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ENDOMETRIAL DISEASE IS RULED OUT BY A HOMOGENOUSLY LIGHT STAINED ENDOMETRIUM ON CHROMOHYSTEROSCOPY

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ABSTRACT

Aim: To study the differential staining of endometrium in different uterine pathologies in patients of abnormal uterine bleeding on chromohysteroscopy.

Study Methods: A prospective study was conducted in 100 perimenopausal women with abnormal uterine bleeding over three years. All women underwent transvaginal sonography, hysteroscopy and chromohysteroscopy followed by the guided biopsy of the endometrial tissue which underwent histopathological examination by a clinical pathologist who was blinded regarding hysteroscopic findings.

Results: Mean age of the study group was 43.49 yrs, mean parity was 3 and mean BMI was 25.41. 40% cases presented with menorrhagia, 38% with polymenorhagia, 9% with metrorrhagia and 4% with postmenopausal bleeding. On TVS, mean size of the uterus was 8.2 cm and the endometrial thickness (ET) varied between 2 to 30 mm with mean ET of 10.21 mm. Conventional Hysteroscopy revealed normal endometrium in 83 cases while diffuse endometrial disease was suspected in 17 cases (hyperplastic in 13 cases and polypoidal in 4 cases; intracavitary lesions were detected in 26 cases (submucous fibroids in 14, endometrial polyps in 11, and growth with areas of necrosis in one case), synechiae in 2 cases. On Chromohysteroscopy, it was found that the endometrium in majority of cases (80%) was homogenously stained, 17% cases showed partial staining pattern and 3% cases attained dark staining of the endometrium. On histopathology, abnormal findings were detected in 13 cases (polypoidal endometrium in four, chronic endometritis in 4, simple hyperplasia in 3 and atrophic endometrium in 2 cases, 1 case had both chronic endometritis with polypoidal endometrium. The conventional hysteroscopic, chromohysteroscopic and histopathologic findings were then compared with each other. No pathology was detected on histology in 76 out of 80 cases that got homogenously stained (Sensitivity-69.23%, specificity- 87.35%, positive predictive value 45.0%, and negative predictive value- 95.0%). Thus, it is evident that in cases with homogenous light staining endometrium (on chromohysteroscopy), detection of an endometrial disease at histology is significantly less frequent *(P< 0.001)*.

Conclusion: No case with homogenously stained endometrium is likely to have an abnormal histopathology i.e. homogenously light stained endometrium on chromohysteroscopy excludes Endometrial Disease.

KEYWORDS :

INTRODUCTION

Traditionally abnormal uterine bleeding (AUB) has been investigated with blind procedures like dilatation and curettage or office endometrial biopsy, but now with changing trends towards minimally invasive investigations, diagnostic hysteroscopy with directed biopsy has become the gold standard[1] in the AUB workup. However, there is a continuing debate about its accuracy in diagnosing diffuse endometrial diseases like endometrial hyperplasia and endometritis. A systematic quantitative review of 3486 articles and 65 primary studies on efficacy of conventional hysteroscopy by Clark et al (2002)[2] indicates that accuracy of hysteroscopy is moderate such that it cannot diagnose or exclude endometrial disease with a high level of certainty and further testing is indicated. Need of the hour is therefore for a technique that would increase the efficacy of hysteroscopy and chromohysteroscopy is proposed to be one such novel chromoendoscopy technique.

Chromoendoscopy or tissue staining techniques like chromohysteroscopy involve application of stains or pigments to improve localization, characterization, or diagnosis of lesions[3]. It enables endoscopists to formulate a diagnosis and to direct biopsies based on a specific reaction or enhancement of surface morphology. In recent years, there has been a resurgence of interest in this technique because it is a simple, safe, quick, widely available, and an inexpensive diagnostic tool that has been extensively used in gastro-endoscopy[4-6]. Methylene blue is a water-soluble vital stain that is actively taken up by absorbing tissues. Though unlike gastrointestinal mucosa, endometrium is not an absorptive epithelium, it has been reported that endometrium can be stained with methylene blue in all phases except in the peri-ovulatory phase[7]. The reason for endometrial staining has been explained with theory of apoptosis and it has been stated that the apoptotic structural damage allows passage of the methylene blue dye into the cell. Mucosal staining by methylene blue has been comprehensively studied in gastroenterology and it has been found to be a safe, inexpensive, reproducible, and a highly accurate method[8] of diagnosing subtle mucosal changes. Inspired from wide success of chromoendoscopy in the field of gastroenterology, possibility of application of vital stains to endometrium came to the mind of gynaecologists and chromohysteroscopy technique came into existence.

