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Factors and Clinical Scenarios Possibly Related to Endometrial Micropolyps and Chronic Endometritis

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Abstract

Objectives: To study factors and clinical scenarios possibly related to the development of endometrial micropolyps, hence chronic endometritis.

Materials and methods: 197 patients with abnormal uterine bleeding, infertility or recurrent miscarriages were studied by early follicular phase transvaginal ultrasound scan examinations and hysteroscopy. Presence of endometrial micropolyps was assessed in relation to sexual intercourse frequency, regular vaginal washing, parity, previous pelvic infection and previous uterine surgery. The likelihood of patients to use vaginal washing was examined against the other four factors. Furthermore, the association of micropolyps with other uterine pathologies was examined. Cross tabulation with chi square test, binary logistic regression analysis and odds ratio were used as appropriate to examine the data.

Results: Hysteroscopic examination revealed 81 cases with micropolyps not diagnosed previously by transvaginal ultrasound scan examinations. 56 of them (69.14%) presented with abnormal uterine bleeding, 13 with infertility (16.04%) and 12 with repeated miscarriages (14.81%), p=0.012. Cross tabulation and chi square test showed micropolyps were significantly associated to parity, sexual intercourse frequency, previous pelvic infection and regular vaginal washing, but not previous uterine surgery. Furthermore, binary logistic regression analysis showed vaginal washing was the most significant factor in this group. It also showed that micropolyps were significantly associated to the presence of endometrial polyps (p=0.022) and symptomatic patients with negative ultrasound findings (p=0.049). Patients who had more frequent sexual intercourse showed high odds ratio to use regular vaginal washing, but not the other three groups.

Conclusion: Women should be advised against vaginal washing, especially those at risk of chronic endometritis. Micropolyps might be precursors to endometrial polyps because of the close association between the two. Chronic endometritis might trigger clonal rearrangements and translocations between the four stromal chromosomes already suspected of initiating endometrial polyps' development.

Keywords: Chronic endometritis; Micropolyps; Hysteroscopy; Vaginal washing

Introduction

Endometrial micropolyps have been described as reliable markers of chronic endometritis with an odds ratio of 124.2 and 95% confidence interval of 50.3-205.4 [1,2]. The sensitivity, specificity, positive and negative predictive values were 54%, 99%, 94% and 89%, respectively. In women without micropolyps, chronic endometritis was significantly less frequent and was diagnosed only in 10.8% of women confirmed histologically. The same authors showed the diagnostic accuracy of fluid hysteroscopic assessment of the endometrial cavity to exceed 90% compared to histological examination. It also had higher sensitivity for detecting chronic endometritis than endometrial microbiological examination [3]. Other hysteroscopic criteria for chronic endometritis included focal or generalised areas of red endometrium flushed with white central points giving a strawberry appearance [4]. On the other hand, acute endometritis may show a different picture characterised by oedema of the bleeding endometrium covered by abnormal mucous.

Affected patients may present with abnormal uterine bleeding, recurrent miscarriages, infertility, leucorrhoea and repeated assisted reproduction treatment (ART) failure. Even increased perinatal complications have been described in patients with chronic endometritis [5]. Despite all these problems, chronic endometritis is not usually considered as a provisional diagnosis during gynaecological clinical assessment of these patients. This is because there is no correlation between the specific clinical features and the intensity of the pathological findings. In fact, most cases showed no noticeable signs or at most presented with only mild symptoms [6]. Furthermore, the intensity of inflammation had no correlation with patients' age or duration of symptoms [7].

Different authors gave different prevalence rates of chronic endometritis. Based on histological examination of hysterectomy specimens, figures of 10 and 11% were reported [8,9]. However, a higher figure of 57.8% was reported in women with recurrent miscarriages [10]. There were also few differences in the reported prevalent bacteria causing endometrial infections in the literature. The most common in one report were *Mycoplasma* and *Ureaplasma* in 25.3% and *Chlamydia* in 12.7% [11]. In another series, *Chlamydia trachomatis* was detected in 44 of 92 patients (48%) with abnormal uterine bleeding. The authors concluded that prevalence of this bacteria was under estimated [12]. Yet again common bacteria (58%) and *Ureaplasma urealyticum* (10%) were reported as the most frequent agents in another series with *chlamydia* isolated in only 2.7% of the cases [13]. The same authors found low agreement between vaginal and endometrial cultures. Unexpectedly,

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a different study reported no significant differences in the rates of microbes isolated from patients with chronic endometritis compared to women with no endometritis [14]. Furthermore, it showed only acute but not chronic endometritis was associated with such microbes as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Proper diagnosis of chronic endometritis is essential as treatment was successful in most reports. Antibiotics treatment normalized the endometrial picture seen during hysteroscopy in 71% of the patients [11]. Irrespective of the endometrial culture, 78.4% of those treated conceived within one year after treatment compared to patients who did not show endometrial normalisation as described by the same authors. A protocol of *doxycycline* 400 mg tablets twice daily for 14 days lead to 96% histological clearance rate of endometrial CD138+plasma cells in patients with repeated implantation failure caused by chronic endometritis. On the other hand, the histopathological cure rate was 73% after using a combination of *ofloxacin* 400 mg and *metronidazole* 500 mg, both twice per day for 14 days [15].

