Evaluation of Accuracy of Chromohysteroscopy as A Diagnostic Strategy for Perimenopausal Bleeding

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Abstract

Objective: To evaluate the role of endometrial dying with methylene blue during diagnostic hysteroscopy to detect new subtle histopathologies missed by the conventional hysteroscopy.

Methods: One hundred patients were included in the study complaining of perimenopausal bleeding with no diagnosed hysteroscopic endometrial abnormalities nor a general bleeding tendency. Endometrial dying was done by instillation of 5 ml of 1% methylene blue into the endometrial cavity after diagnostic hysteroscopy. According to the pattern of methylene blue staining, 60 patients showed focal dark staining with a background of light blue stained endometrium forming **(group I)**, the remaining 40 patients showed non focal diffuse blue staining forming **(group II)**. **Group I** was further subdivided into group A , B according to the age with group A (40-46 years) and group B (>46 years)..

Results: Chromohysteroscopy procedure led to the diagnosis of 48 more new endometrial histopathologies missed by conventional diagnostic hysteroscopy including 16 cases of atrophic endometritis, 29 cases of simple endometrial hyperplasia and 3 cases of atypical endometrial hyperplasia.The overall validity of the chromohysteroscopy procedure was calculated with a sensitivity of 93.2%, specificity of 87.8%, positive predictive value of 91.6 % and negative predictive value of 90%.

Conclusions: Chromohysteroscopy appears to improve the efficacy of hysteroscopy in abnormal uterine bleeding and observation of diffuse light blue staining without dark areas strongly suggests a normal endometrium free of endometritis.

Keywords: Chromohysteroscopy, Abnormal uterine bleeding, Endometrial biopsy, Methylene blue.

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Introduction

Malignant precursors of endometrial cancer such as complex endometrial hyperplasia, become more common during the perimenopausal period in comparison to younger age groups, and early diagnosis with endometrial biopsy should be done to exclude malignancy(1).

An endometrial biopsy is indicated in all patients with perimenopausal bleeding especially if the clinical history suggests a long term of unopposed estrogen exposure even if the endometrial thickness is normal (5 to 12mm)(2).

Traditionally, suspected endometrial pathologies have been investigated with blind biopsy techniques like dilatation and curettage, however, many focal lesions in the uterine cavity were missed with false negative rates between 3% and 7% (3).

Endometrial dying during conventional hysteroscopy using 1% methylene blue for enhancement and detection of subtle endometrial changes not detected by the naked eye during conventional hysteroscopy is a new technique named "Chromohysterosopy" named after the chromoendoscopy which is a widely used technique in gastrointestinal imaging(4).

Unlike the gastrointestinal mucosa, the endometrium is not an absorptive epithelium. Endometrium is not supposed to take any dye under normal circumstances. However, studies reported that endometrium stained by methylene blue except in the pre-ovulatory phase. The reason for endometrial staining is explained by apoptosis. They noted that structural damage of the cells during apoptosis would allow passage of the methylene blue dye into the cell(4).

Aim of Work

The aim of this work was to study the role of chromohysteroscopy as a new and simple modality for evaluation and diagnosis of endometrial pathology in cases of perimenopausal bleeding.

Patients and Methods

This observational cross section study was conducted at the Obstetrics and Gynecology department of Benha University Hospitals after receiving approval by the Research Ethical Committee of Benha Faculty of Medicine with the code RC 13-11-2023. Written Informed consent was obtained from all participants prior to commencing the study.

This study enrolled 100 patients who presented with complaint of perimenopausal bleeding and had the following criteria :

A- Inclusion criteria:

Women with perimenopausal bleeding, with no gross endometrial pathology that can be detected by the conventional diagnostic hysteroscopy.

B- Exclusion criteria:

- Patients with Contraindications of hysteroscopy, general causes of bleeding or not fit for general anaesthesia.
- Women on hormone replacement therapy.
- Patients with obvious ultrasound pathologies that could be the cause of the abnormal bleeding (like fibroid uterus).

All patients were subjected to:

1. Transvaginal sonography as a preliminary diagnostic tool to detect any uterine pathology and to measure the endometrial thickness
2. Conventional hysteroscopy followed by chromohy-steroscopy and the uterine cavity was visualized for staining pattern either focal or diffuse light blue staining, and the patients were divided into two groups according to the staining pattern: group I (with focal dark staining) and group II (with diffuse light staining)
3. In (group I), Two different biopsy spec-

imens were obtained from dark stained and light stained areas by hysteroscopic guided biopsy forceps while random curettage was done for (Group II) patients.

