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ORIGINAL ARTICLE

EVALUATION OF ENDOMETRIUM FOR CHRONIC ENDOMETRITIS BY USING IHC MARKER SYNDECAN-1 IN ABNORMAL UTERINE BLEEDING AT TERTIARY CARE CENTRE.

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ABSTRACT

Background: The endometrium which lines the uterine cavity is one of most dynamic tissues in the human body. The endometrial sampling is chosen to evaluate abnormal uterine bleeding. Chronic endometritis is considered as an infectious or a reactive process

Materials and Methods: It is a prospective study done for period of 2 years in Department of Pathology, Government Maternity Hospital, Hyderabad. Sample size was 50. All cases of Abnormal Uterine Bleeding in Reproductive age group were chosen and their endometrial curettage samples were processed, histopathological & immunohistochemical study was done. The results obtained were tabulated & assessed statistically.

Results: The present study showed that Staining with Immunohistochemical marker CD 138(Syndecan -1) could detect the presence of Plasma cells which were not seen in normal H & E staining. The 16 cases which showed the presence of plasma cells on H & E were positive for CD 138 and other 21 cases showed positivity for CD138 indicating presence of plasma cells in the endometrial stroma though they were not detected in routine H & E staining. The results obtained were statistically significant with 'p' value <0.05.

Conclusion: Syndecan-1(CD138) immunohistochemistry can improve the Chronic Endometritis diagnosis rate. Approximately half of the cases of chronic endometritis responded to an antibiotic regime; thus, this diagnosis is important and may potentially obviate the need for surgical intervention

Keywords : Abnormal uterine bleeding, Plasma Cells, CD138

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INTRODUCTION

The endometrium which lines the uterine cavity is one of most dynamic tissues in the human body. It is characterized by cyclic processes of cell proliferation, differentiation, and death in response to sex steroids elaborated in ovary.[1] Abnormal uterine bleeding is the commonest presenting symptom and major gynecological problem responsible for as many as one-third of all out patient gynecologic visit.[2] Menorrhagia affects 10-30% of menstruating women at any one time and may occur at some time during the perimenopause in upto 50% of women.[3] Abnormal uterine bleeding is defined as any bleeding pattern that differs in the frequency, duration and amount from a pattern observed during a normal menstrual cycle or menopause. It is a common problem having a long list of causes in differentage groups.[4] The endometrial sampling is chosen to evaluate abnormal uterine bleeding because it has several advantages over other diagnostic methods. The hormonal assay is very expensive and laboratories with hormonal assay are not available in rural areas. Other investigations like hysteroscopy and hysterosalpingography are mainly helpful in diagnosing organic pathology.[5] Endometrial curettage is relatively inexpensive and accurate as an outpatient procedure. The only disadvantage of endometrial biopsy is that it is an invasive procedure.

Chronic endometritis (CE), the histopathologic features of which are endometrial superficial edematous change, high stromal cell density, dissociated maturation between epithelium and stroma, and infiltration of endometrial stromal plasmacytes (ESPCs). There are currently no universally accepted standardized definitions or established diagnostic guidelines for Chronic Endometritis, althwwough experts agree that the presence of multiple endometrial stromal plasmacytes is the most specific and sensitive finding in Chronic Endometritis. In contrast to acute endometritis being manifested with fever, pelvic pain, and vaginal discharge, the subtle and nondescript symptoms (pelvic discomfort, spotting, and leucorrhea) of Chronic Endometritis are often unnoticed by patients and ignored by gynecologists.

Accurate histopathologic diagnosis of Chronic Endometritis has been demanding and time consuming until recently. Increasing attention, however, has been focused on the potential association between poor reproductive outcomes and Chronic Endometritis.

Here we aim to address the current literature surrounding Chronic Endometritis and highlight recent advances in research of this long neglected gynecologic disease.

MATERIALS AND METHODS

Study design: Prospective study.

Study subjects: Patients with Abnormal uterine Bleeding.

Study period: 2 years (January 2019- December 2020).

Place: Department of Pathology, Government Maternity Hospital, Osmania Medical college, Hyderabad.

Sample size:50.

Inclusion criteria: All cases of Abnormal Uterine Bleeding in Reproductive age group (19-30 years).