Despite the effective means to manage chronic endometritis, there are no direct clinical or ultrasound markers to facilitate its diagnosis in the clinic, hence cases might pass undiagnosed. Furthermore, both microbiological and histopathological endometrial examinations proved to be time consuming and not very accurate, plus the need for the invasive endometrial biopsy. Moreover, microbiological examination might be marred by endocervical and vaginal bacterial contamination during endometrial sampling [14].

The ultimate objective of this study was to find factors and clinical scenarios which could draw the attention of gynaecologists to patients at risk of chronic endometritis. Special attention was given to vaginal washing which is a fairly common practice in our community. Such practice may alter the normal vaginal flora putting these women at risk of ascending bacterial infections. It may also lead to troublesome local vulval allergic reactions or chemical dermatitis. All patients consented to have their non identifying information used for teaching and research purposes.

Materials and Methods

197 patients who attended the clinic because of abnormal uterine bleeding, infertility or recurrent miscarriages were included in the study. They all had transvaginal ultrasound scan examinations (TVS) as well as saline infusion sonohysterography followed by hysteroscopy. All procedures were done for clinical indications during the early follicular phase of the cycle. The intracavity probe V5-9 was used in all cases mounted on a Samsung Ultrasound Machine, model UGEO WS80A. Factors which might affect the development of chronic endometritis were investigated. The list included sexual intercourse frequency, regular vaginal washing, parity, previous pelvic infection and previous uterine surgery. Also, the likelihood of patients to use vaginal washing was examined against the other four factors. Analysis also included prevalence of endometrial micropolyps in patients with different uterine pathologies. Cross tabulation with chi square test, binary logistic regression analysis and odds ratio were used as appropriate. The Statical Package for Social Sciences (IBM SPSS) was used for data analysis. P<.05 was used to indicate statistical significance.

Results

No case of endometrial micropolyps was diagnosed by ultrasound scanning, yet 81 cases (42.1%) were diagnosed hysteroscopically. 56 of them (69.14%) presented with abnormal uterine bleeding, 13 with infertility (16.04%) and 12 with repeated miscarriages (14.81%), p=0.012. Using crosstabulation and chi-square test, micropolyps were seen more frequently in parous (45 of 89, 50.6%) than nulliparous women (36 of 108, 33.3%), p=0.020. Similarly, there was significant correlation between frequency of intercourse and presence of micropolyps. 38 of 66 women who had sexual intercourse more than once every week showed micropolyps (57.6%) compared to 43 of 131 (32.8%) who were less active sexually, (p=0.001). Furthermore, 45 of 91 (49.5%) women who had previous pelvic infection showed micropolyps compared to 36 of 106 (34.0%) patients who did not (p=0.030). As for vaginal washing, 32 of 47 women (68.1%) who used regular vaginal

Variables	B	S.E.	Wald	df	p value	Exp (B)	95% C.I. for Exp (B)	
							Lower	Upper
Parity	0.571	0.316	3.271	1	0.071	1.769	0.953	3.284
Intercourse frequency	0.523	0.362	2.079	1	0.149	1.686	0.829	3.432
Previous surgery	0.273	0.325	0.704	1	0.401	1.313	0.695	2.482
Previous infection	0.527	0.314	2.82	1	0.093	1.694	0.916	3.134
Vaginal wash	1.081	0.403	7.174	1	0.007	2.947	1.336	6.498
Constant	-4.511	1.029	19.227	1	0	0.011	--	--

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 significant correlation only between the presence of micropolyps and vaginal washing (p=0.007) when all variables were included in the binary logistic regression analysis equation. The odds ratios, Exp (B), with the 95% confidence intervals are shown.

Variables	B	S.E.	Wald	df	p value	Exp (B)	95% C.I. for Exp (B)	
							Lower	Upper
Parity	0.39	0.387	1.011	1	0.315	1.476	0.691	3.154
Intercourse frequency	2.175	0.392	30.766	1	0	8.804	4.082	18.987
Previous surgery	0.501	0.39	1.655	1	0.198	1.651	0.769	3.544
Previous infection	0.597	0.386	2.39	1	0.122	1.817	0.852	3.875
Constant	-4.44	1.114	15.883	1	0	0.012	--	--

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 only frequent sexual intercourse had significant odds ratio, Exp (B), in relation to regular vaginal washing, p<0.001). All variables were included in the binary logistic regression equation. Other studied groups showed no significance.

washing showed micropolyps compared to 49 of 150 (32.7%) women who did not, p<0.001. Uterine surgery fared differently as 40 of 81 (49.4%) women who had previous uterine surgery showed micropolyps compared to 41 of 116 (35.3%) patients who did not, p=0.056. It was evident that except for previous uterine surgery, all other parameters had significant correlation with the presence of micropolyps and could be considered as risk factors.

