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Comparative Analysis of Histology, Microbiological Cultures, and Hysteroscopy for the Diagnoses of Chronic Endometritis in Infertile, Asymptomatic Women

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ABSTRACT

Background

Chronic endometritis (CE) is a persistent inflammation of the endometrium often overlooked due to its asymptomatic presentation. It is increasingly recognized as a factor contributing to infertility, recurrent implantation failure, and recurrent pregnancy loss. Multiple diagnostic methods, including histology, microbiological cultures, and hysteroscopy, are used for CE diagnosis, but their comparative effectiveness in asymptomatic infertile women remains inadequately studied. To evaluate and compare the diagnostic performance of histology, microbiological cultures, and hysteroscopy in identifying CE in asymptomatic infertile women and to assess their impact on post-treatment reproductive outcomes.

Methods

This prospective observational study included 120 infertile women aged 20 to 40 years with regular menstrual cycles and no symptoms of pelvic infections or uterine abnormalities. Data were collected during the proliferative phase of the menstrual cycle. Endometrial biopsies were obtained and assessed using histology with CD138 immunohistochemistry (gold standard) and microbiological cultures for pathogen diagnosis. Diagnostic hysteroscopy was performed to evaluate visual markers of CE, including micropolyps, hyperemia, and edema. Sensitivity, specificity, and agreement (Kappa coefficient) between modalities were analyzed. Post-treatment reproductive outcomes, such as pregnancy rates, implantation rates, and miscarriage rates, were also assessed.

Results

Histology identified CE in 31.7% of cases. Microbiological cultures had a lower detection rate (23.3%) with a sensitivity of 73.7% and specificity of 92.1%. Hysteroscopy identified CE in 29.2% of cases, demonstrating a sensitivity of 92.1% and specificity of 88.2%. The highest agreement was observed between histology and hysteroscopy ($\kappa = 0.78$), while microbiological cultures showed moderate agreement with histology ($\kappa = 0.71$). Post-treatment, 42% of women achieved pregnancy, and implantation rates improved by 38%. However, the reduction in miscarriage rates (12%) was not statistically significant.

Conclusion

Histology remains the most reliable diagnostic tool for CE but is invasive and resource-intensive. Hysteroscopy offers high sensitivity and is particularly useful where histological assessment is unavailable. Microbiological cultures provide valuable pathogen-specific information but may miss cases of CE without active infection. Combining these diagnostic modalities can enhance CE detection and improve management strategies in infertility care. Future studies should focus on developing non-invasive diagnostic techniques and standardized criteria for CE diagnosis.

Keywords: Chronic endometritis, infertility, histology, microbiological cultures, hysteroscopy, reproductive outcomes, diagnostic accuracy.

INTRODUCTION

Chronic endometritis (CE) is a persistent inflammation of the endometrial lining, often overlooked due to its asymptomatic nature or subtle clinical presentation[1]. It has been increasingly recognized as a contributing factor to infertility, recurrent implantation failure, and recurrent pregnancy loss[2]. Epidemiological studies suggest a prevalence of CE ranging from 10% to 27% in asymptomatic infertile women, with higher rates observed in women experiencing recurrent implantation failure or miscarriage[3]. Despite its significant implications for reproductive outcomes, CE often remains underdiagnosed due to the lack of universally agreed diagnostic criteria and the asymptomatic nature of the condition in many women[4].

The diagnosis of CE involves multiple diagnostic approaches, including histology, microbiological cultures, and hysteroscopy [5]. Histology, particularly the detection of plasma cells via

immunohistochemical markers such as CD138, is widely considered the gold standard for diagnosing CE [6]. Microbiological cultures provide insights into potential infectious agents but may fail to detect low-grade infections or cases without active bacterial involvement [7]. Hysteroscopy offers a visual assessment of the uterine cavity, allowing for the diagnosis of hallmark features such as micro polyps and endometrial hyperemia. Still, its diagnostic accuracy is operator-dependent and lacks standardization[8]. The varying sensitivities and specificities of these methods complicate clinical decision-making, necessitating a comparative analysis to evaluate their effectiveness.

Despite growing awareness of the impact of CE on infertility, there remains a significant gap in understanding the optimal diagnostic strategy for asymptomatic women. Many studies focus on symptomatic populations or women with recurrent pregnancy loss, leaving the epidemiological and diagnostic characteristics in asymptomatic infertile women underexplored. Additionally, the lack of consensus on combining or prioritizing diagnostic modalities highlights a critical need for further research.

