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Chromohysteroscopy and Laparoscopy Findings in Infertile Patients with Persistent Midluteal Phase Central Endometrial Echo

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Abstract

Objective: To study the relationship between persistent midluteal central endometrial echo versus polycystic ovaries and chromohysteroscopy and laparoscopy findings in infertile patients with regular menstruation.

Material and methods: 164 infertile patients with regular menstruation were investigated with ultrasound monitored cycles followed by chromohysteroscopy and laparoscopy. Persistent midluteal central endometrial echo was assessed against presence of polycystic ovaries, micropolyps and deep endometrial staining with methylene blue and presence of endometriosis diagnosed laparoscopically.

Results: 51 patients (31.1%) showed persistent central midluteal endometrial echo and 72 (43.9%) showed polycystic ovaries. During chromohysteroscopy 21 patients (12.8%) showed micropolyps and 26 (15.9%) showed deep endometrial staining with methylene blue. Moreover, 30/51 patients with central midluteal endometrial echo (58.8%) showed polycystic ovaries versus 42/113 patients (37.2%) with homogeneous endometrium, p=0.011. Furthermore, 18/51 patients (35.3%) with central endometrial echo showed dark endometrial discolouration with methylene blue versus 08/113 patients (7.1%) with homogenous endometrium, p<0.001. Similarly, 14/51 patients (27.5%) with central midluteal endometrial echo showed micropolyps versus 7/113 (6.2%) with homogeneous endometrium, p=0.001. Polycystic ovaries showed no significant association with either sign of chronic endometritis. During laparoscopy, 31/164 patients (18.9%) showed pelvic endometriosis. 14 of them (45.2%) developed deep endometrial discolouration with methylene blue versus 12/113 patients (9.0%) without endometriosis, p<0.001. Likewise, 21/31 patients with endometriosis (67.7%) had central midluteal endometrial echo versus 30/133 patients (22.6%) with no endometriosis, p<0.001. This association was maintained after excluding patients with chronic endometritis.

Conclusion: Persistent midluteal central endometrial echo might reflect chronic endometritis as it was significantly associated with deep endometrial discolouration with methylene blue and micropolyps. The significant association between endometriosis and midluteal central endometrial echo in cases with and without chronic endometritis indicated that endometriosis might affect the endometrium through more than one mechanism. Conversely, the association of polycystic ovaries with midluteal endometrial echo was independent of chronic endometritis.

Keywords: Mid luteal central endometrial echo; Chronic endometritis; Endometriosis

Introduction

Chronic endometritis was a neglected diagnosis in gynaecological practice but has recently emerged as an important factor associated with implantation failure, repeated miscarriages and neonatal problems [1,2]. Women with histopathological diagnosis of chronic endometritis were shown to have lower implantation rates in subsequent *in vitro* fertilisation and embryo transfer cycles (IVF-ET) [3]. A recent prospective study showed chronic endometritis in 14% of patients with recurrent implantation failure and 27% of patients with recurrent pregnancy loss [4]. On the positive side, treatment of chronic endometritis resulted in successful pregnancies after IVF-ET in patients who had recurrent implantation failures in the past [5]. Furthermore, chronic endometritis was found to be highly prevalent in patients with unexplained infertility and its treatment improved spontaneous pregnancy and live birth rates [6]. An interesting study reported chronic endometritis in 52.94% of patients with endometriosis compared to 27.02% of patients with no endometriosis p=0.05. [7].

Recent studies showed the accuracy of fluid hysteroscopy exceeded 90% in diagnosing chronic endometritis compared to histological examination. It also had higher sensitivity than endometrial microbiological examinations [8-10]. Yet again using chromohysteroscopy further improved the diagnostic power of hysteroscopy. Instillation of methylene blue before hysteroscopic examination of the uterine cavity increased the efficacy for diagnosing abnormal endometrium and targeting endometrial biopsies [11]. This was confirmed by another study which showed chromohysteroscopy to be more effective in detecting endometrial pathology than blind endometrial sampling [12]. At the same time, chromohysteroscopy could give reassuring results as diffuse light blue staining without dark areas strongly indicated normal endometrium free of endometritis [13].

