

Narrative Review on Chronic Endometritis and Its Diagnosis in the Reproductive Process: Focus on Possible Future Diagnostic Perspectives

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Abstract

(1) Background: Chronic endometritis (CE) is a chronic disease of the endometrium characterized by inflammatory infiltration into the endometrial stroma. The diagnosis of CE is complex. Clinical examination and transvaginal ultrasound are not specific for CE. Biopsy is an indispensable tool. Two specific populations can be analyzed at the endometrial level: CD138 positive plasma cells and CD56 positive Natural Killer cells. (2) Methods: Our narrative review was based on an online search with a focus on the last ten years of literature in the English language. (3) Results: Twenty studies on CD138 positive plasma cells and 16 articles on CD56 positive Natural Killer cells highlighted the correlations of CE with diagnostic possibilities and reproductive outcomes. (4) Conclusions: The etiological pathway and management of CE require further scientific studies and investigations. Hysteroscopy is the diagnostic gold standard, but other blind biopsy techniques (i.e., Perma, Pipelle, Novak, etc.) and molecular procedures may help in the diagnosis of chronic endometritis.

Keywords: infertility; plasma cells; Natural Killer cells; recurrent implantation failure; recurrent spontaneous abortion



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1. Introduction

Infertility is defined as the inability to conceive after unprotected sexual intercourse. Guidelines recommend initiating a diagnostic workup after 12 months of unsuccessful conception in women under 35 years of age and after 6 months in women over 35 years of age. However, in women over 40 years of age, a more immediate evaluation may be considered [1].

The extent of investigations depends on multiple factors, including the patient’s age, personal and reproductive history, duration of infertility, and the couple’s preferences.

It is estimated that in 40% of infertile couples, the woman is the sole or contributing cause of infertility; in another 40% of cases, infertility is attributable to the male partner, and in the remaining 20% of cases, there are no identifiable causes.

Transvaginal ultrasound is a fundamental first-line tool for evaluating uterine and adnexal pathologies and for studying ovarian reserve. It allows for the analysis of the number and size of ovarian follicles, especially when performed during the luteal phase [2]. Uterine pathologies account for approximately 16% of the causes of female infertility. They include both more common acquired conditions, such as endometrial polyps, uterine fibroids, and adhesions, as well as congenital pathologies, including bicornuate uterus, septate uterus, or other congenital uterine anomalies [3].

Hysteroscopy, on the other hand, represents a diagnostic but also therapeutic method for intrauterine pathologies [4].

The balance between reproductive difficulties and achieving a pregnancy is very delicate. Another potential cause of recurrent miscarriages or implantation failure is genital infection, connecting intestinal dysbiosis and endometritis. Several microorganisms, including *Ureaplasma*, *Mycoplasma*, and *Chlamydia* [5,6], that cause bacterial vaginosis, also appear to be implicated in first- and second-trimester miscarriages [7].

More recently, increasing attention has been paid to the role of the immune system in reproductive function, particularly the altered inflammatory and immune status of the endometrium, which can lead to unexplained infertility and recurrent miscarriages: this condition is called chronic endometritis (CE).

Chronic endometritis is a chronic inflammatory disease of the endometrium characterized by plasma cell infiltration into the endometrial stroma (Figure 1). The diagnosis of CE is complex. Clinical examination and transvaginal ultrasound are not specific for CE; endometrial biopsy is fundamental. Several diagnostic methods have been suggested for the diagnosis of chronic endometritis, the most widely used of which is hysteroscopy, allowing the identification of the classic signs of endometritis:

- Focal or diffuse hyperaemia (the “strawberry” appearance);
- Stromal edema;
- Micro-polyps (small growths < 1 mm, a highly predictive sign of endometritis).

