Can "chromohysteroscopy" help target endometrial biopsy in postmenopausal bleeding?

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Summary

Summary : A preliminary study was conducted to evaluate the value of endometrial dying during diagnostic hysteroscopy. Twenty-two postmenopausal bleeding cases without hysteroscopic findings were included in the study. Before the random endometrial biopsy 5 ml of methylene blue (1%) was instilled into the uterine cavity. Staining was observed in 19 of the cases. Tissues were obtained from both stained and non-stained areas with grasping forceps. "Chromohysteroscopy" led the diagnosis of three more endometrial pathologies; two more cases of endometritis and one more case of endometrial hyperplasia. In conclusion, chromohysteroscopy seems like a new avenue worth pursuing for better diagnoses of unexplained endometrial pathologies.

Key words: Postmenopausal bleeding; Hysteroscopy; Chromohysteroscopy; Methylene blue.

Introduction

Postmenopausal vaginal bleeding is an alerting condition both for the patient and physician. About 10% of women with postmenopausal bleeding are subsequently found to have endometrial carcinoma [1]. Because of the high incidence of malignancy as a cause of postmenopausal bleeding, all women presenting with this complaint should be thoroughly evaluated until a final diagnosis is reached. Following physical examination and lab work, imaging techniques are warranted for endometrial evaluation. Transvaginal sonogram (TVS) is the most readily applied. When this is sufficient to diagnose a pathology, subsequent endometrial sampling is performed to establish a histopathologic diagnosis.

Traditionally, suspected endometrial pathologies have been investigated with blunt biopsy techniques like dilatation & curettage or Pipelle biopsy. Since hysteroscopy allows visualization of the endometrial cavity, hysteroscopy with directed biopsy has been valued as the "gold standard" for endometrial assessment for the last two decades [2, 3].

When there are gross abnormal hysteroscopic findings like endometrial polyps, submucous myoma or focal outgrowing/ingrowing abnormalities (as in focal endometrial hyperplasia or endometrial carcinoma) it is easy to aim the biopsy. However when there are no abnormal visual findings to direct biopsy (as in diffuse endometrial hyperplasia) a random biopsy is obtained. Without established hysteroscopic criteria even visually directed biopsy can miss atypical lesions. In this case the reliability of diagnosis and the tissue obtained are related to the experience of the physician, which can be extremely variable.

Chromoendoscopy is a widely used technique in gastrointestinal imaging [4]. Over the last decade, endoscopic systems have acquired great power due to high resolution images owing to CCD chip technology and narrow band imaging techniques [5]. Besides imaging enhancement, gastroenterologic endoscopists use chemical agents either to identify specific epithelia, contrast or highlight subtle mucosal irregularities, or tattoo a specific mucosal site.

Unlike the gastrointestinal mucosa the endometrium is not an absorptive epithelium. Endometrium is not supposed to take any dye in under normal circumstances. However Marconi *et al*. [6] reported that endometrium is stained by methylene blue except in the periovulatory phase. The reason for endometrial staining is explained by apoptosis. They noted that structural damage of the cell during apoptosis would allow passage of the methylene blue dye into the cell.

The aim of the current study was to assess the value of "chromohysteroscopy" (endometrial death during hysteroscopy) in postmenopausal bleeding as an indicator of biopsy site.

Materials and Methods

Twenty-seven postmenopausal bleeding patients were included in the study. They were initially evaluated with complete physical examination and TVS. When no diagnosis could be established they were offered diagnostic hysteroscopy. Hysteroscopy was performed after 7-20 days following cessation of the bleeding. In five patients hysteroscopy revealed an endometrial pathology and they were excluded from the study. Conventional hysteroscopy did not show any endometrial pathology in the remaining 22 patients who were included in the study. Institutional review board approval and signed informed consents were obtained.

When no direct abnormality was seen in the endometrial cavity (Figure 1), before taking a random biopsy, distending medium flow was stopped. Then 5 ml of 1% methylene blue dye was introduced through the hysteroscopic inlet. After five minutes distending medium flow was started again to wash the endometrial cavity. The cavity was visualized for staining (Figure 2). Biopsy was obtained from the stained sites and non stained sites and sent for pathologic examination in separate bottles.