All studies reporting on chronic endometritis relied on different hysteroscopic appearances summarised recently by an international randomised controlled observer study [14]. Historically, micropolyps, intense discolouration of the endometrium with methylene blue or toluidine blue during chromohysteroscopy and laboratory studies on endometrial biopsies were the main diagnostic tools. There was no study which showed specific ultrasonic characteristics of chronic endometritis in relation to infertility, reduced implantation rates or recurrent miscarriages. A recent transvaginal ultrasound study with saline infusion sonohysterography failed to diagnose micropolyps in 81 patients investigated for abnormal uterine bleeding, infertility and

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repeated miscarriages [15]. Nevertheless, nonhomogeneous midluteal phase endometrial patterns were reported to be associated with lower implantation rate during assisted reproduction treatment cycles [16,17]. Similarly, a recent study reported persistent midluteal central endometrial echo in 26 of 72 infertile regularly menstruating patients (36.1%) investigated with repeated ultrasound scan examinations [18]. Local factors were postulated to be important in this respect as endometrial thickness, uterine arteries blood flow and midluteal serum progesterone levels did not correlate to the presence of the persistent midluteal central endometrial echo.

In the current study I looked at a possible association between ultrasonically diagnosed persistent midluteal central endometrial echo against polycystic ovaries and signs of chronic endometritis diagnosed during chromohysteroscopy. I also investigated whether laparoscopy could add useful information in relation to this problem, as endometriosis was shown previously to be associated with chronic endometritis [7].

Material and Methods

A total of 164 infertile patients with regular menstrual cycles were monitored with repeated ultrasound scan examinations during a whole cycle. This was followed by chromohysteroscopy with methylene blue and diagnostic laparoscopy during the early follicular phase of a subsequent cycle. All procedures were done as part of the routine clinical assessment for infertility. Presence of polycystic ovaries, chromohysteroscopic signs of chronic endometritis and presence of laparoscopically diagnosed endometriosis were noted. They were assessed against the ultrasound diagnosis of persistent midluteal central endometrial echo. All patients consented to have their nonidentifying information used for teaching and research purposes. Patients with submucous fibroids or history of previous uterine surgery were not included in the study.

Cross tabulation with chi square test and binary logistic regression analysis were used as appropriate. The Mann-Whitney *U* test was used for nonparametric data. The Statical Package for Social Sciences (IBM SPSS) was used for data analysis. $P \leq 0.05$ was used to indicate statistical significance with an observed power=0.8.

Results

During ultrasound monitored cycles, 51 patients (31.1%) showed persistent central midluteal endometrial echo and 72 (43.9%) showed polycystic ovaries. During chromohysteroscopy 21 patients (12.8%) showed micropolyps and 26 (15.9%) showed deep endometrial staining with methylene blue. Figures 1 and 2 show samples of the cases seen. Moreover, 30/72 patients with polycystic ovaries (41.7%) showed central endometrial echo versus 21/92 patients (22.0%) with normal ovaries, p=0.011. Furthermore, 18/51 (35.3%) patients with central endometrial echo showed dark endometrial discolouration with methylene blue versus 08/113 patients (7.1%) with homogenous luteal endometrium, p<0.001. Similarly, 14/51 (27.5%) patients with

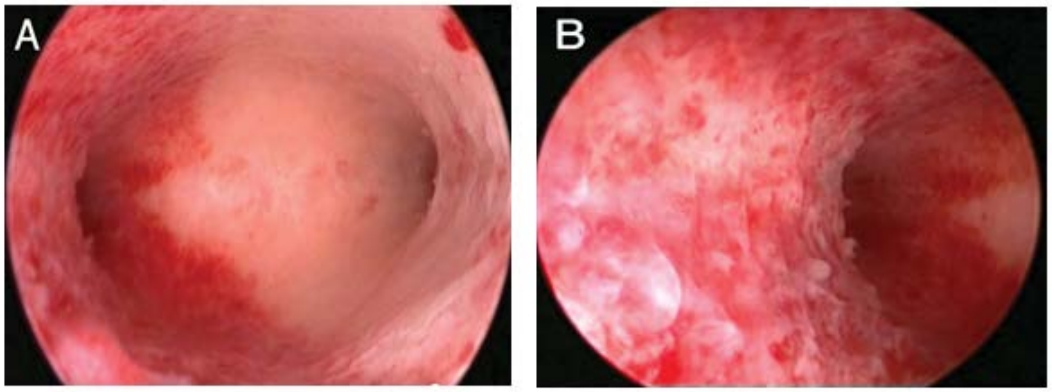

Figure 1: (A) A hysteroscopic panoramic view of a uterine cavity with hyperaemic area involving the left sidewall and parts of the posterior wall and fundus. (B) A magnified view of the left sidewall of the same uterus showing micropolyps.

