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Chronic endometritis: "Clinical presentation and attributing specific etiological factor"

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Abstract
Introduction: Endometritis is the inflammation of the endometrial lining of the uterus. In addition to the endometrium, inflammation may involve the myometrium and occasionally, the parametrium.
Aim of the study: the study aimed to find

1. The correlation of endometritis with various clinical characteristics of the patients e.g. pelvic pain, dysfunctional uterine bleeding, dyspareunia, vaginal discharge, infertility, recurrent miscarriage and amenorrhea.
2. To determine the various attributing etiological factors and history e.g. its relation with PID, IUD, Postpartum factor, Post abortal factors, postmenopausal, tubercular and idiopathic cause.

Material and Method: A retrospective study was done of chronic endometritis reports and cases that were diagnosed as chronic endometritis after aspiration biopsy using pipelle procedure. The duration of the study was from January 2016 to September 2020 at a private clinic and a pathology centre of Shivpuri. Out of cases, 353 cases 34 histopathological reports of chronic endometritis were reviewed to identify the cause of endometritis and its association with clinical findings and any significant history.
Results: In our study Out of 353 cases 34 cases found to be reported as endometritis. A total of 34 cases were studied. The prevalence of endometritis was 9.6%. The age of women ranges from 20 to 70 years. A maximum number of patients was between 25-35 years. Most of the patients were rural (79.41%), most of them were married (97.06%) and (47.06%) cased were multiparous.
The most common presenting complain was (35.29%) abnormal uterine bleeding followed by (17.65%) abnormal vaginal discharge, lower abdominal pain (14.71%) and infertility (14.71 %). Recurrent miscarriage 8.82%, Dysmenorrhoea 2.94%, Dysparaaunia 2.94% and Amenorroea 2.94%.
The most common finding on trans abdominal and Trans-vaginal ultrasound scan was thickened and heterogeneous endometrium, asynchronous with the phase of the menstrual cycle (47.05%).
In 58.82% cases, no significant past history was there, in 14.71% cases the history of instrumentation was there and in 8.82% cases history of IUD insertion was there. 5.88% cases posted abortal, 2.94% were postpartum, 2.94% were postmenopausal with cervical stenosis and with hematometra and 5.88% were Tubercular.
Conclusion: Chronic endometritis though asymptomatic is associated with infertility and poor reproductive outcome, Diagnosis is usually done by hysteroscopy, histopathology, and microbial examination.

Keywords: chronic nonspecific endometritis, aspiration biopsy, abnormal uterine bleeding

1. Introduction

The endometrium is the internal lining of the womb (uterus), where the embryo implants and grows during pregnancy. Endometritis is the inflammation of the endometrial lining of the uterus. In addition to the endometrium, inflammation may involve the myometrium and occasionally, the parametrium. The exfoliation of the endometrium provides a natural scavenging effect which prevents endometrial infection from becoming established. Chronic endometritis, characterized by an infiltrate of lymphocytes and plasma cells (often with an additional minor component of eosinophils) [1] may follow pregnancy or abortion. Be the result of an intrauterine device (IUD), be associated with a submucosal leiomyoma, or be accompanied by mucopurulent cervicitis and/or pelvic inflammatory disease (PID) [2, 3]. Patients suffering from chronic endometritis may have an underlying cancer of cervix or endometrium. Pyometra is usually met within elderly women and is one of the best-recognized forms of chronic endometritis. The clinical term, senile endometritis, suggested a chronic infection of the endometrium, usually low-grade [4]. CE is often asymptomatic or present with non – specific clinical symptoms, such as pelvic pain, dysfunctional uterine bleeding, dyspareunia, vaginal

discharge, vaginitis, recurrent cystitis and mild gastrointestinal discomfort [5]. Current evidence suggested that chronic endometritis is associated with infertility and poor reproductive outcome [6]. Chronic endometritis can affect up to a third of infertile women. However, it can be the cause of repeated implantation failure or recurrent pregnancy loss in many cases. Chronic deciduitis was reported to be linked to preterm labor (41%) [7, 8]. Chronic endometritis is often clinically silent. Therefore, it is impossible to accurately determine its true prevalence in the general population [9]. The prevalence of CE ranges from 8% to 72% in women of reproductive age [10].