Exclusion Criteria: Cases not meeting the below mentioned histological criteria for suspicion of Chronic Endometritis**.**

1. Stromal break down 2.Stromal edema 3.Stromal infiltrate 4.Gland irregularity

Of total 370 samples of Dilatation and Curettage for endometrial sampling received in our pathology department, 85 cases had histopathological features matching to our histopathological criteria of Stromal breadown, stromal irregularity, stromal edema, gland irregularity. It is of 23% of the total endometrial samples received. Of 85 cases, 50 cases(59%) were falling in the range of 19 - 30 years, With predominant clinical presentation of AUB and infertility.

The dilatation and curettage specimens received in the department during the study period of these age group with history of AUB, fulfilling the inclusion criteria, were fixed in 10%neutral buffered formalin (NBF).

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After fixation of the specimen for 24 hours, the specimen was grossed using standard protocol. Adequate sampling was done, labeled and then processed in tissue processor and embedded in paraffin wax. Four to five-micron thickness sections were prepared from the corresponding paraffin blocks, one on albumin coated slide for Haematoxylin and Eosin (H&E) staining and the other on poly-L- lysine coated slide for immuno-histochemical staining. Sections showing features of histopathological inclusion criteria were identified. There after diagnosis made on H&E stained sections were taken for the immunohistochemistry study. Appropriate sections were prepared on Poly-L-Lysine coated slides for IHC using selective antibodies that included CD138 using standard protocol. Normal tonsillar sections were kept as control for CD 138. Results obtained were tabulated.

Statistical Analysis-

Analysis was done by IBM SPSS software trail/student version 21. Results were expressed in numbers, frequencies, means and standard deviations. Chi- square test was analysed and p-value < 0.05 was considered statistically significant.

OBSERVATION AND RESULTS

The present study comprises of evaluation of 50 endometrial curetting samples of AUB for chronic endometritis using IHC marker CD 138(syndecan- 1) received at Department of Pathology, **Government Maternity Hospital**, Osmania Medical college,Hyderabad. Mean age of patients was 25.3yrs(age range 19-30yrs) , 22cases(44%) were para 2, 18cases(36%) and 10cases(20%) were para 1 and nullipara respectively.

Table 1. Distribution of Bleeding Pattern

Bleeding Pattern	Number	Percentage
Heavy menstrual Bleed(HMB)	32	64%
Intermenstrual bleed(IMB)	10	20%
Heavy and prolonged bleed(HPB)	06	12%
FrequentMenstrual bleeding(FMB)	02	4%

H &E staining and IHC with CD 138 (Syndecan -1) done on the endrometrialcurettings of the AUB patients, showed following results

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Figure3a: Photomicrograph showing Plasma cell nfiltrate in endometrial stroma on H & E.

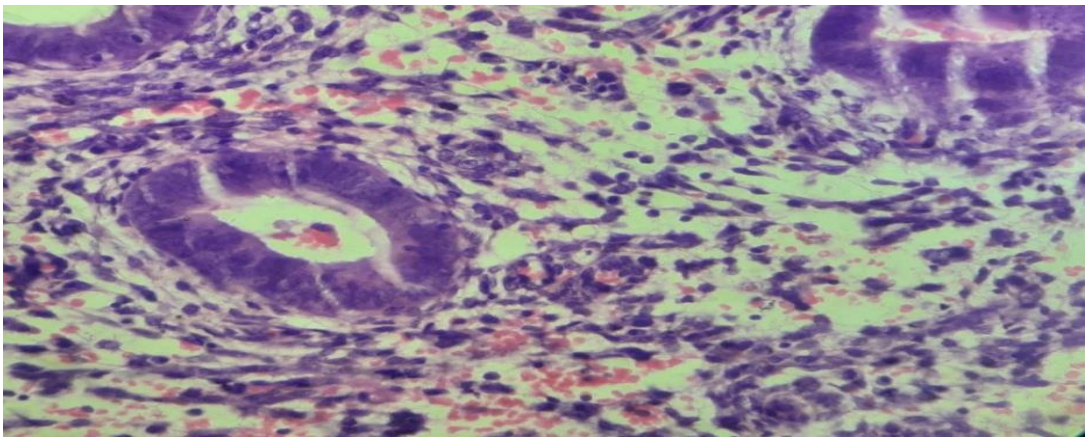

Figure 3b : Photomicrograph of the same case showing strong positivity for CD138(Syndecan-1)[Lowpower-10x]