MATERIAL METHODS

The subjects of the present prospective study were 100 perimenopausal women aged ≥40 years who presented with complaints of abnormal uterine bleeding and met the inclusion criteria. The aim and procedures of the study were explained to each potential subject. Subjects who did not give informed consent and those with pelvic infection, pregnancy, pregnancy related complications, carcinoma cervix, deranged thyroid profile, abnormal liver functions and coagulopathy were excluded. The study protocol was approved by the Institute's Ethics Committee. A comprehensive history was taken and a clinical (general, systemic and pelvic) examination was done in all subjects. All cases were subjected to transvaginal sonography.

Following the necessary pre-operative preparation, all women underwent diagnostic hysteroscopy, chromohysteroscopy and targeted biopsy of the endometrial tissue in the operation theatre. With patients under suitable anaesthesia, fully assembled hysteroscope i.e. attached to the fibreoptic light source, distending medium (0.9% sodium chloride solution) and video endocamera was introduced into the cervical os and the irrigating system was turned on. Adequate focussing of the image was done prior to insertion of the hysteroscope which was advanced slowly into the uterine cavity under direct vision. The cervical canal was visualised in its totality. Once the junction between cervix and uterus was crossed, the uterine cavity was first observed panoramically and then, bilateral tubal ostia were inspected. Following this, all portions of uterine wall: - fundus, anterior wall, left lateral wall, posterior wall and right lateral wall were systematically (clockwise) inspected. Slight rotation of the hysteroscope was needed to observe the utero-tubal regions, aided by its inbuilt fore-oblique view. The hysteroscopic findings were recorded and any abnormal areas if detected were noted.

This was followed by chromohysteroscopy. 5 ml of 1% methylene blue was introduced through the hysteroscopic inlet. After 3 minutes (staining time) distending medium flow was started again to wash the endometrium and the uterine cavity was then visualised for staining pattern. First the staining pattern over the intracavitary lesion (if present) was noted and then the adjacent endometrial staining patterns were studied. In cases without cavity lesions differential staining pattern of the endometrium was directly studied. Different patterns of staining observed were: homogenous light blue staining, dark blue staining, partial staining and unstained areas. Diffuse light blue staining was considered normal. Partial staining, dark blue staining or unstained areas above the internal cervical ostium regardless of size and number of stained areas were considered positive findings. These findings were compared with the diagnostic hysteroscopy findings. Biopsies were obtained from differentially stained areas and when no specific staining pattern was seen, a single aspiration biopsy was obtained. Biopsy obtained from the differentially stained sites and non stained sites were sent for pathologic examination in separate bottles. All the endometrial biopsy specimens were examined by the same pathologist who was blinded about the hysteroscopic findings. The hysteroscopic and chromohysteroscopy findings were then compared with the histopathology results and the diagnostic accuracy of both the techniques were calculated. The results were statistically analyzed using SPSS Software using T test, Chi square test and Mann Whitney tests.

RESULTS

Mean age of the study group was 43.49 ± 4.42yrs, average parity was 3 and mean BMI was 25.41± 3.41 Kg/m^2. Forty percent cases presented with menorrhagia, 38% with polymenorhagia, 9% with metrorrhagia and 4% with postmenopausal bleeding.

Conventional hysteroscopy revealed normal cavity in 59 cases, intracavitary lesions were detected in 26 cases (submucous fibroids (Fig1) in 14, endometrial polyps (Fig2) in 11, and growth with areas of necrosis in one case), and synechiae in 2 cases, diffuse endometrial disease was suspected in 17 (hyperplastic in 13 cases) and polypoidal in 4 cases cases.

On chromohysteroscopy, endometrium got homogenously stained (Fig3) in 80% cases whereas differentially stained in 20%; 17% partially (Fig4) and 3% dark stained (Fig5) cases (Table1). The staining pattern of the surrounding endometrium in cases with intracavitary lesions were taken into account while studying the chromohysteroscopy findings of the endometrium. No pathology was detected on histology in 76 out of 80 (95%) cases that got homogenously stained.

