sampling is advisable [18]. However, Studies by Kekre et al. and Jacobs et al. [19] showed that TVS screening alone for endometrial cancer has good sensitivity in postmenopausal women and further endometrial sampling is not required if ET is <5 mm [19]. Soguktas et al. [20] compared the diagnostic effectiveness of Trans Vaginal Sonography (TVS), Saline Infusion Sonohysterography (SIS) and diagnostic Hysteroscopy (HS), with the pathologic specimen as a gold standard in premenopausal women with abnormal uterine bleeding. The positive and negative likelihood ratios of TVS, SIS and HS were calculated by comparison with the final pathological diagnosis. Polypoid lesion was the most common abnormal pathology. LR+ and -LR of TVS, and HS were 3.13 and 0.15, and 13.7 and 0.02 respectively in detection of any abnormal pathology. HS had the best diagnostic accuracy, and the diagnostic accuracy of HS was superior to TVS [20].

Özdemir et al. [21] evaluated endometrial thickness with transvaginal ultrasonography and histopathology in premenopausal women with abnormal vaginal bleeding. Of the 144 women, 113 (78.4%) had normal and 31 (21.6%) had an abnormal endometrium. The abnormal endometrium was composed of 11.8% hyperplasia (simple + atypical complex), 4.2% endometrial polyp, and 5.5% adenocarcinoma. An optimal sensitivity and specificity (83.6% and 56.4%, respectively) and negative predictive value with 95.6% for detection of abnormal endometrium were obtained with an endometrial thickness of 8 mm. The accuracy rate of preoperative Pipelle biopsy was 94.7% in a total of 57 women [21].

Conclusion

It is concluded that the combined use of transvaginal ultrasonography and endometrial sampling for HPE as office procedure in women with vaginal bleeding may be the reliable diagnostic protocol for detecting endometrial disease.

It is also concluded that office sampling of endometrium with pipelle, endometrial polyps and submucosal myomas may be missed. Hence, these cases require correlation with TVS findings.

It is suggested that if endometrial thickness is 5 mm or less, further investigations are not required but in cases of recurrent episodes of postmenopausal bleeding further investigations are indicated.

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