Revised manuscript accepted for publication December 3, 2007

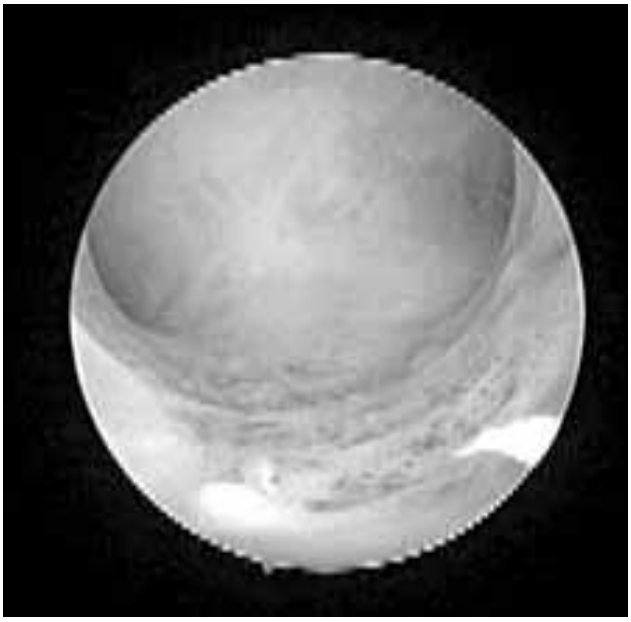

Figure 1. — Before endometrial death.

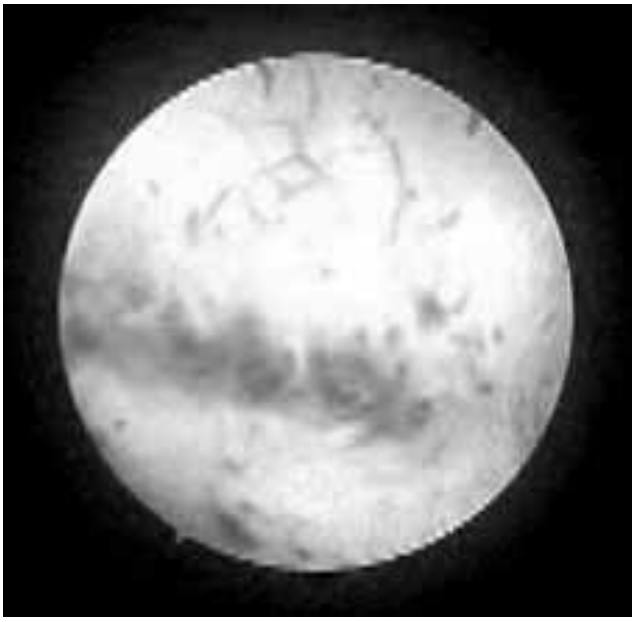

Figure 2. — After endometrial death.

All procedures were performed in an operating room. The classic dorsal litotomy position was appropriated for all vaginoscopic approaches and a 2.9 mm 30° rigid telescope with an operative sheath of 3.5 mm was used for examination (Karl Storz, Germany). Neither speculum nor tenaculum was used in a "no-touch technique" as described by Bettochi *et al*. [7]. All patients were given intraoperative antibiotic prophylaxis with 1 g ceftriaxone (Rocephin, Roche, Istanbul).

Endometrial biopsies were obtained using hysteroscopic grasping forceps. With the jaws open, the forceps were pushed into the endometrium until sufficient tissue was grasped.

Results

Hysteroscopy and chromohysteroscopy procedures were successful in all 22 patients. Before dying of the endometrium there was no direct visual finding in any of the patients. Prior to obtaining a random biopsy in the uterine fundal region cromohysteroscopy was performed.

With endometrial dying, focal dark staining was observed in 19 of 22 patients. Two biopsies were taken, one from a non-stained site and another from the stained site. They were sent for pathological examination separately.