The most frequent causative agents for chronic endometritis are Infectious agents: Gonorrhea, Chlamydia, Mycoplasma, Ureaplasma, Escherichia Coli, Streptococcus spp., Staphylococcus spp, Enterococcus faecalis, Yeast, and Tuberculosis [11]. Specific infections agents causing endometritis include herpesvirus, which may be associated with neonatal infections [12] cytomegalovirus [13] which can also be an associated with parental infections as well as spontaneous abortions; toxoplasma [14] which can also be responsible for spontaneous abortion; mycoplasma organisms [15] which are suggested as a cause of infertility; and actinomycetes [16, 17] frequently seen in women using intrauterine contraceptive devices. For diagnosis of chronic endometritis- in blood Test elevations in the peripheral white blood count and erythrocyte sedimentation rate can be seen.

Histopathological diagnosis using H & E (Hematoxylin & Eosin) staining is the gold standard for the diagnosis but it is time-consuming and low diagnostic rate <10% [18, 19]. The Presence of 1-5 plasma cells/HPF of discrete clusters of plasma cells is generally accepted as the histological diagnostic criterion for chronic endometritis.

TB endometritis is often focal. The demonstration of a typical caseous granuloma with giant epithelioid cells is suggestive of TB. Histopathological screening of patients by dilation and curettage, though most accurate, is expensive, time-consuming and involves hospitalization with complications of surgery and hazards. An endometrial aspiration biopsy can be a useful alternative to DNC. Aspiration cytology is better than conventional D&C because in this procedure no cervical dilation is required, it is cost-effective, it provides adequate tissue samples, it can be done in an office setting, no anaesthesia is required and diagnostic accuracy is 90-98%. Variety of devices can be used for endometrial biopsy aspiration like Novak curette VABRA curette Pipelle Device or gynosampler. The histopathological diagnosis is usually available in 3-4 days.

TB endometritis is often focal, and pathological changes such as ulceration, caseous nacreous and tuberculosis.

HPE of the specimens shows typical features of TB infection in the form of granulomatous caseous lesions. The demonstration of a typical caseous granuloma with giant epithelioid cells is suggestive of TB.

Immunohistochemistry (IHC) with CD138 (syndecan – 1): This method has higher sensitivity of 56% as compared to 13% for H&E staining [19], it is more accurate [20].

It reduces the false-negative diagnosis [19] but this method is not yet recommended in daily practice and not widely used for the diagnosis of chronic endometritis.

Microbiological culture: Microbial culture (growing bacteria in the lab) is the conventional method for identification of bacteria and infection. However, it has been shown that between 20-60% of bacteria cannot be cultured in the laboratory.

Microbial culture, the most reliable of the three classic methods, has few limitations like contamination of the microbial culture with skin or environmental bacteria: Usually remains Positive in 75% of histologically confirmed CE Commonly cultured bacteria are Streptococcus agalactiae: 77.5%, Mycoplasma / Ureaplasma: 25%, Chlamydia: 13% [11].

Ultrasound: TVS is better than abdominal Ultrasound. Indirect sonography signs are- increase in endometrial thickness, asynchronous with the phase of the menstrual cycle, Persistently thin endometrium (Tuberculosis), Irregularity of the endometrium, Endometrium with hyperechogenic spots Intracavitary synechiae, Micropolyps, Fluid or debris accumulated within the endometrial cavity. Hematometra, Hypervascular endometrium in the secretory face, Sometimes Calcification of entire endometrium can be seen [21, 22].

