Exploring the Association Between Chronic Endometritis and the Risk of Endometrial Hyperplasia

Rafal M.Murshid, F.I.C.O.G* Alaa Abdulqader, Ph.D. (pathologist)** Susan Abed Zaidan, F.I.C.O.G***

ABSTRACT

Background: chronic inflammation of the inner layer of the uterus (endometrium) play a role in different gynecological and obstetrical complaints including infertility, abnormal uterine bleeding, miscarriage, and implantion failure in patients underwent invitro fertilization.

Patients and methods: This prospective (case-control study) was done including 400 women (200 cases, 200 control). Women with abnormal uterine bleeding and women with subfertility were included. These patients underwent dilatation and curettage under General anasthesia and endometrial samples were obtained,These specimens were examined histologically and by IHC marker assessments using CD138 for confirmation of chronic endometritis.

Results: 161 (80.5%) case presented with abnormal vaginal bleeding and 39 case (19.5%) presented with infertility, 120 case (60%) had chronic pelvic pain, recurrent pregnancy loss was demonstrated in 111 case (55.5%). All the cases 200 case had endometrial hyperplasia while the control group appear to be either secretory or proliferative endometrium according to time of curate (day of cycle). There is significant association between abnormal uterine bleeding and history ofrecurrent pregnancy loss and endometrial hyperplasia.

20% (40 case) of endometrial hyperplasia were diagnosed to have chronic endometritis and confirmed by IHC (CD138) which was significant result and 80% (160 case) were negative both in histopathological and IHC marker and appear to be significant with OR (0.44) and 95% CI (0.28-0.68),

Conclusion: The current study shows there is a clear association and possible etiopathogenic link between chronic endometritis and endometrial hyperplasia .Treatment of chronic endometritis even if asymptomatic might help in decreasing the incidence of endometrial carcinoma.

Keywords: **chronic endometritis, endometrial hyperplasia, CD138, immunohistochemistry.**

INTRODUCTION

Chronic endometritis (CE) is an incessant inflammatory process of the inner-most layer of the uterus (endometrium), with plasma cell infiltration being the main feature on histological examination [(1)].

The precise pathological ground of this disease is still ill-defined and it is thought to be due to a disturbed immune mechanism within the uterine cavity[(2)].

The uterus is considered a relatively sterile area while there is heavy bacterial inhabitance in the vagina and the cervix between them acts as an important physical barrier preventing ascending of these organisms to the uterine cavity [(3)].

CE is frequently caused by bacteria commonly detected in the genital tract like streptococcus, E.coli, Ureaplasma urealyticum, Enterococcus faecalis, Gardnerella vaginalis, and Mycoplasma [(4,5)] .

Unlike acute endometritis, CE is either asymptomatic or it might be presented with constitutional symptoms like lower abdominal pain, abnormal vaginal bleeding, painful intercourse, and abnormal discharge [(6)]. However, CE is closely associated and possible underlying pathology of unexplained infertility, repeated failure of implantation (in vitro fertilization), and recurrent miscarriages [(7,8,9)] .

CE is diagnosed by finding of plasma cells during the histological examination of the endometrial sample but the accuracy of this way of diagnosis is questionable with a high rate of misdiagnosis [(10)], That is why an immunohistochemical stain to detect CD138 which is a surface antigen-specific to plasma cells was introduced for the ideal diagnosis of this inflammation; as it has higher sensitivity for detection of CE in comparison with traditional staining and histological assessment alone [(11)].

Many bacterial and viral infections are known to be involved in malignancy as many infections cause cellular proliferation and excess cell turnover [(12)] .Endometrial hyperplasia is an abnormal proliferation of the endometrial glands that might progress into endometrial carcinoma, one of the commonest malignancies [(13)] . It is widely accepted that the main risk for endometrial hyperplasia is excess oestrogen exposure [(14)] but there is very limited studies regarding a possible relationship with chronic endometritis.

*,*** Department of Obstetrics and Gynecology
University of Anbar , Iraq.
E-mail: dr.alaaalmansour@gmail.com
** Ibn Sina University of Medical and Pharmaceutical Sciences
Baghdad , Iraq.