On histopathology, abnormal findings were detected in 13 cases; polypoidal endometrium in 4 cases, chronic endometritis in 4 cases, simple hyperplasia in 3 cases and atrophic endometrium in 2 cases. Endometrium in all cases with chronic endometritis got partially stained and all cases with simple hyperplasia showed dark staining endometrium. In cases with partial staining endometrium, likelihood of finding chronic endometritis and in cases of dark-stained endometrium, likelihood of detecting simple hyperplasia was found to be high.

TABLE1: STAINING PATTERNS OF THE ENDOMETRIUM ON CHROMOHYSTEROSCOPY

Staining patterns of the endometrium on chromohysteroscopy	No of cases	Percent
Homogenous Light Staining	80	80.0
Partial Staining	17	17.0
Dark Stained	3	03.0
Total	100	100.0

By studying the endometrial staining patterns on chromohysteroscopy, two more cases of chronic endometritis, two more cases of polypoidal endometrium and three more cases of hyperplastic endometrium were detected which got otherwise missed on hysteroscopy. Endometrial disease was found to be significantly less frequent in cases with homogenous light staining endometrium i.e. Almost no case with homogenously light stained endometrium is likely to have an abnormal histopathology *(P< 0.001)*. Endometrial disease was diagnosed in 12 out of 20 cases with non-homogenously or differentially stained endometrium. Chromohysteroscopy thus detected 12 out of 13 (92.30 %) cases with endometrial disease. The diagnostic accuracy of chromohysteroscopy in detecting endometrial disease was found to be high (Sensitivity-92.30 %, specificity- 87.35%, negative predictive value 95.0%, positive predictive value- 60.0 %).

DISCUSSION

Uterine cavity was considered to be normal on hysteroscopy when all the following three criteria were met: good visualization of the entire uterine cavity, no structural abnormalities in the uterine cavity and a uniformly thin, homogenous-appearing endometrium without variations in thickness. Hysteroscopic detection of focal or extensive endometrial thickening, irregular vascularity or architectural distortion was considered endoscopic features consistent with diffuse endometrial disease. However, differentiation between endometritis and endometrial hyperplasia could not be made out on conventional hysteroscopy.

Chromohysteroscopy was done in all and it was found that the endometrium in majority cases was homogenously stained and in 95.0% of these cases, histopathology was normal. It can thus be concluded that endometrial disease is significantly less frequent (P< 0.001), in homogenously stained endometrium. This finding is in accordance with the studies by Safali et al [10] and Kucuk et al [11].

Table2 compares the endometrial staining findings of our study with those in various other studies on chromohysteroscopy in patients of postmenopausal bleeding[9], recurrent in vitro fertilization failure[10] and recurrent miscarriage cases[11].

TABLE 2: CHROMOHYSTEROSCOPIC FINDINGS OF DIFFERENT STUDIES

Studies / Findings	**Devici (2007)[9]**		**Safali (2007)[10]**		**Kucuk (2007)[11]**		**Our Study**	
	No of cases	%	No of cases	%	No of cases	%	No of cases	%
Homogenously stained Endometrium	22	81.48	41	64.06	15	44.12	80	80.0
Partially Stained Endometrium	0	0.0	1	1.67	0	0.0	17	17.0
Darkly Stained Endometrium	5	18.51	22	34.37	19	55.88	3	3.0
Total cases	27	100.0	64	100.0	34	100.0	100	100.0

Four (4%) cases in our study group were in the postmenopausal age. The mean age among the postmenopausal women was 43.49 (± 4.416) yrs. On diagnostic hysteroscopy, two of these postmenopausal women were found to have intracavitary lesions (polyp was in one and fibroid in another); the endometrium appeared normal in third case and diseased in the fourth. On chromohysteroscopy, three cases were found to have a homogenously stained endometrium (including the one that appear diseased on hysteroscopy) and the one with a polyp had a partially stained endometrium. On histopathology, all three with homogenously stained endometrium were found to be normal and chronic endometritis was detected in the case with a partial staining endometrium. Devici S et al[9] had studied twenty-two women with postmenopausal bleeding and with chromohysteroscopy, diagnosed three more endometrial pathologies i.e. two more cases of endometritis and one more case of endometrial hyperplasia. However, cases with endometrial disease in Devici study had shown focal dark staining on chromohysteroscopy, conflicting with our study findings in which endometrium in cases with endometritis got partially stained. This may be due to observer variations as endometrial areas with partial staining may sometimes be interpreted as focal areas with a higher stain uptake though that uptake may be normal and adjacent endometrium may be relatively less or partially stained.