Hysteroscopic diagnosis: Hysteroscopy is a useful diagnostic Procedure to detect endometritis. It is usually done in the follicular phase of the menstrual cycle Hysteroscopy is usually done in the follicular phase (between D6 and 12) of the menstrual cycle. Mucosal edema, Focal or diffuse endometrial hyperemia or Micro Polyps can be seen [23]. Office Hysteroscopy is having sensitivity 40%, specificity 80% (Bouet *et al.*, 2016), Accuracy of hysteroscopy was observed in 93.4% [24].

Molecular Diagnosis: Reverse- Reverse transcription-polymerase chain reaction (RT-PCR) test can be used for the molecular diagnosis of chronic endometritis.

NAAT- The nucleic-acid amplification tests (NAAT) provide results in a few hours. PCR is a rapid molecular method.

Nowadays various tests are available to assess the health of the endometrium. CRGH offers a comprehensive assessment of the endometrium [25]. The quarter includes.

ERA (endometrial Receptivity Assay)

EMMA (Endometrial Microbiome Metagenomic Analysis)

ALICE (Analysis of infectious chronic Endometritis)

NKT (Natural Killer Test) (please refer to the section on natural killer cell test and immunotherapy

These tests are very useful in cases of recurrent implantation failure.

Treatment: Generally, the drug of choice is doxycycline, administered in doses of 100 mg every 12 hours for 14 days. Alternatively, the administration of cephalosporins, macrolides, or quinolones is possible. Partner is advised to undergo the same antibiotic treatment. If endometritis persists then endometrial culture should be considered and appropriate antibiotic treatment should be given. Women with cured endometritis showed a higher pregnancy rate and live birth rate in comparison with women with chronic endometritis [26].

In the presence of confirmed tuberculous (isoniazid, ethambutol, rifampicin, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for another 4 months) should be given.

Aim of the study

The study aimed to find

1. The correlation of endometritis with various clinical characteristics of the patients e.g. pelvic pain, dysfunctional uterine bleeding, dyspareunia, vaginal discharge, infertility, recurrent miscarriage and amenorrhea.
2. To determine the various attributing etiological factors and history e.g. its relation with PID, IUD, Postpartum factor, Post abortal factors, postmenopausal, tubercular and

idiopathic cause.

2. Material and method

The Inclusion Criteria for the study were those women presenting with complaints of: Abnormal uterine bleeding, abnormal vaginal discharge, Lower Abdominal pain, Dysmenorrhoea, Dysparaaunia, Unable to conceive (Infertility), Recurrent miscarriage, Amenorrhea and backache.

The exclusion criteria were

A. Pregnant women

B. History and signs were suggestive of acute pelvic infection.

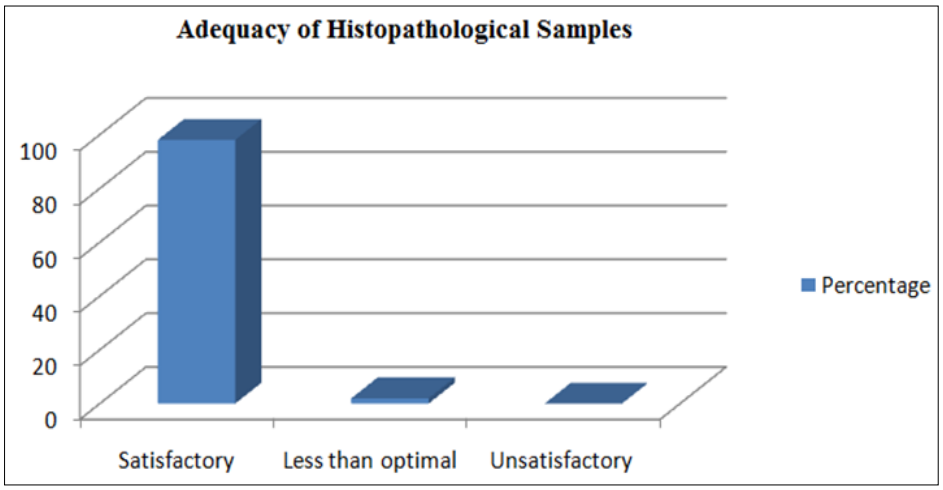
A retrospective study was done of the reports of Diagnosed cases of chronic endometritis (Endometrial samples were obtained by an office procedure in which aspiration by piipelle forceps was done on the Outdoor examination table (without need for cervical dilatation and anaesthesia and sent for the histopathological examination (HPE)). The duration of the study was from January 2016 to September 2020 at a private clinic and a pathology centre of Shivpuri district. Total 360 reports of endometrial aspiration were there, 7 reports were labelled as less than optimal. So Out of 353 cases, 34 cases reported as endometritis 34 histopathological reports were reviewed to identify the cause of endometritis and its association with clinical findings. Complete clinical history, age, residence, parity, literacy, marital status, presenting symptoms and clinical evaluation, ultrasound findings and all histopathological reports of endometrial samples were analyzed.