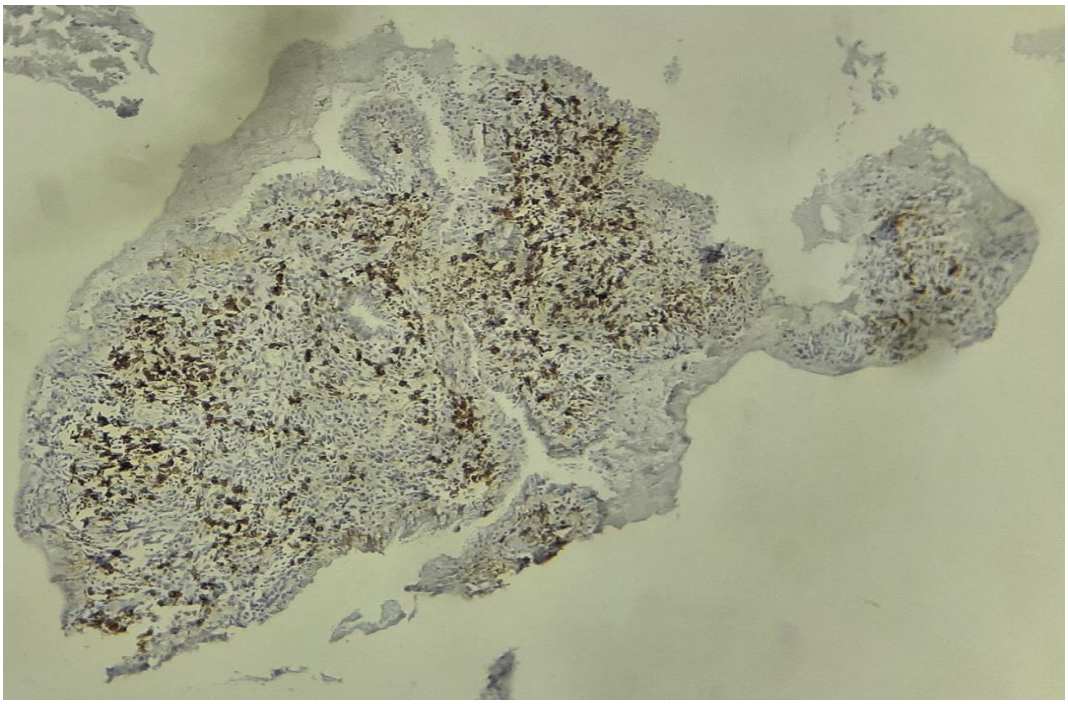

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Figure 3c: Photomicrograph of the same case showing strong positivity for CD138(Syndecan -1) [High power-40x].