Table 1 shows the raw data of the cases. Compared to conventional diagnostic hysteroscopy chromohysteroscopy-directed biopsy resulted in establishment of diagnoses in three more cases; two cases of endometritis and one endometrial hyperplasia. The pathologist was blinded during the initial histopathologic examination. After completion of the study, specimens were rechecked and the histopathologic diagnosis confirmed.

Discussion

The value of a 'negative' hysteroscopic view is not well established. Loffer [3] suggested that if the criteria for a negative view are followed, tissue sampling will add little to the diagnosis of the case, except possibly when endometritis is present. Our small series contradicts this suggestion; in addition to two endometritis cases we found one more case of hyperplasia using chromohysteroscopy.

A negative hysteroscopic view does not warrant the omittance of endometrial sampling. Due to the risk of missing the correct site of biopsy in a small tissue sample, gynecologists prefer aspiration curettage in these cases to feel more comfortable about the diagnosis.

Table 1. — *Raw data of the cases*.

Case	Age	Years since menopause	Hysteroscopic finding	Histopathology	Chromo-hysteroscopic staining	Histopathology
1	51	4	None	NNE	Yes	NNE
2	53	3	None	Atrophy	Yes	Atrophy
3	59	9	None	Atrophy	No	-
4	49	1	None	NNE	Yes	NNE
5	56	6	None	Endometritis	Yes	Endometritis
6	61	16	None	Atrophy	Yes	Atrophy
7	52	6	None	NNE	Yes	NNE
8	55	4	None	NNE	No	-
9	59	7	None	NNE	Yes	NNE
10	55	9	None	NNE	Yes	Endometritis
11	62	14	None	Atrophy	Yes	Atrophy
12	50	2	None	Hyperplasia	Yes	Hyperplasia
13	54	3	None	NNE	Yes	NNE
14	60	11	None	Atrophy	Yes	Atrophy
15	64	20	None	Atrophy	Yes	Atrophy
16	58	9	None	Atrophy	Yes	Atrophy
17	59	9	None	Atrophy	Yes	Atrophy
18	57	5	None	NNE	Yes	Hyperplasia
19	52	2	None	NNE	Yes	NNE
20	48	2	None	NNE	No	-
21	58	10	None	Atrophy	Yes	Atrophy
22	57	10	None	Atrophy	Yes	Endometritis

NNE: Non-neoplastic endometrium.

However in that case a vaginal speculum and a tenaculum are used and possibly anesthesia is required, but then, the philosophy of performing a no-touch diagnostic hysteroscopy is broken.

The diagnosis of endometrial hyperplasia is challenging for hysteroscopists [8, 9]. There is no established diagnostic criteria for the diagnosis of endometrial hyperplasia, and there is overlap with the normal late secretory endometrium. An attempt of establishing hysteroscopic criteria for endometrial pathologies has been made [10]. Garuti *et al.'s* study to correctly diagnose endometrial hyperplasia using his own criteria failed [11]. Thus the final diagnosis is still established with histopathologic examination.

Cicinelli *et al*. reported on correct diagnoses of endometritis in hysteroscopy [12]. The observation of micropolyps at fluid hysteroscopy was associated with a 94% probability of chronic endometritis. However, in patients with confirmed endometritis, micropolyps were only observed in 54% of cases. The addition of endometrial dying to the diagnostic criteria in hysteroscopy will possibly increase the accuracy of hysteroscopic diagnoses.

Dying of the endometrium with methylene blue was first reported by Marconi *et al*. [6]. They used methylene blue in various phases of the endometrial cycle in 20 premenopausal women. Although epithelium is "non-absorptive" they showed staining of endometrium except in the periovulatory phase. There is only one possible explanation for staining of the endometrial cells: disruption of the integrity of the cell membrane. Membrane cell integrity is disrupted during apoptosis, and apoptosis is increased in abnormal conditions such as infection or hyperplasia. These are two challenging conditions for the hysteroscopist to diagnose.

In conclusion, the results of this preliminary study suggest that chromohysteroscopy can increase the diagnostic acuracy of conventional hysteroscopy. Even though the number of cases was small, it opens a new avenue worth pursuing. Testing the procedure with other vital dyes and for other indications like implantation failure in ART cycles in randomized controlled studies is warranted.

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