The objective of this study is to assess the association between chronic endometritis and endometria hyperplasia.

PATIENTS AND METHOD

An observational case control study was performed on 400 women (200 cases and 200 control) in Arrazi and AL_Safwa hospitals in Al_Ramadi city, West of Iraq. Histopathological examination and IHC (immunohistochemistry) assessment were conducted at Dr. Alla abdulqaers private lab_Al-Ramadi city for the duration from August 2022 to March 2023. The study was approved by the ethical approval committee of the college of medicine in Anbar University.

All patients where phoned, the purpose of the study was explained, and verbal consent was taken about current study.A questionnaire was prepared to collect information regarding the previous pregnancy loss and chronic pelvic pain in addition to the age and the indication for endometrial biopsy already recorded in patients files.

Two hundred cases who underwent dilatation and curettage for abnormal uterine bleeding or subfertility, randomly consecutively selected, whom their histopathological examination of their endometrial samples showed endometrial hyperplasia are case group. Two hundred cases who underwent dilatation and curettage for the same indication, randomly consecutively selected, whom their histopathological examination of their endometrial samples showed normal proliferative or secretory endometrium are control group.

Inclusion criteria : all patients underwent diagnostic curettage under general anesthesia for abnormal uterine bleeding or subfertility were included in the study while those who previously diagnosed and treated for endometrial hyperplasia and endometrial biopsy repeated after her treatment were excluded.

All endometrial samples were subjected to histopathological examination. The samples were represented by formalin-fixed, paraffin-embedded blocks. The blocks are sectioned at 4-micron thickness and stained by Hematoxylin and Eosin stain.The criteria for diagnosis of endometrial hyperplasia are based on glandular crowding in relation to endometrial stroma (with or without cytological atypia). In the endometrial biopsy, the observation of one or more plasma cells / 10 HPF indicates a positive result for chronic endometritis. The confirmation of chronic endometritis is done by using an IHC marker / CD138 an antigen specific to plasma cells. Paraffin-embedded endometrial sections were stained using mouse monoclonal antibody for CD138.

Statistical analysis

Analysis of data was carried out using the available statistical package of IBM SPSS-29 (IBM Statistical Packages for Social Sciences- version 29, Chicago, IL, USA). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means while the difference of different percentages (qualitative data) were tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05.

Sample size

All eligible patients filled out the consent form and completed the research tool in a written format. The sample size was calculated using the following formula:

$$n = \frac{Z^2_{1-\alpha/2}\sigma^2}{d^2}$$

RESULTS

In the current study the age group ranged from 30-60 years with most cases between 40-49 years, about 161 (80.5%) case presented with abnormal vaginal bleeding and 39 case (19.5%) presented with infertility, 120 case (60%) had chronic pelvic pain, recurrent pregnancy loss was demonstrated in 111 case (55.5%). All the cases 200 case had endometrial hyperplasia while the control group appear to be either secretory or proliferative endometrium according to time of curate (day of cycle).

There is significant association between abnormal uterine bleeding and history of recurrent pregnancy loss and endometrial hyperplasia. (table 1).

20% (40 case) of endometrial hyperplasia were diagnosed to have chronic endometritis and confirmed by IHC (CD138) which was significant result and 80% (160 case) were negative both in histopathological and IHC marker and appear to be significant with OR (0.44) and 95% CI (0.28-0.68) as shown in (table 2and figure 1).

Table 1: The association between endometrial hyperplasia with age, clinical presentation.