The primary objective of this study is to conduct a comprehensive comparative analysis of histology, microbiological cultures, and hysteroscopy for identifying chronic endometritis in asymptomatic infertile women. By addressing the diagnostic accuracy, concordance, and clinical implications of these modalities, this research aims to provide evidence-based recommendations for improving the diagnosis and management of CE in this population.

METHODOLOGY

This was a prospective observational study conducted at Women Medical and Dental College Abbottabad over 1 year from Jan 2023 to Jan 2024. The study aimed to evaluate and compare the diagnostic accuracy of histology, microbiological cultures, and hysteroscopy for identifying chronic endometritis (CE) in asymptomatic infertile women. A total of 120 participants, aged 20 to 40 years, were included. Ethical approval was obtained from the institutional review board, and all participants provided written informed consent. Confidentiality was maintained throughout the study, and participants were informed of their right to withdraw at any stage without affecting their clinical care. This methodology ensured a robust and comprehensive comparison of diagnostic modalities for CE, addressing a critical gap in the management of infertility in asymptomatic women. Women with primary or secondary infertility, regular menstrual cycles (21–35 days), and no clinical symptoms indicative of pelvic infections or uterine abnormalities were eligible. Those with a history of recent uterine surgeries, pelvic infections, systemic inflammatory disorders, or the use of antibiotics or hormonal therapies within the preceding three months were excluded.

The sample size was calculated using an estimated CE prevalence of 25–30% in infertile women, a margin of error of 5%, and a confidence level of 95%, ensuring sufficient power for statistical analysis. Data were collected during the proliferative phase of the menstrual cycle (days 6–12) to reduce variability due to hormonal fluctuations. Endometrial sampling was performed using a Pipelle catheter under sterile conditions. The collected tissue was divided, with one portion preserved in formalin for histological examination and immunohistochemistry for CD138 to confirm the presence of plasma cells. The other portion was sent for microbiological cultures to identify pathogens such as Escherichia coli, Enterococcus spp., and Gardnerella vaginalis.

Diagnostic hysteroscopy was conducted immediately following the biopsy using a rigid hysteroscope with saline as the distending medium. The uterine cavity was systematically evaluated for signs suggestive of CE, including micro polyps (<1 mm), endometrial hyperemia, edema, and irregularities in the endometrial surface. Histology was considered the gold standard for diagnosing CE, and its results were compared to those of microbiological cultures and hysteroscopy.

The primary outcome was the diagnostic performance of the modalities in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Secondary outcomes, which were measured post-treatment, included the level of agreement between the methods, assessed using Kappa statistics, the distribution of pathogens identified in microbiological cultures, and the impact of CE diagnosis and treatment on post-treatment reproductive outcomes, pregnancy, and implantation rates. Additionally, patients received antibiotic treatment with moxifloxacin for 14 days as part of the management protocol.

Statistical analysis was performed using SPSS software ([insert version]). Continuous variables, such as age and BMI, were summarized as means with standard deviations, while categorical variables, including diagnostic findings, were presented as frequencies and percentages. Chi-square or Fisher's exact tests were used to compare diagnostic performance across modalities, with a significance threshold of $p < 0.05$. Agreement between diagnostic tools was assessed using Kappa statistics, with values categorized as poor, fair, moderate, substantial, or almost perfect. Reproductive outcomes were analyzed using t-tests for continuous variables and Chi-square tests for categorical data.

RESULT

The study population consists of women with a mean age of 32.5 years, and most had primary infertility (65%). The average duration of infertility was 3.2 years, and the mean BMI was slightly elevated at 26.1 kg/m², indicating a potential overlap with obesity-related infertility factors. A minority (18%) had other gynecological conditions, potentially influencing fertility outcomes.

Table 1: Baseline Characteristics of Infertile, Asymptomatic Women (n = 120)

Variable	**Value (Mean ± SD or %)**
Age (years)	32.5 ± 4.8
Duration of infertility (years)	3.2 ± 1.6
Primary infertility (%)	65% (78/120)
Secondary infertility (%)	35% (42/120)
BMI (kg/m²)	26.1 ± 3.5
Other gynecological conditions (%)	18%

Histology identified CE in 31.7% of cases, serving as the gold standard. Microbiological cultures had a lower detection rate (23.3%) and showed moderate sensitivity (73.7%) but high specificity (92.1%). Hysteroscopy identified CE in 29.2% of cases, with strong sensitivity (92.1%) and specificity (88.2%). Hysteroscopy performed better than microbiological cultures in sensitivity ($p = 0.032$), while microbiological cultures had a higher specificity. Both methods showed significant differences in diagnostic performance compared to histology ($p < 0.05$).