4. Different biopsy specimens were subjected to histopathologic examination using H&E.

Results

Comparison between group I & group II regarding age range showed a highly statistically significant increase in the appearance of focal dark stained areas in the age range above (>46yrs) while a higly significant elevation in diffuse light stained pattern was in the age range (40-46yrs) ($p<0.001$) (table 1).

Ultrasound evaluation resulted in exclusion of many cases, and from the included cases results of the histopathology of the endometrial samples were correlated with the results of the ultrasound calculated endometrial thickness, and showed a statistically non significant correlation between the endometrial thickness and the histopathology either in the group I or group II in the range of (5mm – 12mm) taken in the study where the mean endometrial thickness in group I was 8.7 mm and 9.02 in group II (table 2). Specimens from the dark stained areas in group I revealed that 18 patients (30%) had atrophic endometritis, 30 patients (50%) had simple endometrial hyperplasia, 4 patients (6.7%) showed complex endometrial hyperplasia without atypia , 3 patients(5%) had complex endometrial hyperplasia with atypia and 5 cases (8.3%) had a non neoplastic non inflammatory endometrium (table 2). Histopathological examination of specimens from the diffuse light stained areas in group I revealed 2 patients (3.3%) with atrophic endometritis, 3 pateints (5%) with simple endometrial hyperplasia, 4 patients (6.7%) with complex endometrial hyperplasia without atypia, and 51 patients (86%) with non neoplastic non inflammatory endometrium. (table 2). The total number of patients in group I who showed abnormal histopathological findings in focal dark stained areas were (55) , 48 of them (85.4%) were newly diagnosed by chromohystroscopy (table 2). Of the 40 patients included in group II, one case (2.5%) showed histopathological atrophic endometritis, 3 cases (7.5%) revealed simple endometrial hyperplasia & 36 cases (90%) showed non neoplastic non inflammatory endometrium (NNE) with a high statistically significant value (table 1).

There was a high statistically significant difference between the values of the mean age of the cases with atrophic endometritis (48.55±2.38), simple endometrial hyperplasia without atypia (47.54±2.26), complex endometrial hyperplasia without atypia (48.25±2.21), complex endometrial hyperplasia with atypia (49.0±2.82) and the non neoplastic non inflammatory endometrium (44.0±3.1) ($P<0.001$) (table 3) Of the 60 patients with focal dark stained areas 55 patients showed abnormal histopathological findings. This indicated a positive predicive value Of (91.6%) Of the 40 patients with diffuse light staining in chromohystroscopy, 36 showed normal findings .This indicated a negative predictive value of (90%).59 cases showed endometrial pathologies on microscopic examination. 55 of them showed focal dark stained areas with chromohysrtoscopy. This indicated that the sensitivity of chromohystroscopy was (93.2%) 41 patients had normal histopathologic examination, 36 of them showed no focal dark staining by chromohystroscopy. This indicated that specificity of chromohystroscopy was (87.8%) (table 4).

Table 1. Comparison between Group I and Group II according to age range, endometrial thickness measured by 2D transvaginal ultrasound and histopathological patterns in each group (values are given as n, % and mean ± SD)

	Group I (n = 60)	Group II (n = 40)	p
Age Range			
40 - 46 (A)	16 (26.7%)	31 (77.5%)	χ^2 <0.001*
> 46 (B)	44 (73.3%)	9 (22.5%)	
Endometrial Thickness (mm)			
Mean ± SD.	8.7±1.3	9.05±1.2	t 0.17
Histopathological patterns			
Atrophic endometritis	18 (30%)	1 (2.5%)	χ^2 <0.001*
Simple endometrial hyperplasia without atypia	30 (50%)	3 (7.5%)	
Complex endometrial hyperplasia without atypia	4 (6.7%)	0 (0%)	
Complex endometrial hyperplasia with atypia	3 (5%)	0 (0%)	
Non neoplastic non inflammatory endometrium	5 (8.3%)	36 (90%)	

χ^2: Chi square test t: Student t-test SD: Standard deviation mm: Millimeter
p: p value for comparing between the studied groups n: number
*: Statistically significant at p ≤ 0.05

Table 2. Frequency of different histopathological findings in group I regarding specimens retrieved from lightly stained and dark stained endometrium with statistical analysis of newly cases diagnosed by chromohysteroscopy