Data were coded and entered into Microsoft Excel worksheet. All the data was analyzed using IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare tables, data is expressed as percentage.

3. Result

1. Adequacy of Histopathological Samples

Adequacy of a sample obtained was reported by histopathologist based on the amount of sample obtained as (a) unsatisfactory, (b) less than optimal (c) satisfactory.



Graph 1: shows that out of 360 samples, 353 samples (98.05%) were satisfactory, seven cases (1.94%) were less than optimal, and no case was reported as unsatisfactory.

2. Prevalence of endometritis

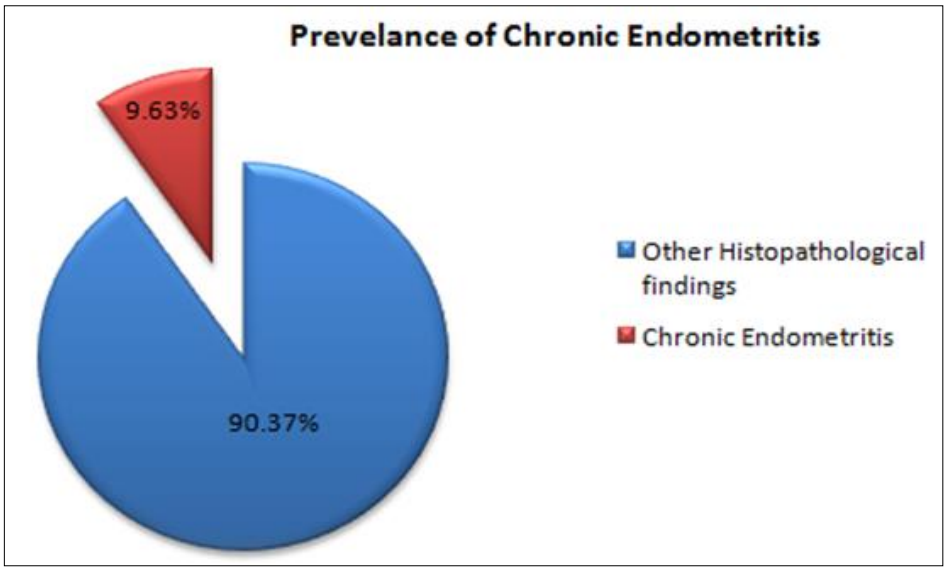


Fig 1: Prevalence of Chronic Endometritis- in our study Out of 353 cases 34 cases reported as endometritis the prevalence of endometritis was 9.6%.