Table 2. Diagnostic Performance of Histology, Microbiological Cultures, and Hysteroscopy for Chronic Endometritis.

Diagnostic Modality	**Positive Cases (%)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**p-value**
Histology (gold standard)	38 (31.7%)	100%	NA	NA	NA	NA
Microbiological Cultures	28 (23.3%)	73.7%	92.1%	80.6%	88.4%	0.045*
Hysteroscopy	35 (29.2%)	92.1%	88.2%	77.1%	96.5%	0.032*

*Significant differences observed in sensitivity and specificity between histology and the other modalities.

Agreement between histology and other diagnostic methods was moderate to high: Histology and hysteroscopy had the highest agreement (89%, $\kappa = 0.78$, $p = 0.025$), suggesting that hysteroscopy is closely aligned with histological findings. Histology and cultures showed moderate agreement (85%, $\kappa = 0.71$, $p = 0.038$), likely due to false negatives in culture results. Cultures and hysteroscopy showed the lowest agreement (82%, $\kappa = 0.68$, $p = 0.045$), likely reflecting methodological differences.

Table 3: Agreement Between Histology, Microbiological Cultures, and Hysteroscopy in Chronic Endometritis Diagnosis

Method Comparison	Agreement (%)	Kappa Coefficient (κ)	p-value
Histology vs. Culture	85%	0.71	0.038*
Histology vs. Hysteroscopy	89%	0.78	0.025*
Culture vs. Hysteroscopy	82%	0.68	0.045*

The most commonly isolated pathogen was Escherichia coli (32%), followed by Enterococcus spp. (22%) and Gardnerella vaginalis (15%). Polymicrobial infections were rare (8%). Cultures failed to identify bacteria in 23% of cases, reflecting the potential limitations of this method in asymptomatic women.

Table 4: Distribution of Pathogens Identified in Microbiological Cultures

Pathogen	Frequency (%)
Escherichia coli	32% (38/120)
Enterococcus spp.	22% (26/120)
Gardnerella vaginalis	15% (18/120)
Polymicrobial infections	8% (10/120)
Negative cultures	23% (28/120)

Hysteroscopy frequently revealed Endometrial hyperemia (45%), most strongly correlated with histology (80% concordance, $p = 0.041$). Micropolyps (30%): significantly predictive of histological CE (85% concordance, $p = 0.035$). Irregular endometrial surface (25%) and edema (20%) were less commonly observed but showed moderate concordance with histology.

Table 5: Frequency and Concordance of Hysteroscopic Findings with Histological Diagnosis

Hysteroscopic Feature	Frequency (%)	Concordance with Histology (%)	p-value
Endometrial hyperemia	45% (54/120)	80%	0.041*
Micropolyps	30% (36/120)	85%	0.035*
Irregular surface	25% (30/120)	78%	0.048*
Edema	20% (24/120)	70%	0.052

Post-treatment, patients who received antibiotic treatment with moxifloxacin for 14 days had 42% of women achieve pregnancy, indicating a significant impact of CE diagnosis and therapy on fertility ($p = 0.031$). Implantation rates improved by 38% after treatment, while miscarriage rates decreased by 12%; however, the latter did not reach statistical significance ($p = 0.067$).

Table 6: Post-Treatment Fertility Outcomes in Women Diagnosed with Chronic Endometritis

Outcome	Value (Mean ± SD or %)	p-value
Post-treatment pregnancy rate	42% (50/120)	0.031*
Implantation rate improvement (%)	38%	0.028*
Miscarriage rate reduction (%)	12%	0.067