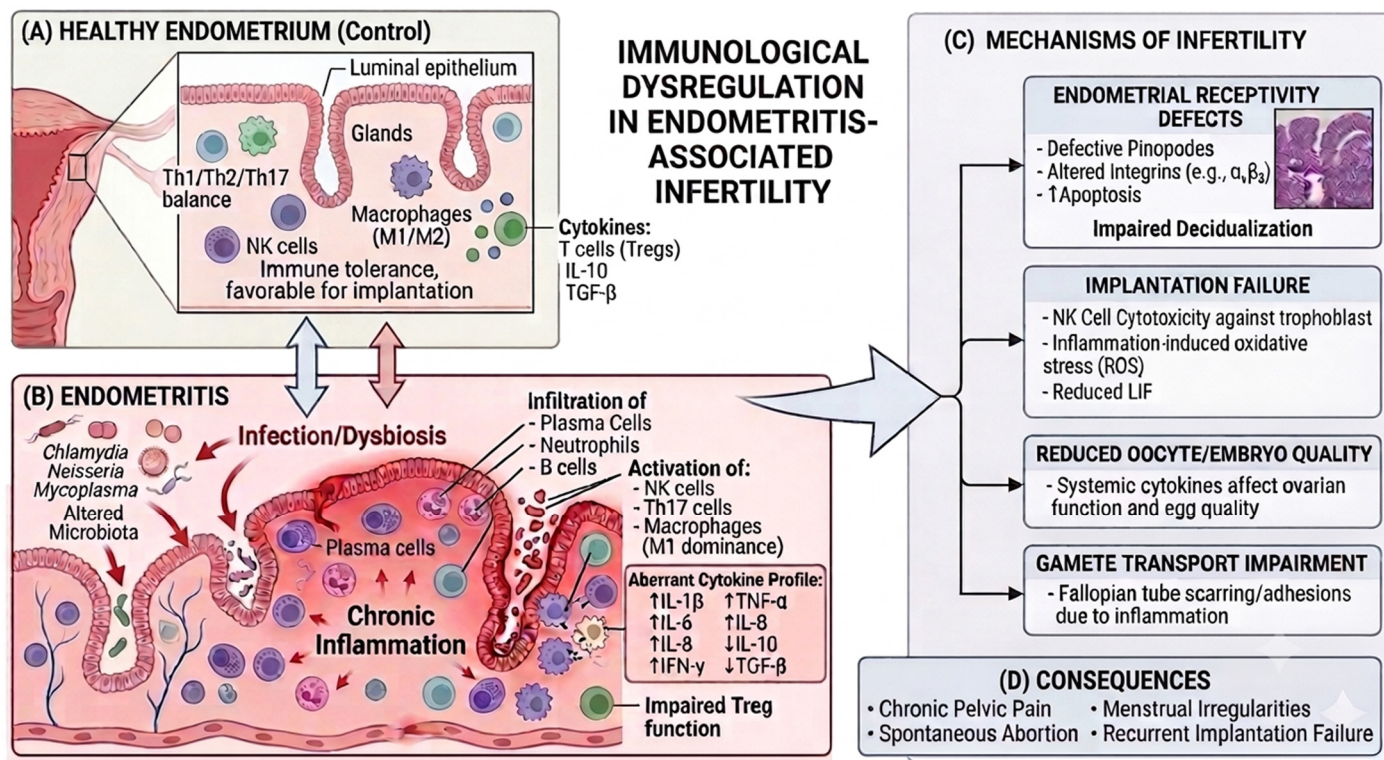


Figure 1. Impaired immunological function, endometritis and infertility.

Moreover, the endometrial biopsy is fundamental for studying these diagnostic populations: CD138 plasma cells and CD56 Natural Killer cells.

Immunohistochemistry for the plasma cell marker CD-138 at the endometrial histological level is currently the most reliable and rapid diagnostic method for CE. However, this technique has several limitations [8,9].

Endometrial epithelial cells can express CD-138 on the basolateral side of their plasma membrane, potentially leading to misdiagnosis. Therefore, additional specific staining techniques for CE would be useful. CE may represent a substrate for the development of proliferative endometrial lesions, including endometrial polyps [8]. Furthermore, CE may impair endometrial receptivity to the embryo, resulting in infertility and recurrent miscarriages. Unfortunately, the exact mechanisms underlying chronic endometritis-related infertility are still unknown, potentially involving other cells, such as Natural Killer (NK) CD56+ [8,9]. The risk of CE may also be significantly related to the presence of endometrial polyps: it appears more likely in women with polypoid endometrium, as well as in those with three or more endometrial formations compared to those with a single one [8,9]. Available evidence in premenopausal women suggests that this condition may represent two consecutive phases of a common pathological process, which requires further study to fully clarify its role in infertility [8,9].

In most cases, patients are asymptomatic or present with nonspecific symptoms such as pelvic pain, dyspareunia, leukorrhea, and dysmenorrhea [8].