3. Socio-demographic characteristics

Table 1: Socio-demographic characteristics A total of 34 cases were studied. The age of women ranges from 20 to 70 years. The maximum number of patients was between 25-35 years. Most of the patients were rural (79.41%), most of them were married (97.06%) and (47.06%) cases were multiparous

Age Group (years)	No. of cases	Total (%)
<25	1	2.94%
25-34	16	47.06%
35-44	9	26.47%
45-54	5	14.71%
>55	3	8.82%
Residence		
Rural	27	79.41%
Urban	7	20.59%
Marital Status		
Married	33	97.06%
Unmarried	1	2.94%
Parity		
Nulliparous	6	17.65%
Primiparous	12	35.29%
Multiparous	16	47.06%

4. Principal presenting symptoms

Table 2: Principal presenting symptoms in 34 cases the most common presenting complaint was (35.29%) abnormal uterine bleeding followed by (17.65%) abnormal vaginal discharge, lower abdominal pain (14.71%) and infertility (14.71 %)

Presenting symptom		No. of cases	Percentage of cases
Abnormal uterine bleeding	Intermenstrual Bleeding	12	35.29%
	Menorrhagia		
	Menometrorrhagia		
Lower Abdominal pain		5	14.71%
Amenorrhoea		1	2.94%
Abnormal Vaginal discharge		6	17.65%
Dysmenorrhoea		1	2.94%
Dyspareunia		1	2.94%
Unable to conceive (Infertility)		5	14.71%
Recurrent miscarriage		3	8.82%
Total		34	100

5. Endometrial Findings on trans abdominal and Trans-vaginal ultrasound scan

Table 3: Endometrial Findings on trans abdominal and Trans-vaginal ultrasound scan- The most common finding on trans abdominal and Trans-vaginal ultrasound scan was Thickened and Heterogeneous endometrium, asynchronous with the phase of the menstrual cycle (47.05%)

Finding on Ultrasound	No.	Percentage
Normal Endometrium	9	26.47%
Fluid or debris accumulated within the endometrial	3	8.82%
Persistently thin endometrium	3	8.82%
Thickened and Heterogeneous endometrium, asynchronous with the phase of the menstrual cycle.	16	47.05%
Endometrium with hyperechogenic spots (Intracavitary synechiae)	2	5.88%
Sometimes Calcification of entire endometrium	1	2.94%
Total	34	100

6. Histopathological finding and attributing specific Etiological factors

Table 4: Histopathological finding and Associated past history -The most common histopathological finding was chronic nonspecific endometritis. In 58.82% cases, no significant past history was there, in 14.71% cases the history of instrumentation was there and in 8.82% cases history of IUD insertion was there. 5.88% cases were postabortal, 2.94% were postpartum, 2.94% were postmenopausal with cervical stenosis and with hematometra and 5.88% were Tubercular

Histopathological finding	Significant history	Number	Percentage
Chronic nonspecific endometritis	No significant history only clinical finding	20	58.82%
	history of instrumentation	5	14.71%
	history of IUD insertion	3	8.82%
	Post abortal	2	5.88%
	Postpartum	1	2.94%
	Post menopausal (Cervical stenosis with hematometra)	1	2.94%
Tubercular endometritis (Past History of Tuberculosis, History & clinical symptoms suggestive of Tuberculosis)		2	5.88%
Total		34	100

4. Discussion

Diagnosis of CE represents a challenge for the gynaecologist. The clinical manifestations of CE such as pelvic pain, vaginal discharge, dyspareunia and abnormal vaginal bleeding are non – specific, while about 25% of patients with CE are asymptomatic [27].

A total of 34 cases were studied. The age of women ranges from 20 to 70 years.

In our study, the chronic endometritis was most common in 25-35 years of age which was not consistent with one another study in which chronic endometritis was most common, 41.1% in 41-50 years of age [28].

In our study, most of the patient was multiparous (47.06%) which was not consistent with one another study in which 80.5%

multiparous 9.2% primiparous, and 10.3% nulliparous [28].

In our study chronic endometritis was found in 9.4% cases which were lower than the study of Adegboyega PA *et al*. Who reported 15.6% prevalence of endometritis [1]. And the prevalence rate of chronic endometritis was consistent with another study in which the prevalence rate of CE to be approximately 10% to 11% based on biopsies of patients who underwent hysterectomies due to benign gynecologic conditions [29].