Group I (60 Patients had focal dark staining with a background of light stained endometrium)				
Histopathological patterns in relation to stained specimens	**Lightly stained specimens**	**Dark stained specimens**	**Newly diagnosed cases by chromohysteroscopy**	**p**
Detected Pathology (55/60) Atrophic endometritis (N = 18)	X (%) 2 (3.3%)	Y (%) 18 (30%)	(Y-X)/N 16/18 (89%)	χ^2 <0.001*
Simple endometrial hyperplasia without atypia (N = 30)	3 (5%)	30 (50%)	27/30 (96.7%)	χ^2 <0.001*
Complex endometrial hyperplasia without atypia (N = 4)	4 (6.7%)	4 (6.7%)	0/4 (0%)	------
Complex endometrial hyperplasia with atypia (N = 3)	0 (0%)	3 (5%)	3/3 (100%)	χ^2 <0.001*
NO Detected Pathology (5/60) Non neoplastic non inflammatory endometrium	51 (85%)	5 (8.3%)		

N: number of detected pattern per total group (60 cases)
X: number of detected pattern regarding specimen taken from lightly stained endometrium
Y: number of detected pattern regarding specimen taken from dark stained endometrium
p: p value for comparing between the studied groups χ^2: Chi square test
*: Statistically significant at p ≤ 0.05

Table 3. Statistical comparison between Mean values of age and frequency of histopathology in group I detected in darkly stained areas :

Histopathological pattern	Age (Mean± SD)	p
Atrophic endometritis (N = 18)	48.55± 2.38	$\chi^{2\,(FE)}$ <0.001*
Simple endometrial hyperplasia without atypia (N = 30)	47.54±2.26	
Complex endometrial hyperplasia without atypia (N = 4)	48.25±2.21	
Complex endometrial hyperplasia with atypia (N = 3)	49.0± 2.82	
Non neoplastic non inflammatory endometrium (N = 5)	44.0±3.1	

N: number of detected pattern per total group (60 cases) SD: Standard deviation FE: Fisher Exact
p: p value for comparing between the studied groups $\chi 2$: Chi square test
*: Statistically significant at $p \leq 0.05$

Table (4): Validity of chromohysteroscopy in detection of abnormal endometrial pathologies missed by hystroscopy:

Validity	%
Sensitivity	93.2
Specificity	87.8
Positive predictive value (PPV)	91.6
Negative predictive value (NPV)	90

Discussion

With the advancement of hysteroscopy and outpatient sampling techniques, there is regression of D&C procedures, especially in developed countries, in the evaluation of abnormal uterine bleeding (5).

Indeed, the negative predictive value of hysteroscopy is >90%, when no structural abnormality is disclosed in a completely visualized uterine cavity and when the endometrium appears uniformly thin and homogeneous (6) theoretically, no further medical investigations should be necessary.

However, because of the frequent lack of hysteroscopic diagnosis in cases like endometritis, systematic endometrial sampling may be recommended for pathological examination, even though the hysteroscopic view is negative.

This study focused on the detection of the hidden endometrial abnormalities not detected by the conventional hysteroscopy causing the abnormal uterine bleeding in the perimenopausal age group through employing chromo-hysteroscopy as a new technique for hysteroscopic guided endometrial sampling.

The study included 100 patients complaining of perimenopausal bleeding, without any obvious medical or anatomical abnormalities explaining this bleeding evidenced by a meticulous history taking and a thorough general and local examination and transvaginal sonographic evaluation.

The patients were divided according to the pattern of staining into two groups: group I (with positive focal staining) and group II (without focal staining).

In this study , evaluation with transvaginal sonography was performed for all patients as a preliminary step to exclude cases with obvious pelvic pathology that could cause abnormal uterine bleeding and the final results of the endometrial samples were correlated with the results of the ultrasound calculated endometrial thickness, and showed a non significant correlation between the ultrasound calculated endometrial thickness and the final histopathology results. Other studies found transvaginal sonography as a very valuable sole diagnostic tool for the detection of the endometrial pathology in the perimenopausal age group; a difference which can be explained by the narrow cut off value for the endometrial thickness taken in our study (5-12 mm) and the exclusion of the cases with obvious pelvic pathologies like submucosal myoma and adenomyosis (7,8) .

The neglect of the three dimensional character of the endometrial cavity and the occasional propensity of the ultra -sonographic operator to obtain a limited number of two dimensional views and assume that this represents the entire endometrial cavity may also explain this non significant correlation ,Opening the way for the new three-dimensional ultrasound equipment to eliminate errors that may occur if the operator does not pay meticulous attention to mentally recreating three-dimensional anatomy (9).

Our result illustrates the observation that a diffuse light blue staining without focal dark areas strongly suggests a normal endometrium free of pathology; a finding which is in accordance with the other study that viewed dark staining in 19 of 24 cases of postmenopausal bleeding and discovered 3 new pathologies , two atrophic endometritis and one endometrial hyperplasia (10).