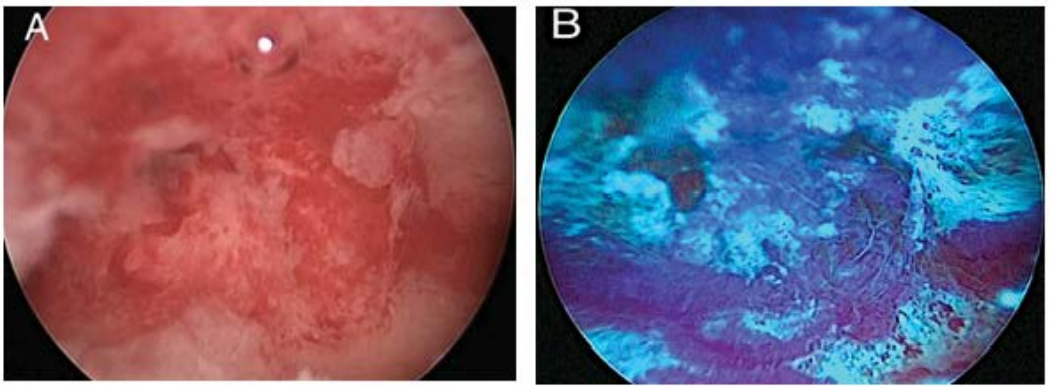

Figure 2: Hysteroscopic views of an inflamed uterine cavity before (A) and after instillation of methylene blue (B). Note the wide distribution of deeply stained endometrium almost mirroring the hyperaemic area in image (A).

Variables	B	S.E.	Wald	df	P value	Exp(B)	95% C.I. for Exp (B)	
							Lower	Upper
PCO	0.824	0.371	4.929	1	0.026	2.28	1.101	4.721
Endometriosis	1.939	0.445	19.001	1	0	6.95	2.907	16.619
Constant	-3.907	0.998	15.321	1	0	0.02		
B: Coefficient for the constant in the null model; SE: Standard error around the coefficient for the constant; Wald: Wald chi-square tests the null hypothesis that the constant equals 0; df: Degrees of freedom for the Wald chi-square test; Exp (B): Exponentiation of the B coefficient; which is the odds ratio; 95% C.I. for Exp (B): 95% confidence interval for the odds ratio.								

Table 1: Shows both polycystic ovaries and endometriosis were significantly associated to persistent midluteal central endometrial echo after binary logistic regression analysis.

Variables	B	S.E.	Wald	df	P value	Exp(B)	95% C.I. for Exp (B)	
							Lower	Upper
PCO	0.777	0.382	4.129	1	0.042	2.174	1.028	4.599
Endometriosis	1.575	0.476	10.961	1	0.001	4.831	1.902	12.275
Endometritis	1.452	0.519	7.822	1	0.005	4.273	1.544	11.822
Constant	-5.845	1.329	19.339	1	0	0.003		
B: Coefficient for the constant in the null model; SE: Standard error around the coefficient for the constant; Wald: Wald chi-square tests the null hypothesis that the constant equals 0; df: Degrees of freedom for the Wald chi-square test; Exp (B): Exponentiation of the B coefficient; which is the odds ratio; 95% C.I. for Exp (B): 95% confidence interval for the odds ratio.								

Table 2: Shows the result of logistic regression analysis when chronic endometritis was included in the equation together with polycystic ovaries and endometriosis. Endometriosis had the highest exponentiation coefficient (odds ratio) followed by endometritis then polycystic ovaries. Despite the significant association between endometriosis and chronic endometritis shown by this study, each of them maintained an independent high significant association to the persistent midluteal endometrial echo in logistic regression analysis.

persistent midluteal endometrial echo showed micropolyps versus 7/113 patients (6.2%) with homogeneous luteal endometrium, p=0.001.

During laparoscopy, 31/164 patients (18.9%) showed pelvic endometriosis. Deep endometrial discolouration with methylene blue was seen in 14/31 patients (45.2%) with endometriosis versus 12/113 patients (9.0%) without endometriosis, p<0.001. Comparably, 10/31 patients with endometriosis (32.3%) showed endometrial micropolyps versus 11/133 patients (8.3%) with no endometriosis, p=0.001. Persistent central endometrial echo was seen in 21/31 patients (67.7%) with endometriosis compared to 30/133 patients (22.6%) with no endometriosis, p<0.001. This association was maintained even after excluding cases with chronic endometritis. In patients with no sign of endometritis, 9/16 patients (56.3%) with endometriosis showed central endometrial echo versus 23/121 patients (19.0%) with no endometriosis, p=0.003.