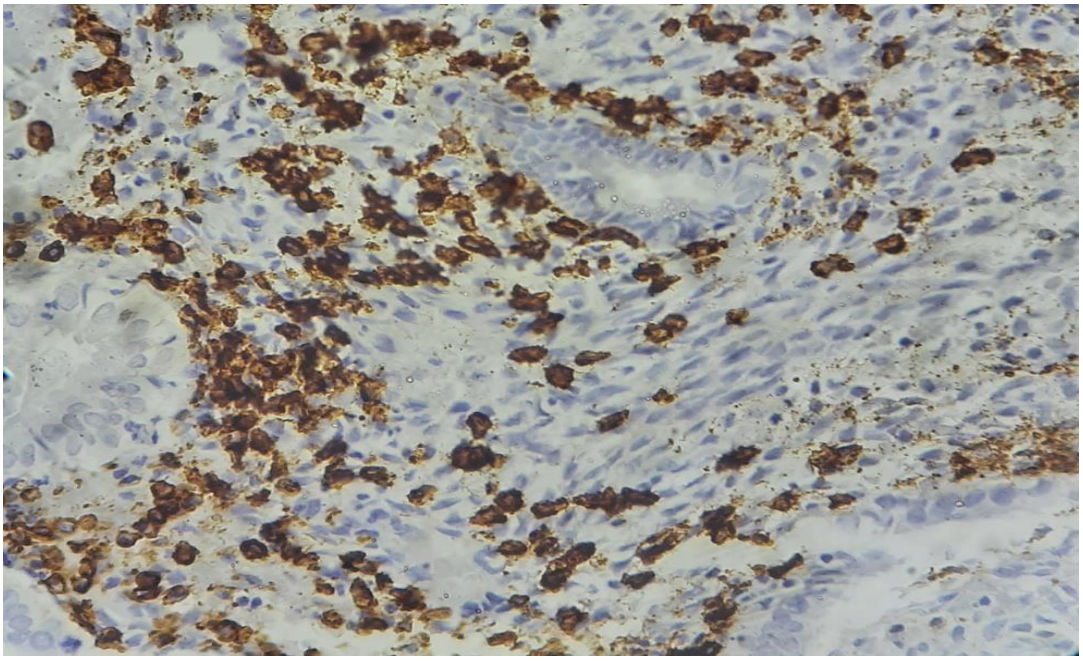

Figure 4a: Photomicrograph showing endometrial stromal breakdown and infiltration on H & E, Plasma cells were not identified.

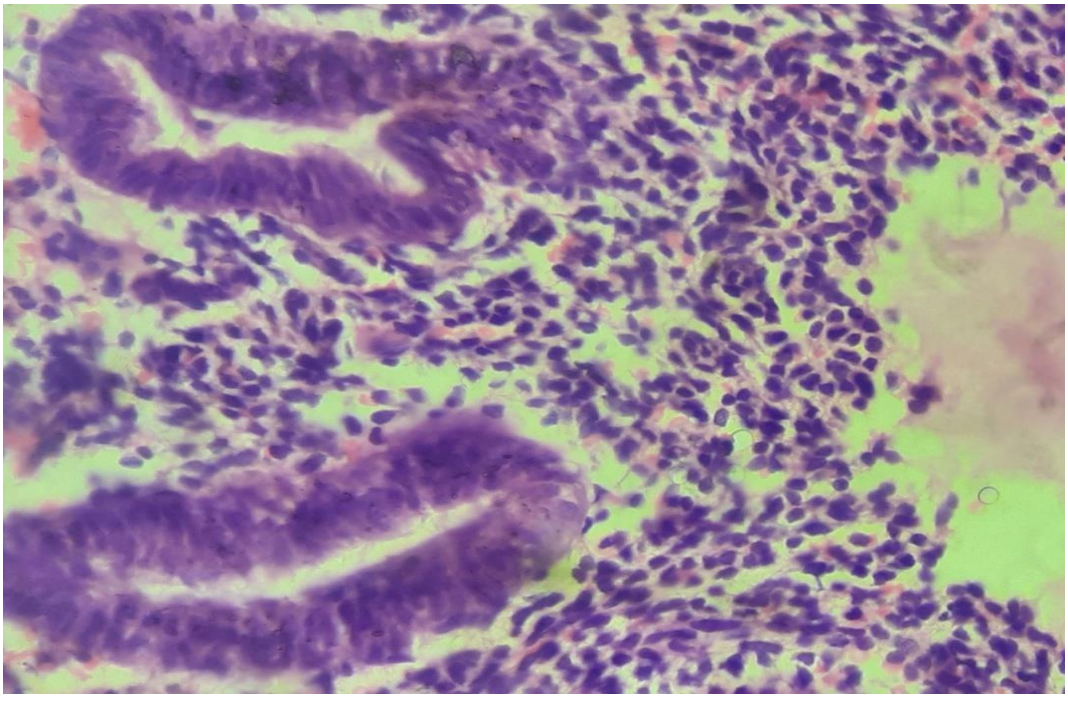

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Figure 4b: Photomicrograph of the same case showing weak positivity for CD138(Syndecan -1) [Low power-10x].