Six cases with partially staining endometrium had abnormal histopathology; four cases had chronic endometritis and two cases had polypoidal endometrium. Diffuse endometrial disease could be suspected only in two of these six cases on diagnostic hysteroscopy. Thus, it can be noted that the conventional hysteroscopy missed four cases with endometrial disease which were picked on chromohysteroscopy as partial staining endometrium and were further, confirmed on histology. This is in agreement with findings of a study by Deveci et al[9].

Endometrium got dark-stained in 3 cases on chromohysteroscopy. All these cases (100%) were diagnosed as simple hyperplasia. It can be concluded that darkly stained endometrium is very less likely to be normal on histology. However studies with a larger sample size are warranted further to assess these findings. Studies by Devici et al [9], Safali et al [10] and Kucuk et al [11] also suggest that dark staining of endometrium on chromohysteroscopy indicates endometrial pathology.

The diagnostic efficacy of chromohysteroscopy in detecting the disordered proliferative phase was studied. Disordered proliferative phase is considered to be qualitatively similar to simple hyperplasia but is focal lesion. It is characterized by irregularly shaped and enlarged glands that are focally interspersed among normal proliferative glands. However, there is no proliferation of glands. So, it is not taken as hyperplasia. It is basically dysfunctional endometrium seen more commonly in women with anovulatory cycles. Ten cases had disordered proliferative endometrium in our study. Endometrium in nine of these cases showed homogenously light staining whereas only one cases had a partially staining endometrium on chromohysteroscopy. It may be concluded that an endometrium which is in disordered proliferative phase is most likely, not a type of endometrial pathology

Two cases were found to have atrophic endometrium on histology. Endometrium in both cases got homogenously stained on chromohysteroscopy. The observation that atrophic endometrium got stained is in accordance with the study by Devici et al (2007) [9]. In this study by Devici, 8 out of 10 cases (80%) of atrophic endometrium got stained by chromohysteroscopy. However, focal dark staining pattern was also observed in cases of atrophic endometrium in that study which contradicts our observations. A study with a larger sample size is warranted to evaluate the staining patterns obtained in atrophic endometrium and to assess whether it can be detected on chromohysteroscopy.

Polypoidal endometrium was diagnosed in four cases in our study group. Endometrium in two cases (50%) showed homogenous staining and the other two cases (50%) showed partial staining on chromohysteroscopy. Thus, no specific pattern could be associated with presence of polypoidal endometrium. However, no other study on chromohysteroscopy mentions its efficacy in diagnosing polypoidal endometrium. Four cases of chronic endometritis were detected in our study and endometrium in all cases was found to be partially stained. It is thus evident that the likelihood of cases with partial staining endometrium to have chronic endometritis at histopathological examination is very high. In a study by Safali et al[10] on chromohysteroscopy in recurrent IVF cases, 22 cases showed dark-stained endometrium and 9 of these cases had endometritis on histopathology. Endometrium in 41 cases was homogenously stained. However, 4 cases of endometritis were diagnosed in this group with homogenous staining as well. Kucuk et al[11] had studied chromohysteroscopy patterns in recurrent miscarriage cases, 19 cases showed dark-stained endometrium and 10 of these cases had endometritis confirmed on histopathology. Endometrium in the rest 15 cases was homogenously stained and all had normal histopathology.

Homogenous light blue staining was considered normal. Partial staining, dark blue staining or unstained areas above the internal cervical ostium regardless of size and number of stained areas were considered as positive findings. After chromohysteroscopy, guided biopsy of endometrial tissue was obtained and sent for histopathology.Histopathological examination was done by a clinical pathologist who was blinded regarding hysteroscopic findings. Diagnostic accuracy of hysteroscopy and chromohysteroscopy in detection of endometrial lesions was then studied.