Unlike endometriosis there was no significant association between PCO and hysteroscopic signs of chronic endometritis. 12/72 patients with PCO (16.7%) showed micropolyps versus 9/92 patients (9.8%) with normal ovaries, p=0.241. The equivalent numbers for patients with deep endometrial staining with methylene blue were 15/72 (20.8%) and 11/92 (12.0%) for patients with PCO and normal ovaries respectively p=0.136. Furthermore, crosstabulation with chi square test showed no association between endometriosis and polycystic ovaries in the whole group. 17/72 patients with PCO had endometriosis (23.6%) versus 14/92 patients (15.2%) with no PCO, p=0.228.

Next step I used polycystic ovaries and endometriosis as independent factors against the persistent central midluteal endometrial echo in a binary logistic regression analysis. Both showed significant association with the abnormal endometrial echo. However, the odds ratio (exponentiation of the B coefficient) of endometriosis was 3.04 times that of polycystic ovaries (Table 1). This represented a higher likelihood of endometriosis to affect the endometrium than PCO. Next, I introduced deep methylene blue staining of the endometrium as a sign of chronic endometritis as a third independent factor in the logistic regression equation as shown in Table 2. Each factor proved to have significant and independent association with the persistent midluteal central endometrial echo. However, endometriosis retained the highest exponentiation coefficient (odds ratio) followed by chronic endometritis, then polycystic ovaries. Nevertheless, there was 30.5% reduction in endometriosis odds ratio after introducing chronic endometritis in the logistic regression equation. This difference represented the contribution of chronic endometritis to the total negative effect of endometriosis on the midluteal phase endometrium. On the other hand, the odds ratio of polycystic ovaries changed by only 4.6% after including chronic endometritis in the equation as shown by the corresponding figures in Tables 1 and 2.

Last I assessed the association of age and body mass index (BMI) to the presence of central endometrial echo. Both parameters did not show normal distribution using Shapiro-Wilk test (p<0.001 for BMI and p=0.011 for age). Accordingly, non-parametric analysis was done using Mann-Whitney *U* test. Both parameters showed no significant association with the central endometrial echo. The mean rank and sum of ranks for age were 82.95 and 4230.50 respectively for patients with central endometrial echo. The equivalent figures for patients who did not show central endometrial echo were 82.30 and 9299.50 respectively. The Mann Whitney *U* test was 2858.500, *Z* was -.082 and the 2 tailed significance tests =.935. The equivalent mean rank and sum of ranks for BMI were 80.17 and 4088.50 respectively for women with central endometrial echo. The corresponding figures for women with no similar endometrial echo were 83.55 and 9441.50 respectively. The Mann-Whitney *U* test was 2762.500, *Z* was -.425 and 2-tailed significance =.671.

Discussion

This study showed significant association between persistent midluteal central endometrial echo with signs of chronic endometritis, polycystic ovaries and endometriosis. It also showed significant association between endometriosis with micropolyps and deep endometrial discolouration with methylene blue. This confirmed a previous finding which showed significant association between endometriosis and chronic endometritis [7]. Despite the highly significant association between the two, endometriosis and chronic endometritis maintained an independent significant association to midluteal central endometrial echo as shown by logistic regression analysis. Also, endometriosis had significant association with the

same echo even after controlling for signs of chronic endometritis. This suggested that endometriosis might also affect the luteal phase endometrium by another mechanism other than chronic endometritis. Lessey [19] reported low expression of secretory phase endometrial cells integrins (adhesion molecules) in some women with endometriosis. This was seen more often in minimal and mild endometriosis compared to the more severe grades despite the endometrium being histologically in phase. The same author reported increased endometrial integrins levels after treatment of endometriosis. Accordingly, chronic endometritis and low levels of luteal phase endometrial integrins might be separately responsible for the midluteal unfavourable endometrium represented by the persistent central echo. On the other hand, the corresponding association of polycystic ovaries with the midluteal phase endometrial echo proved to be independent of chronic endometritis. This might be affected through local endometrial hyperandrogenisation as postulated before [18]. Unexpectedly, neither age nor BMI showed significant association with the central endometrial echo.

Conclusion

Persistent midluteal central endometrial echo might reflect chronic endometritis as shown by its significant association with deep endometrial discolouration with methylene blue and micropolyps. The likelihood of endometriosis to negatively affect the endometrium proved to be higher than PCO. Beside its negative effect on endometrial integrins levels, endometriosis might affect endometrial function by causing chronic endometritis. On the other hand, the significant association of polycystic ovaries with midluteal central endometrial echo was independent of chronic endometritis. Age and BMI had no effect on midluteal endometrial texture.

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