Chronic endometritis compromises the uterine environment by altering cytokine production, reducing the expression of implantation-related genes, and promoting stromal fibrosis [9].

Our aim is to summarize the updated literature known so far about the topic to deepen our understanding of the diagnostic criteria and management in infertility.

2. Materials and Methods

Our study aims to conduct a narrative review of the literature on CD138+ plasma cells and CD56+ NK cells, focusing on endometritis and reproductive outcomes such as abortion/pregnancy rate/recurrent implantation failure, etc., using searches from PubMed, Scholar, Embase, Scopus, etc.

The identification of the articles in the English language was based on the keywords: (“Infertility” [MeSH Terms]) AND (“CD138” [Title/Abstract] OR “syndecan-1” [Title/Abstract] OR “plasma cells” [MeSH Terms]), (“Infertility” [MeSH Terms]) AND (“Natural Killer Cells” [MeSH Terms] OR “NK cells” [Title/Abstract]).

Literature from the last 10 years (2016–2026) was then filtered, according to the scientific research evidence (based on strength of evidence, sample size, quality of studies, etc.). Our narrative review is written following the Equator Guidelines [10] (Figure 2).

Inclusion and Exclusion Criteria

-Inclusion Criteria:

- Observational studies (cohort, case–control, cross-sectional) and clinical trials (randomized or otherwise) evaluating the role of CD138+ plasma cells and/or NK cells in patients with infertility.
- Studies that included an assessment of CD138+ (by immunohistochemistry) or CD56+ NK cells (using flow cytometry, immunohistochemistry, or endometrial biopsy).
- Comparative studies with fertile control groups or pre-/post-treatment designs.

-Exclusion Criteria:

- Preclinical studies using animal models or in vitro cell lines.
- Abstracts without full text available.

- Case reports, editorials, letters to the editor, and narrative reviews.
- Studies not directly related to infertility (e.g., oncology).

Gemini AI 3.5 Flash was used to create Figure 1 (Branch • CD56, CD138 and implantation failure—Google Gemini <https://gemini.google.com/app/b2888b43343800b0?hl=it>), accessed online on 29 May 2026.

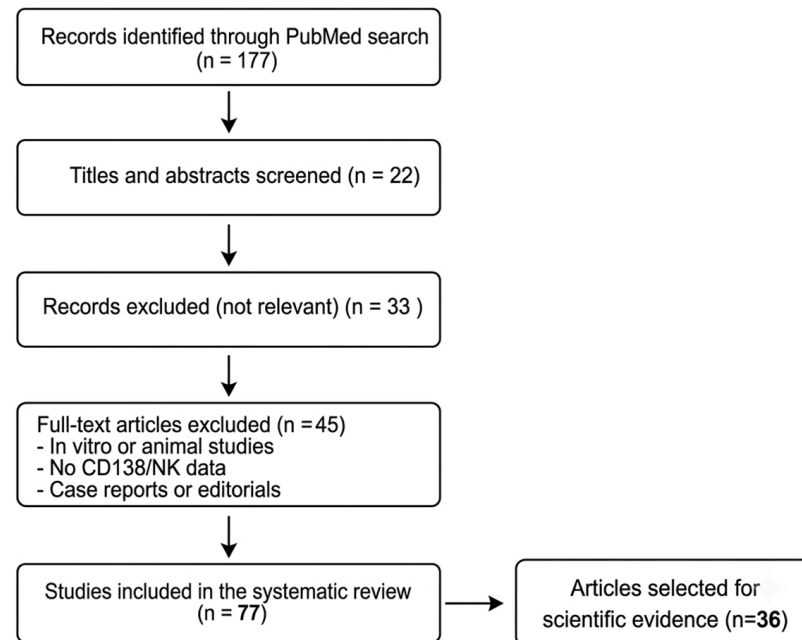


Figure 2. Flow-chart of the literature evaluation.

3. Results

The initial identification of 77 articles was based on the keywords and scientific evidence; 36 articles in the English language were then filtered according to the last 10 years of production for table description.

3.1. Plasma Cells CD138 (Table 1)

CD138+ plasma cells (Syndecan-1) are the main diagnostic marker of chronic endometritis. Although immunohistochemical detection of CD138+ plasma cells is now globally accepted as the best marker for diagnosing CE, there is no consensus on the cut-off that is considered statistically significant. This variability may be due to the different methods used to quantify CD138+ cells. The most common approach is to count CD138+ cells per high-power field (HPF). The study by Chen et al. recommends a cutoff of >5 CD138+ cells/HPF [11]. Bouet et al. [12] proposed a minimum of five plasma cells in 10 non-overlapping HPFs as the diagnostic threshold for chronic endometritis; Kitaya et al. [13] instead suggested a cutoff of >5 cells in 20 non-overlapping HPFs.