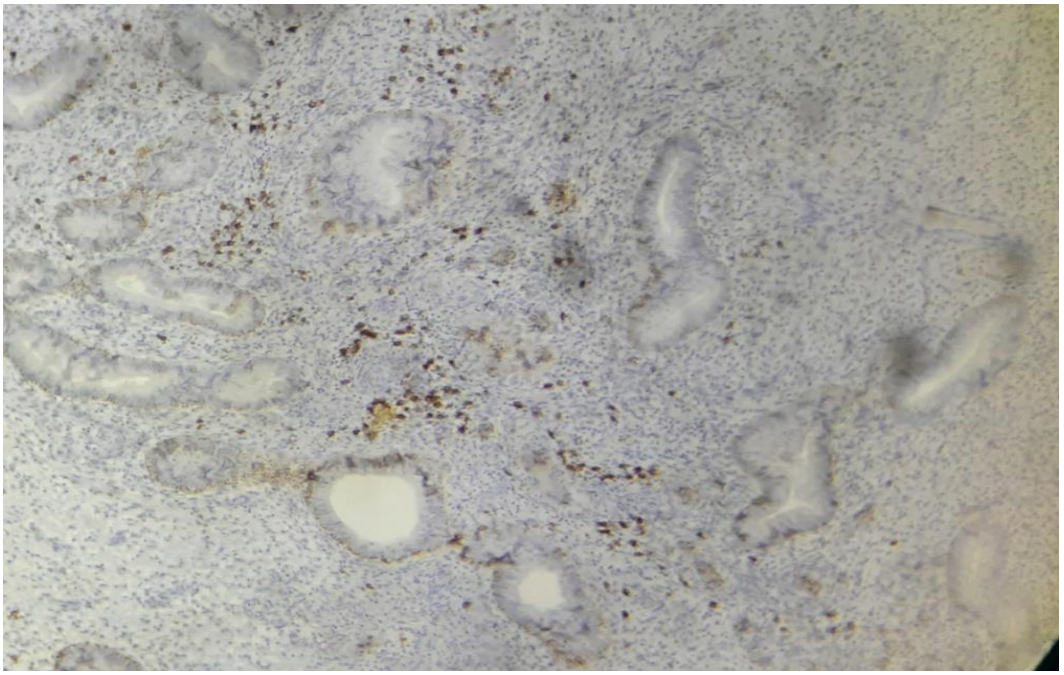
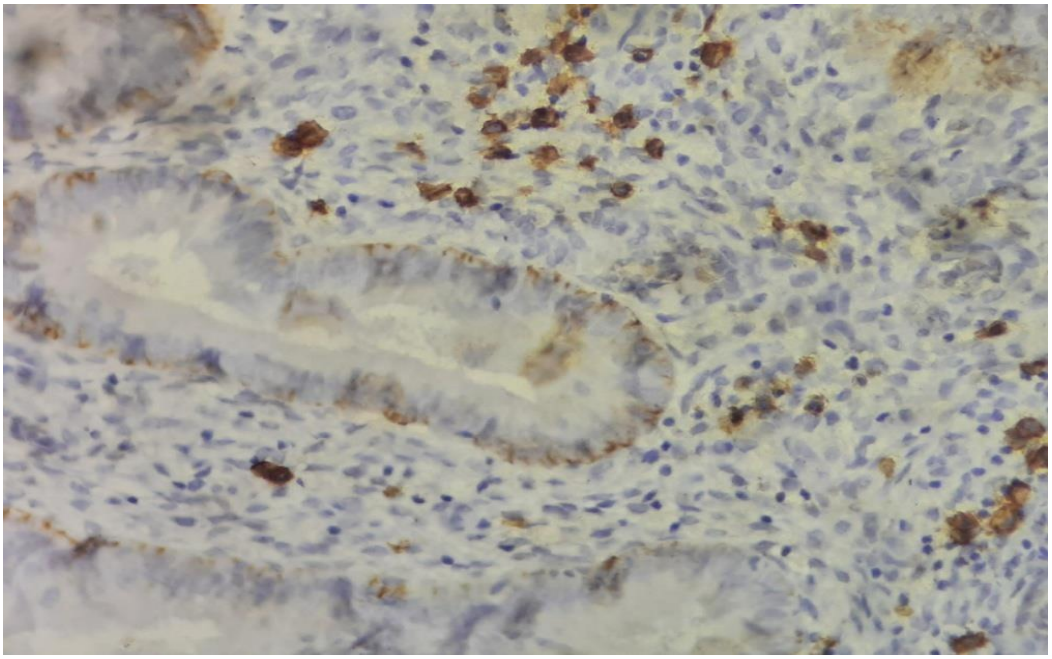


Figure 4c: Photomicrograph of the same case showing weak positivity for CD138(Syndecan -1)[High power-40x].



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The present study showed that Staining with Immunohistochemical marker CD 138(Syndecan -1) could detect the presence of Plasma cells which were not seen in normal H & E staining. Only 16 cases showed plasma cells on H &E , Other 34 cases showed no Plasma cells on H & E but the cases were selected based on stromal breakdown , stromal edema ,gland irregularity and IHC was performed on the curetting specimens.