Further analysis of the same data was done using the odds ratio to measure the risk of each group to develop endometrial micropolyps. Patients using regular vaginal washing scored 4.397 (95% confidence interval 2.180-8.871) which was the highest in the group. Higher frequency of sexual intercourse was second in line with an odds ratio of 2.777 (95% confidence interval 1.510-5.108). This was followed by parous women with an odd ratio of 2.045 (95% confidence interval 1.149-3.642), then previous pelvic infections with a ratio of 1.902 (95% confidence interval 1.071-3.380). However, unlike cross tabulation, using the odds ratio showed previous surgery to be a risk factor. It was 1.785 (95% confidence interval 1.001-3.183), with the lower limit of the 95% confidence interval very close to 1. Accordingly, binary logistic regression analysis was used to explore the most important of these factors (Table 1). With all variables in the equation, vaginal washing proved to be the most significant factor, p=0.007.

Cross tabulation with chi-square test was also performed to check the frequency of micropolyps diagnosis in relation to symptomatic patients with normal ultrasound findings and those with endometrial polyps compared to all other pathologies put together. The ratio was highest for cases with endometrial polyps being 58.2% (39 of 67 cases), followed by symptomatic patients with normal ultrasound findings being 48.6% (18 or 37 cases) and least were all the other uterine cavity pathologies being 25.8% (24 of 93 cases); p<0.001.

Taking the whole study group as a snapshot of our gynaecological community, I tested whether a certain group of women might be more likely to use vaginal washing. It was evident that women having more frequent sexual intercourse had the highest probability to do so. Their odds ratio was 8.804 (95% confidence interval 4.082-18.987). The other 3 tested groups did not show significant likelihood to use vaginal washing as shown by Table 2.

Discussion

It is a common observation that vaginal and endocervical microbiology do not represent upper genital tract microorganisms and could not be used for that purpose. Accordingly, this study was set to explore factors and clinical scenarios which might possibly be related to the development of micropolyps, hence chronic endometritis. This information might help gynaecologists and primary care providers to identify women at risk. Vaginal washing proved to be the prime one as shown by this study. Chemicals might change the normal vaginal bacterial flora allowing other organisms to grow and cause ascending infections. However, parous women and those who had frequent sexual intercourse or had previous pelvic infection were shown to be at risk, even without using vaginal washing. The higher likelihood for the more sexually active women to use regular vaginal washing might have increased their risk yet further of developing chronic endometritis. Maybe they felt obliged to do so for hygienic reasons or to feel fresh before or after sexual intercourse. It is naturally possible to have a frequently sexually active parous woman who had pervious pelvic infection to be using regular vaginal washing. This combination would further increase her risk to develop chronic endometritis. Accordingly, such scenario should be taken into consideration should such a patient present in the clinic with abnormal uterine bleeding, infertility, repeated miscarriages or any related complaint. Beside TVS, office hysteroscopy would be indicated as it does not only diagnose and assess the severity of chronic endometritis but could also be used to monitor response to treatment [16]. Another example included patients with abnormal uterine bleeding and normal TVS findings as 69.14% of patients with micropolyps fitted this scenario. These are just two examples of many more we should look for in the clinic during our practice to suspect chronic endometritis. This is especially so as antibiotics proved to be effective in dealing with most of these cases negating the need for further surgical interventions.

Micropolyps might be precursors to endometrial polyps because of the strong association between the two as shown by this study. This is an important observation which needs further investigations as it might shed new light on the possible aetiology of endometrial polyps. This is especially so as their exact cause and pathogenesis have not been clarified. Decreased oestrogen and progesterone receptors expression in stromal cells with relative insensitivity to cyclic hormonal changes have been described as possible causes [17]. On the other hand, different clonal rearrangements and translocations between stromal chromosomes 6 and 20 as well as 2 and 12 were described as the initial steps triggering the development of polyps [18,19]. With both scenarios in mind, chronic endometritis might be the triggering factor initiating these chromosomal rearrangements. In turn, these chromosomal changes may reduce oestrogen and progesterone receptors expression in stromal cells leading to the development of endometrial polyps.

Conclusion

Women in general should be discouraged from using vaginal washing because of the associated risks of developing chronic endometritis. This is especially so for parous women and those who had previous pelvic infections or those having frequent sexual intercourse. Gynaecologists and primary care providers should take a lead on this subject and advise women accordingly. Chronic endometritis should also be included in the provisional diagnosis of women presenting with abnormal uterine bleeding, infertility and recurrent miscarriages, especially those with normal TVS findings. Furthermore, office hysteroscopy should be incorporated in the diagnostic repertoire of these patients to exclude chronic endometritis.

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