These above-mentioned studies, however, do not definitively correlate the number of CD138+ cells with adverse reproductive outcomes.

The optimal diagnostic window is also still unclear regarding the optimal timing for endometrial sampling, and results are controversial. Furthermore, Li et al.'s research [9] evaluated 716 women highlighting that a number of CD138+ cells ≥ 5 in at least one of 30 HPFs was statistically significantly associated with adverse pregnancy outcomes. In this study, endometrial biopsies were performed during the proliferative phase, highlighting how the result may vary depending on the phase of the menstrual cycle in which the sampling was performed [9].

Previous studies have suggested the follicular phase as the best time to perform biopsy, as the luteal phase may show inflammatory infiltration, leading to false positives [14].

Selmi et al.'s study on 249 patients found no statistically significant differences in the detection of CE between the proliferative and secretory phases in patients with RIF (recurrent implantation failure) and RPL (recurrent pregnancy loss), suggesting that this is a persistent rather than cyclical condition [15].

A prospective study from 2021 [16] observed that the mean CD138+ score (calculated as the number of CD138/HPF cells) was significantly altered in women with full-term pregnancies compared to those with infertility and recurrent miscarriages. Women with >16 CD138/HPF had a significantly higher risk of miscarriage.

The rate of chronic endometritis in infertile women undergoing in vitro fertilization (IVF) reaches 30–40%, decreasing to approximately 10% after antibiotic and probiotic therapy [16].

Table 1. Literature review about plasma cells CD138+ and infertility.

Article	Sample	Results	Article	Sample	Results
(1) Huang et al. 2026 [17]	Retrospective analysis on 1401 infertile women. CE was defined as ≥ 1 plasma cell CD138+ per 10 high-power fields. Therapy consisted of doxycycline 100 mg twice daily for 14 days.	No significant associations between CE and RIF or RSA.	(11) Ryan et al. 2022 [18]	Retrospective cohort study. Biopsies from 91 patients in the follicular phase and 60 in the luteal phase.	Plasma cell density was higher in the follicular phase group than in the luteal phase group (59.3% versus 19.7%).
(2) Torres et al. 2026 [19]	Prospective observational cohort study.	CE associated with unexplained infertility. Diagnostic concordance between hysteroscopic evaluation and immunohistochemistry was 71.1%.	(12) Herlihy et al. 2022 [20]	Endometrial samples from 80 women undergoing IVF. Three reviewers assessed the presence of plasma cells.	A total of 49% of samples had ≥ 1 plasma cell per 10 high-power fields (HPFs), 11% had ≥ 5 cells per 10 HPFs, and 4% had ≥ 10 cells per 10 HPFs. No reproductive differences were found between patients with and without CE.
(3) Halouani et al. 2025 [21]	This is a prospective, multicenter, observational study. A total of 70 patients were definitively included.	Hysteroscopy is not the only diagnostic test of choice. Novak may be a valuable tool. % of inter-observer agreement for hysteroscopy of CE was high ($\kappa = 0.62$), while intra-observer agreement was moderate ($\kappa = 0.58$).	(13) Kuroda et al. 2021 [22]	A total of 222 women diagnosed with CE after polypectomy, 62 treated with doxycycline and 160 not treated (control group).	Most patients recovered with polypectomy without doxycycline ($p < 0.0001$). The duration of healing was shorter in the group not treated with antibiotics (42.6 ± 41.0 days and 56.5 ± 32.3 days, $p < 0.0001$), with a higher pregnancy rate (63.2% and 43.8%, respectively, $p = 0.034$).

Table 1. Cont.