All the 16 cases which showed the presence of plasma cells on H & E were positive for CD 138(presence of more than 5 positive foci i.e>5 plasma cells in a HPF) and 21 cases showed positivity for CD138 indicating presence of plasma cells in the endometrial stroma though they were not detected in routine H & E staining. The results obtained were statistically significant with 'p' value <0.05.

Table 2: CD 138 expression.

Expression of CD138	**No of cases**	**Percentage**
Positivity	37	74%
Negativity	13	26%

Table 3: Histopathological Diagnosis correlation w**ith Syndecan-1(CD138)IHC**

HPE diagnosis	NO	CD138 positive(%)	Cd138 negative(%)
Proliferative Phase	25	22(88%)	3(12%)
Secretory Phase	4	-	4(100%)
Irregular Shedding	9	6(67%)	3(33%)
Disordered Proliferative Endometrium	9	9(100%)	-
Simple hyperplasia	3	-	3(100%)

Table 3 shows the presence of plasma cells in all the 9cases(100%) of Disordered proliferative endometrium, 22cases(88%) of proliferative endometrium and 6cases (67%) of irregular shedding. All the cases were negative for plasma cells ith CD138 in secretory phase(4cases,100%) and simple endometrial hyperplasia(3cases,100%).

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***Table 4: Histological findings in favour of Chronic* Endometritis**

HPE finding	No of cases	CD138positive	Cd138 negative	P value
Stromal Breakdown	28	27	1	<0.01
Stromal Edema	10	6	4	0.25
Stromal Infiltration	18	12	6	0.37
Gland irregularity	12	7	5	0.15

Above table shows stromal breakdown showed statistically significant correlation with the presence of plasma cells($p<0.01$), other HPE findings like stromal edema($p=0.25$), stromal infiltration($p=0.37$), gland irregularity($p=0.15$) were not statistically significant. Few cases showed multiple findings.

DISCUSSION

Plasma cells (PCs) represent the terminal differentiation step of mature B lymphocytes. These cells are most recognizable for their extended lifespan as well as their ability to secrete large amounts of antibodies (Abs) thus positioning this cell type as a key component of humoral immunity. Recent studies shows that Plasma cells function as key regulators of processes such as hematopoiesis as well as neuro-inflammation. In part, Plasma cells accomplish this by integrating extrinsic signals from their environment which dictate their downstream functionality. Symptomatology does not seem to help gynecologists diagnose Chronic Endometritis as a quarter of the affected patients lack symptoms. Thus, whistopathologic detection of multiple endometrial stromal plasmacytes in endometrial biopsy is of primary importance in the diagnosis of Chronic Endometritis in current clinical practice. Be that as it may, identification of endometrial stromal plasmacytes by conventional tissue staining alone is not easy even for experienced pathologists.

Histopathologic evaluation using immunohistochemistry for plasmacyte marker CD138 (also known as syndecan-1, a transmembrane-type heparin sulfate proteoglycan) is currently the most reliable and time-saving diagnostic method for Chronic Endometritis. It was shown that CD138 immunostaining is greatly superior in the detection of Endometrial stromal plasmacytes to conventional tissue staining using methyl green pyronin, hematoxylin and eosin.

Syndecan-1 is a cell surface proteoglycan that is expressed on plasma cells7 and on keratinocytes, but it is not expressed by mononuclear cells, lymphocytes, or endometrial stromal cells. It is used extensively in flow cytometry to identify plasma cells and is also used as a marker to identify both malignant and benign plasma cells

in paraffin-embedded tissue. Its function is to mediate cell migration and proliferation as well as cell-cell adhesion and cell–extracellular matrix adhesion. Syndecan-1 also participates in growth factor activities in that it acts as a receptor for heparin-binding growth factors. Syndecan-1 immunohistochemistry increased the sensitivity for detection of the plasma cells in endometrial curettage specimens. In cases where the clear-cut features of plasma cells were not evident on the H&E slides, syndecan-1 immunohistochemistry enabled the identification of plasma cells and differentiated them from plasmacytoid stromal cells.[6]

The study was conducted over a period of 24 months and the data was analysed. The results obtained from the

presented study were comparable to number of previous studies in various aspects.

Table 6: Comparison of present study with the previous study.