Another study by the same author on the role of chromohysteroscopy in the evaluation of the endometrium in recurrent IVF failure showed a sensitivity (69.2%), specificity (74%), positive predictive value (40.9%) and negative predictive value (90.2%) for detection of endometritis; where they suggested that removal of local endometrial defects may lead to replacement by healthy cells and receptivity is restored, eventually successful implantation is achieved.

However, this study had a fewer number of cases (only 63 patients) and a much different age range (women in the reproductive age range 24-37 years old) (11).

Our result showed that 55 histopathologies were dicovered in group I in the hysteroscopic guided specimens taken from the focal dark stained areas after being considered normal by the conventional hysteroscopy and included:

- 18 cases with Atrophic endometritis(over all 19 cases"19%" in both groups).
- 30 cases with Simple endometrial hyperplasia without atypia (overall 33 cases"33%") .
- 4 cases with Complex endometrial hyperplasia without atypia "4%" .
- 3 cases with Atypical endometrial hyperplasia"3%" .

And all the previous findings constituted abnormal findings, with no single case of overt malignant changes discovered.

5 cases in the group I with focal dark stained areas showed a non neoplastic non inflammatory endometrium "NNE"(overall 41 cases in both group I and group II "41%"). (including all the other histologic entities normaly found in endometrial specimens in this age group due the frequent occurrence of periods of anovulation like disordered proliferative endometrium (2)

In comparison to other a study done to evaluate the endometrial pathology in cases of perimenopausal bleeding where conventional D&C biopsy was performed for 748 cases with perimenopausal bleeding and showed 5 cases with atypical hyperplasia(0.7%) , 41 cases with simple hyperplasia

(6%) , 51 cases with atrophic endometritis (7%) ,550 cases with a non neoplastic non inflammatory pathology (74%) and only two cases with endometrial carcinoma (0.4%) (12) .

The findings which denoted a better detection rate of chromohysteroscopy for endometrial pathologies in the perimenopausal women with abnormal uterine bleeding especially for the diagnosis of atrophic endometritis and the precancerous lesion , atypical endometrial hyperplasia.

Regading group II, our result illustrates the Observation that a diffuse light blue staining without focal dark areas strongly suggests a normal endometrium free of pathology. Where most of the cases of group II (36 cases , 90%) showed a non neoplastic non inflammatory histology in their specimens; the results which are partially in agreement other study in terms of the validity of the test for diagnosis of endometritis. Because they studied a group of patients at younger age than our patients. Also the indications for hysteroscopy were different (dysfunctional uterine bleeding, failed intrauterine insemination, unexplained infertility and recurrent first trimester abortion).(13)

So chromohysteroscopy would be a very valuable simple office screening tool without the need for endometrial biopsy using only the simple office hysteroscopy followed by follow up by the same procedure after 6 months with a very high confidence.

The observation of micropolyposis was reported to be associated with endometritis in a study imploying fluid hysteroscopy aiming at the detection of floating endometrial micropolyps with the high resolution hysteroscopic image, however in this study about half of the cases were misdiagnosed (with a sensitivity of about 57%) when compared to the final diagnosis by the histopathology (14).

In current study , when endometrial dying was employed instead of observation of micropolyposis, with the diagnosis of 55 histopathologies in a total no. of 100 cases with 48 (87.3%) new histopathologies diagnosed only in the focal darkly stained areas with a special increased sensitivity for the diagnosis of atrophic endometritis (16 newly diagnosed cases) and simple endometrial hyperplasia (29 new cases) missed by the conventional hysteroscopic view, and three cases of atypical endometrial hyperplasia diagnosed only by chromohysteroscopy with a very high significance measured by Mc Nemar's test with a Sensitivity of (93.2%) , specificity (87.8 %), +ve predictive value (91.6%) , -ve predictive value (90%).

Endometrial hyperplasia is a histological diagnosis characterized by the proliferation of the endometrial glands resulting in a greater gland-to-stroma ratio than observed in normal endometrium (15) and when pre-operative endometrial sampling shows atypical complex hyperplasia, the pathologist frequently has to sample the entire endometrium to rule out a focus of endometrial carcinoma. This means that over 10 cassettes of formalin-fixed, paraffin-embedded tissue must be examined and the chromohysteroscopy may allow for more accurate sampling with no need for a vast number of formalin-fixed, paraffin-embedded tissue. (16).

Recommendations

In this study, Endometrial dying was able to detect new subtle endometrial pathology which was missed by conventional hysteroscopy especially when target biopsy taken from dark-stained endometrium; so we recommend that application of chromohysteroscopy would improve the efficacy and reliability of endometrial guided biopsy in cases of abnormal uterine bleeding.

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