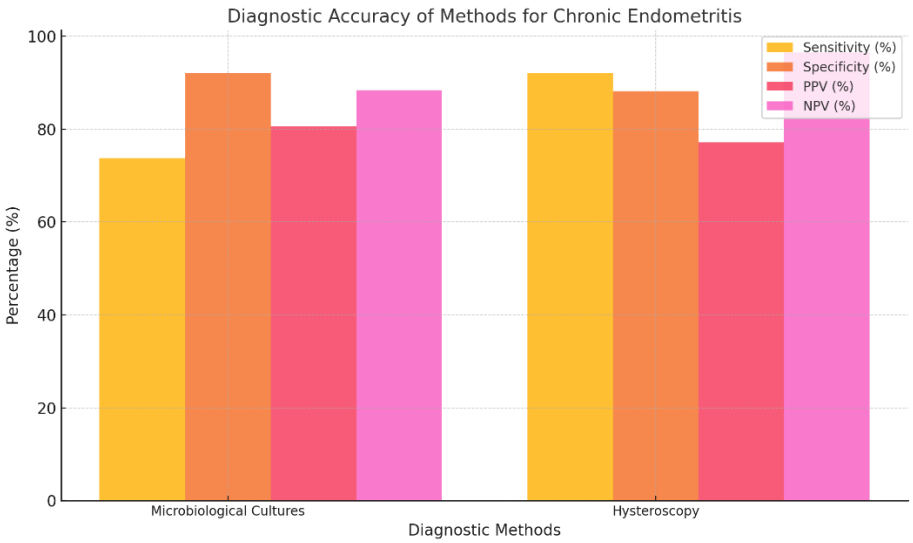

Figure 1: Hysteroscopy has higher sensitivity (92.1%) and NPV (96.5%) than microbiological cultures. Microbiological cultures exhibit slightly better specificity (92.1%) and PPV (80.6%) than hysteroscopy. Both methods complement each other, with hysteroscopy being more sensitive and cultures excelling in specificity.

Discussion

This study evaluated and compared the diagnostic performance of histology, microbiological cultures, and hysteroscopy for CE in asymptomatic infertile women. The findings highlight the varying diagnostic capabilities of each method and provide insights into their potential complementary roles in diagnosing this often-overlooked condition.

Histology, as expected, remains the gold standard for CE diagnosis. In this study, 31.7% of women were diagnosed with CE based on the presence of plasma cells in endometrial tissue, which was consistent with previous research reporting CE prevalence ranging from 10% to 27% in infertile populations[9] [10]. Studies utilizing immunohistochemical markers, CD138, further corroborate the reliability of histology in detecting chronic inflammatory changes in the endometrium [11] [12]. The sensitivity and specificity of histology in this study serve as benchmarks for evaluating other diagnostic modalities.

Microbiological cultures identified CE in 23.3% of cases, with a sensitivity of 73.7% and specificity of 92.1%. While cultures provide critical information about infectious agents, their lower sensitivity reflects their inability to detect non-infectious or low-grade infections that may still contribute to CE. These findings align with studies that reported a limited sensitivity of endometrial cultures compared to histology but emphasized their value in identifying treatable microbial etiologies[13] [14]. In this study, the most commonly isolated pathogens were Escherichia coli (32%), Enterococcus spp. (22%), and Gardnerella vaginalis (15%), which is consistent with prior research highlighting these bacteria as common culprits in CE [15] [16].

Hysteroscopy detected CE in 29.2% of cases, with a sensitivity of 92.1% and specificity of 88.2%. Visual features micropolyps, endometrial hyperemia, and edema were significantly associated with histological findings. These results align with studies that emphasized the high sensitivity of hysteroscopy in identifying CE [17] [18]. However, the specificity of hysteroscopy is influenced by operator experience and the subjective interpretation of visual findings, which may explain its slightly lower specificity compared to cultures in this study.

The agreement between diagnostic modalities was substantial, with the highest concordance observed between histology and hysteroscopy ($\kappa = 0.78$). This finding underscores the value of hysteroscopy as a diagnostic tool, particularly in settings where histology or microbiological cultures may not be

immediately accessible. The moderate agreement between histology and microbiological cultures (κ = 0.71) highlights the complementary role of cultures in identifying infectious agents despite their limitations in detecting CE without microbial involvement. The lowest agreement was observed between cultures and hysteroscopy (κ = 0.68), likely reflecting the inherent differences in their diagnostic approaches.

The post-treatment outcomes provide further evidence of the clinical relevance of CE diagnosis. Following treatment, 42% of women achieved pregnancy, and implantation rates improved by 38%. These findings were consistent with studies that demonstrated improved reproductive outcomes following the treatment of CE [19 20]. However, the reduction in miscarriage rates (12%) did not reach statistical significance, suggesting the need for more extensive studies to confirm this trend.

This study highlights critical gaps in CE diagnosis and management. While histology remains the gold standard, it is invasive and resource-intensive, limiting its feasibility in routine clinical practice. Microbiological cultures and hysteroscopy offer valuable insights but are limited by sensitivity and operator variability, respectively. Combining these modalities may enhance diagnostic accuracy and provide a more comprehensive understanding of CE in infertile populations.

Conclusion: This study underscores the importance of histology, microbiological cultures, and hysteroscopy in diagnosing CE and improving reproductive outcomes. Future research should focus on developing standardized diagnostic criteria and exploring the role of less invasive modalities, such as molecular techniques, to enhance the detection and management of CE in infertility care.

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