Study	Age group	Sample size	Duration	Proliferative Endometrium	Secretory Endometrium	Others
Present study	19-30yrs	50	Jan 2019 – Dec 2020	50%	8%	42%
Vidyavathikannar et al[7],	19-50yrs	50	July 2011 - Dec 2012	40%	7%	53%
Yu-qing Chen et al[8]	23-43yrs	93	April 2013 – Dec 2013	30%	10%	60%
Kotaro Kitaya et al[9],	25-45yrs	234	Jan 2010 – Dec 2010	28%	22%	50%
Ilene B, Bayer-Garner et al[10]	28-77yrs	47	Jan 2003 – Dec 2003	47%	10%	43%

Vidyavathikannar et al[7] study shows Fifty endometrial biopsies with a clinical diagnosis of AUB were taken. Endometrium in proliferative phase, secretory phase, endometrial polyps, and disordered proliferative endometrium were studied for the presence of plasma cells. IHC was done using syndecan‐1. The secondary histologic features of chronic endometritis like gland architectural irregularity, spindled stroma, stromal edema and hemorrhage with the presence of plasma cellswas statistically analysed. Values of $P < 0.05$ were considered as significant.

Yu-qing Chen et al[8] study shows Ninety-three patients, with normal uterine shape confirmed by examination and who were planning to undergo assisted conception treatments, were selected as research subjects. Endometrial tissue was isolated for routine hematoxylin and eosin (HE) and CD138 immunohistochemical staining. Additionally, the disease histories of patients were collected, and the reproductive prognosis was followed up. CE detection rate: The rate of CD138 immunohistochemical staining was greater than that of HE staining (27.96 % vs.
26.89 %, P <0.05),Pregnancy rate: the pregnancy rate of CD138-positive patients (7.7 %) was lower than the pregnancy rate of CD138-negative patients (31.3 %) ($p = 0.017 < 0.05$).

Kotaro Kitaya et al[9], studied 234 endometrial specimens obtained b hysterectomy were immunostained for

the plasmacyte marker syndecan-1 to identify chronic endometritis. Endometrial morphology was dated by using the standard criteria. The immunoreactive cells were enumerated in 10 non-overlapping endometrial stromal areas. Chronic endometritis was identified in 11.1% of cases.**Ilene B, Bayer-Garner et al[10],** studied Immunohistochemistry stains for syndecan-1 were performed on 3 levels of 47 endometrial biopsies from patients with abnormal uterine bleeding. None of the patients had endometrial hyperplasia or an underlying malignancy. Clinical correlation and follow-up was attempted in 20 cases that showed evidence of plasma cells by syndecan-1 by immunohistochemistry. Plasma cells were identified in 20 cases, 7 of which were initially diagnosed as chronic endometritis. The remaining 13 positive cases were diagnosed as tubal metaplasia, secretory endometrium, proliferative endometrium, menstrual endometrium, endometrial polyp, secretory endometrium with endometrial polyp, and endometrial polyp with exogenous hormone effect based on the original hematoxylin-eosin section**.**

Majority of Disordered Proliferative Endometrium cases showed grade one plasma cells.Proliferative Endometrium with Breakdown also showed predominantly grade one plasma cells. There was also a significant association between stromal breakdown and the presence of plasma cells on biopsy. However, there was no significant association between other secondary histologic features like stromal edema, spindled stroma and gland architecture irregularity. Gilmore et al[11] in their study found an increased incidence of plasma cells in DPE, followed by PEB, but rare in normal proliferative endometrium. This suggests that plasma cells are commonly seen in endometrium of women with focal stromal breakdown.

A higher incidence of plasma cells in proliferative endometrium was seen when compared to secretory endometrium, which was similar to the fwwindings by Eckert

LO[12] *et al*. However Kitaya and Yasuo[9] found an equal incidence in proliferative phase (10.9%) and secretoryphase (9.3%). This could be wattributed to the type of endometrium sampled in their study. Endometrium from hysterectomy samples were studied where plasma cells were seen in the deeper endometrial stroma, where as biopsy included only the superficial endometrial stroma.