		Endometrial hyperplasia		Controls		P value
		No	%	No	%	
Age (years)	<30	7	3.5	5	2.5	0.082
	30---39	35	17.5	38	19.0	
	40---49	68	34.0	80	40.0	
	50---59	66	33.0	68	34.0	
	=>60years	24	12.0	9	4.5	
	Mean±SD (Range)	47.9±9.9 (23-69)		46.6±8.6 (24-62)		0.138
Presentation	Abnormal uterine bleeding	161	80.5	134	67.0	0.002*
	Infertility	39	19.5	66	33.0	
Chronic pelvic pain	Present	120	60.0	120	60.0	-
	Absent	80	40.0	80	40.0	
Recurrent pregnancy loss	Present	111	55.5	135	67.5	0.014*
	Absent	89	44.5	65	32.5	
Endometrial hyperplasia	Endometrial hyperplasia	200	100	-	-	-
	Secretory	-	-	102	51.0	
	Proliferative	-	-	98	49.0	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

#Significant difference between two independent means using Students-t-test at 0.05 level.

Table 2: The association between endometrial hyperplasia and chronic endometritis.

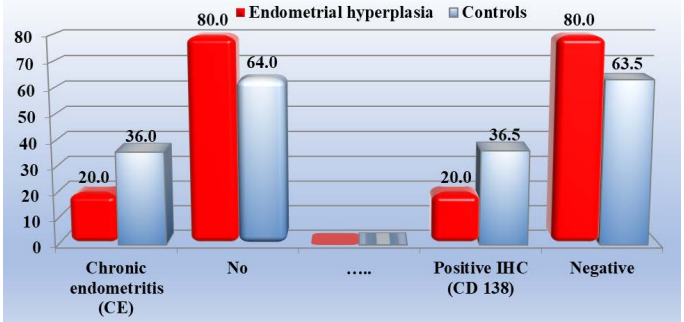
		Endometrial hyperplasia		Controls		P value
		No	%	No	%	
Chronic endometritis (CE)	Positive	40	20.0	73	36.5	0.0001*
	Negative	160	80.0	127	63.5	
OR (0.44) 95%CI (0.28-0.68)						

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

#Significant difference between two independent means using Students-t-test at 0.05 level.

OR: Odd's ratio (risk measurement in case control study)

95%CI : the 95% confidence interval for the OR.



DISCUSSION

Chronic inflammation has been implicated in tumourigenesis for a long time.Leukocytes were found within tumours since 19th century and during the last decades, a clear bond between inflammation and cancer development was found [15].

Chronic inflammation enables tumor evolution. Multiple cellular signaling pathways are involved in inflammatory process including nuclear factor kappa B, cytokines, tumor necrosis factor, interferon, and growth factors . The stimulated immune response toward infection appear to play a substantial role in tumour development and progression .

Normally, lymphocytes (type B) are always invariable present at the basal layer only of endometrium, (about 1% of inflammatory cells). On the other hand, in CE they are found at basal, epithelial glandular elements of the endometrium & glandular luminal part intermixed with plasma cells[17,18] . Specific types of bacteria (Gram-negative), within the endometrium, play a role in provoking an immune response leading to the immigration of circulating B lymphocytes to the stroma [19] .

Enometrial hyperplasia is a premalignant condition characterize by abnormally increased endometrial gland proliferation that may progress into endometrial cancer. Endometrial cancer, globally the second most common gynecological malignancy, was consider a disease affecting postmenopausal women but an alarmin rising incidence registered among 40–44-year-old age group [20] .

In our study a significant association was found between CE and endometrial hyperplasia cases and this finding is noval and no other study assess this relation directly. Similar to our coutcome, a study done by Di Pietro et al. [21] found that the many genes about (25 genes) coded for inflammatory proteins, cellular multiplication, and programmed cell death at the endometrial microenvironment . These gene expression alterations are strongly associated with the development of endometrial hyperplastic lesions in women with CE. In addition , a similar finding was declared by Ettore Cicinelli et al. who find out that changes in genes expression involved in inflammatory process in women with CE promote cellular proliferation and anti-apoptotic activity inducing endometrial hyperplasia [22] .

CONCLUSION

The current study shows there is a clear association and possible etiopathogenic link between chronic endometritis and endometrial hyperplasia .Treatment of chronic endometritis even if asymptomatic might help in decreasing the incidence of endometrial carcinoma. The findings emphasize the importance of recognizing and addressing chronic endometritis in clinical practice to mitigate the risk of endometrial hyperplasia and subsequent carcinoma.

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Competing Interest: None

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