In our study, the most common presenting complaint was abnormal uterine bleeding (35.29%). Followed by (17.65%) abnormal vaginal discharge, lower abdominal pain (14.71%) and in our study infertility was in (14.71 %) and Recurrent miscarriage was in 8.82% cases.

The most common symptoms were menstrual disturbances, present in virtually every patient and pelvic pain or tenderness, found in 50% of the women.

The abnormal vaginal bleeding was observed in a higher number of patients than another study in which Chronic endometritis is observed in 3-10% of women who undergo endometrial biopsy for abnormal uterine bleeding (AUB) [30] and our study was consistent with one another study in which abnormal vaginal bleeding was the most common presenting symptom [28].

In Study of "Dana" overall prevalence rate of chronic endometritis was 9% The prevalence in (REPL) recurrent early pregnancy loss was 7% in FD (fetal death) group was 40% and in combined (REPL) /FD group was 11% The cure rate was 100% after a course of antibiotic.

In the study of Fuminori Kimura [31] prevalence of chronic endometritis was found to be 2.8-56.8% infertile women, 14% - 67.5% in women recurrent implantation failure and 9.3% - 67.6% in women with recurrent pregnancy loss and found antibiotic administration is an effective therapeutic option. The prevalence of chronic endometritis in infertility 2.8% and 24.3% by different authors [32].

The prevalence of chronic endometritis in RPL (Recurrent pregnancy loss) was reported 43.0%, 52.0%, 8.9% by different authors [33].

According to a recent prospective study of patients with RIF of RPL, the CE prevalence rate in the RIF group was 14% (Six of 43) and 27% in the RPL group (14 of 51) [34] in our study there was no data of RIF (recurrent implantation failure).

The most common finding on Trans abdominal and Trans-vaginal ultrasound scan was Thickened and Heterogeneous endometrium, asynchronous with the phase of the menstrual cycle (47.05%) which was consistent with one another study.

The most common histopathological finding was chronic nonspecific endometritis.

In 58.82% cases, no significant past history was there, history of IUD insertion in 8.82% cases which was consistent with one another study in which IUD insertion history was found in 11% cases [31].

In our study 14.71% cases the history of instrumentation was there, in 8.82% cases history of IUD insertion was there. 5.88% cases were postabortal, 2.94% were postpartum, 2.94% were postmenopausal with Cervical stenosis and with hematometra and 5.88% were Tubercular.

In one another study Chronic endometritis could be attributed to a specific etiologic factor in 84% of the patients: pelvic inflammatory disease in 25%, intrauterine contraceptive device in 14%, postpartum factors in 12% and postabortal factors in 41% [35].

In a large 1978 review, 53 per cent of the cases of chronic non-granulomatous endometritis were considered to be post-infectious in origin (postpartum, postabortal, or associated with intrauterine contraceptive devices or pelvic inflammatory disease, 26 per cent were the result of stagnation, 4.5 per cent were associated with carcinoma in situ of the cervix, and 16.5 per cent were idiopathic, although there was a high rate of oral contraceptive usage among these idiopathic cases [1].

5. Conclusion

Chronic endometritis is a low-grade infection of the endometrium. Most of the women remain asymptomatic. Various risk factors like childbirth, miscarriage, caesarian delivery, STDs; Pelvic procedures like D&C, Endometrial biopsy, hysteroscopy, and IUD insertion are the reason for the uterus lining to be inflamed.

Untreated Chronic endometritis has been linked with fertility issues, including an inability to conceive, recurrent implantation failure (RIF) and spontaneous abortion and poor reproductive outcome. Antibiotic treatment improves implantation rates and decreases the rate of abortion and the poor reproductive outcome so it is must to think about endometritis in such type of patient and to treat it timely.

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