Chronic endometritis usually presents with abnormal uterine bleeding but is often asymptomatic or may present with mild symptoms. Hence actual prevalence in population is unknown. Adegboyega PA *et al*.[13], detected a 15.6% prevalence in their study which was higher than the 3%-10% reported in previous studies. Smith M

et al.[14], found a 16% misdiagnosis of CE on biopsies. This has been attributed to the specific immunostaining of plasma cells by Syndecan‑1, which not only stains typical plasma cells, but also spindle shaped plasma cells which may be missed on a H and

E. There are currently a number of different criteria used in literature to diagnose upper genital tract inflammation. These include the presence of five or more neutrophils per high powerfield (HPF) and 1 or more

plasma cells within endometrial stroma per low power field (LPF),[17]>2 plasma cells per HPF and even the presence of a single plasma cell in the entire specimen. Few authors believe that presence of one or two plasma cells with associated stromal and/or glandular changes in AUB is sufficient for the diagnosis of chronic endometritis. On the other hand, if many plasma cells are present even in the absence of prominent stromal changes, a diagnosis of chronic endometritis may still be given, as the associated stromal and glandular changes are dependent on the duration of the disease, as early in the disease stromal or glandular changes may not be prominent.

The presence of plasma cells may suggest the need for microbiological investigation to rule out any specific etiology for chronic endometritis, especially C.Trachomatis. If no infectious etiology is identified, then reactive cause for chronic irritation should be considered. The diagnosis of chronic endometritis in infertile patients may result in a successful pregnancy outcome, and treatment in HIV-infected patients may prevent morbidity from a hysterectomy.[15]

The association between plasma cells and AUB still remains to be established. Kitaya *et al*[16]., demonstrated that endometrium with Chronic Endometritis uniquely expresses the chemokines CXCL1, CXCL13 and adhesion molecules selectin E,
implicating that local B lymphocytes are recruited from endometrial microcirculation and differentiate *in situ* into plasmacytes. Such unusual leucocyte composition in Chronic Endometritis may disrupt the integrity of the epithelial lining and cause endometrial shedding resulting in AUB. In the present study, Chronic Endometritis was significantly detected in DPE. This could probably due to the effect of unopposed estrogen in the endometrium which predisposes to an inflammatory milieu by the production of cytokines and
growth factors.We believe that the presence of plasma cells in AUB patients suggests that these cells should be regarded as indicators of upper genital tract inflammation. Immunohistochemistry could help pathologists save time searching for plasma cells.
In conclusion, the recognition of chronic endometritis is important as treatment with antibiotics may lead to resolution of the symptomatology as well as prevent morbidity associated with a hysterectomy. Syndecan-1 may aid the recognition of plasma cells in the milieu of chronic endometritis when characteristic features of plasma cells are not easily found. It may also aid to the recognition of plasma cells in cases that are masked by a mononuclear cell infiltrate, features of late menstrual or early proliferative endometrium, stromal cell proliferation with plasmacytoid stromal wcells, abundant stromal mitoses, or a pronounced predecidual reaction in late secretory endometrium.

CONCLUSION

Syndecan-1 may be a useful adjunct in the diagnosis of chronic endometritis. Approximately half of the cases of chronic endometritis responded to an antibiotic regime; thus, this diagnosis is important and may potentially obviate the need for surgical intervention**.** A previous history of prolonged menstrual bleeding episodes, an abortion history, and a history of fallopian tube obstruction are risk factors for chronic endometritis, and a CD138 immunohistochemical examination should be advised among them. It is noteworthy to mention that use of Syndecan‑1 for plasma cells may be helpful in unusual cases where chronic endometritis is suspected as the cause of clinically significant on‑going abnormal bleeding.

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INSTITUTIONAL ETHICS COMMITTEE CERTIFICATE
(ECR/300/Inst/AP/2013/RR-16)

To

Dr. Aravind K
Post Graduate Student
Department of Pathology
Osmania Medical College
Koti, Hyderabad.

PROTOCOL TITLE : " A Study of Chronic Endometritis by using IHC marker syndecan – 1 in Abnormal Uterine Bleeding at tertiary care centre "
(Reg.No. 18118001020D)

Dear Dr. Aravind K ,

The Institutional Ethics Committee reviewed and discussed in detail the above mentioned protocol. After clearing all queries raised in the meeting, the committee has granted ethical clearance for the study.

Any changes in the protocol and patient information/informed consent shall be communicated to the Institutional Ethics Committee (IEC).

The Institutional Ethics Committee has working procedures in compliance with ICMR Guidelines, ICH GCP Guidelines, Schedule Y and applicable local laws.

Member Secretary