DIAGNOSTIC ACCURACY OF CONVENTIONAL HYSTEROSCOPY AND CHROMOHYSTEROSCOPY IN DETECTING ENDOMETRIAL DISEASE

Thus, on conventional hysteroscopy endometrial disease was suspected in 17 cases whereas endometrium in 83 cases was diagnosed to be free from endometrial disease on hysteroscopy. Conventional hysteroscopy missed 10 out of 13 (76.92%) cases with endometrial disease detected on histopathology. Thus, the diagnostic accuracy of conventional hysteroscopy in detecting endometrial disease was found to be very poor. Whereas on,chromo- hysteroscopy endometrium got homogenously stained in 80 cases. No pathology was detected on histology in 76 out of 80 cases that got homogenously stained. Chromohysteroscopy detected 11 out of 13 cases with histopathologically confirmed endometrial disease.

CONCLUSIONS

Endometrial disease is significantly less frequent in cases with homogenously light stained endometrium (*P< 0.001)*. That is, the homogenously light stained endometrium on chromohysteroscopy excludes endometrial disease. Chromohysteroscopy is a novel technique that improves the efficacy of conventional hysteroscopy by detecting the missed endometrial pathologies.

IMPLICATIONS OF THE STUDY

Chromohysteroscopy is thus a useful adjunct to conventional hysteroscopy that facilitates the detection as well as exclusion of endometrial diseases in AUB thereby helping in diagnosing DUB (a diagnosis of exclusion).Thus, a routine use of chromohysteroscopy in the evaluation of women with AUB in addition to the conventional hysteroscopy technique is worth consideration However, more studies and with a larger sample size needs to be undertaken to further expand the uses of chromohysteroscopy and work out its final indications.It is therefore strongly concluded various endometrial staining patterns on chromohysteroscopy facilitate the detection as well as exclusion of endometrial pathologies. Chromohysteroscopy is thus a useful cost-effective adjunct to hysteroscopy that is worth consideration.

REFERENCES

1. Speroff Leon, Fritz MA. Clinical Gynecologic endocrinology and infertility. 8th ed. Philadelphia : Lippincott Williams & Wilkins; 2011;591-604
2. Clark TJ,Voit D, Gupta JK, et al. Accuracy of hysteroscopy in diagnosis of endometrial cancer and hyperplasia: A systematic quantitative review. JAMA 2002; 288: 1610-1621
3. Fennerty MB. Tissue Staining: Gastrointestinal Endoscopy. Clinical N Am. 1994; 4(2):297-311
4. Conto M. Staining in Gastrointestinal Endoscopy: The Basics. Endoscopy. 1999,31 (6):479-486
5. Park SY, Lee SK, Kim BC, Han J, Kim JH, Cheon JH, Kim TI, Kim WH. Efficacy of chromoendoscopy with indigocarmine for the detection of ascending colon and cecum lesions. Scand J Gastroenterol. 2008; 43(7):878-85.
6. Duncan MB, Horwhat JD, Maydonovitch CL, Ramos F, Colina R, Gaertner E, Yang H, Wong RK. Use of methylene blue for detection of specialized intestinal metaplasia in GERD patients presenting for screening upper endoscopy. Dig Dis Sci. 2005;50(2): 389-93
7. Marconi Guillermo. New observations on endometrial physiology after transcervical injection of methylene blue dye. Fertility and Sterility. 2004: 82(6): 1700-04
8. Dinis-Ribiero M Moreira Dias L. There is no clinical evidence of consequences after methylene blue chromoendoscopy. GI Endoscopy. 2008; 67(7):1209
9. Deveci S et al. Can "chromohysteroscopy" help target endometrial biopsy in postmenopausal bleeding? Eur J Gynecol Oncol. 2008; 29(2):165-7.
10. Safali M. et al "Chromohysteroscopy" for evaluation of endometrium in recurrent in vitro fertilization failure. J Assist Reprod Genet. 2008; 25(2-3):79
11. Küçük T, Deveci S. "Chromohysteroscopy" for evaluation of endometrium in recurrent miscarriage. Clin Exp Obstet Gynecol. 2008; 35(2):133-6