Article	Sample	Results	Article	Sample	Results
(4) Szafarowska et al. 2025 [23]	Retrospective analysis on 136 infertile women undergoing hysteroscopy. The diagnosis of CE was based on the presence of at least 5 plasma cells per 10 HPF. A single oral dose of azithromycin was administered after the procedure.	Patients treated with antibiotics have a higher probability of conceiving. Secondary infertility was associated with greater reproductive success after therapy (54% vs. 24%, $p = 0.022$).	(14) McQueen et al. 2021 [14]	Cohort study. Endometrial samples from 50 women with unexplained recurrent miscarriages and 26 controls were evaluated.	Plasma cells and endometrial stromal changes was limited to the RPL cohort. CE is defined as $\geq 1/10$ HPF with endometrial stromal changes. Women with RPL had a significantly higher rate of CE.
(5) Amrani et al. 2025 [24]	A total of 82 patients were recruited; 49 (59.8%) were assigned to Group A and 33 (40.2%) were assigned to Group B.	Biopsy is preferable in the follicular phase, the diagnostic cutoff is 5/HPF, the antibiotic eradicated 80% of CE improving reproductive outcomes.	(15) Li et al. 2021 [9]	Retrospective study of 716 infertile patients, on endometrial scratching in the mid-luteal phase before in vitro fertilization.	In the CD138+high group, the β -hCG positivity, clinical pregnancy, and live birth rate were significantly reduced ($p = 0.04$, $p = 0.01$, $p = 0.04$, respectively). Immunohistochemical analysis is a reliable method for detecting CE (≥ 5 plasma cells in at least one out of 30 HPF).
(6) Ilic et al. 2025 [25]	A retrospective study. Of the 661 infertile patients, 51 underwent hysteroscopy and endometrial biopsy; 23 had a normal uterine cavity (45%), and among the 28 patients with an abnormal uterine cavity, 10 (35.7%) had hysteroscopic findings suggestive of CE.	Increased pregnancy rate after antibiotic therapy OR 4.4 (95% CI: 1.17–16.8; $p = 0.03$), hysteroscopy is not always the best diagnostic option.	(16) Mitter et al. 2021 [26]	A retrospective cohort study of 108 women with RIF or RM. A total of 41 women underwent hysteroscopy only; 67 women underwent diagnostic endometrial biopsy and hysteroscopy. If positive, the therapy was doxycycline 100 mg twice daily orally for 2 weeks.	The biopsy group showed a higher % of pregnancy (hazard ratio 2.28; 95% CI 1.23–4.24; $p = 0.009$) and term delivery (hazard ratio 2.76; 95% CI 1.30–5.87; $p = 0.008$). Biopsy and antibiotics in patients with RIF and RSA increase the % of pregnancy.

Table 1. Cont.

Article	Sample	Results	Article	Sample	Results
(7) Furui et al. 2024 [27]	399 eligible hysteroscopic procedures were included in this study, with 200 patients in the CE group and 199 in the non-CE group.	Endometrial congestion correlates with CE, hysteroscopy is not always the best diagnostic option.	(17) Volodarsky-Perel et al. 2020 [28]	Seventy patients were included. All infertile women with CE were treated with oral doxycycline 100 mg twice daily for 14 days.	CE-positive polyps were more frequent in infertile patients (22.6% vs. 8.6%; $p = 0.001$). Infertility was associated with CE (odds ratio, 3.16; 95% CI, 1.53–6.49).
(8) Xiong et al. 2023 [29]	A total of 298 infertile women undergoing endometrial biopsy were included. In 100 women, sections were cut from each paraffin-embedded tissue block for single immunohistochemical (IHC) staining to train an artificial intelligence (AI)-based diagnostic system. In the other 198 women, tissue sections stained with CD138/MUM1 DS were used to test the AI system in the diagnosis of CE.	The sensitivity, specificity and accuracy of CD138/MUM1 DS in the diagnosis of CE were 100% ($p < 0.05$).	(18) Liu et al. 2018 [30]	Four groups of women: patients with proven fertility ($n = 40$), unexplained RM; $n = 93$, RIF $n = 39$, and infertile subjects in a natural cycle before frozen–thawed embryo transfer ($n = 48$).	The prevalence of CE in women with RM, recurrent infertility, and infertility was 10.8%, 7.7%, and 10.4%, respectively, and was not substantially higher than that in fertile women (5.0%).
(9) Qiao et al. 2023 [31]	Retrospective study on 201 infertile women with minimal/mild endometriosis undergoing hysteroscopy and laparoscopy. Immunohistochemistry was used to detect CD138+.	CE is correlated with a negative effect in infertile women with endometriosis, with lower cumulative pregnancy and live birth rate than women without CE (46.51% vs. 71.13% [$p = 0.004$]; 44.19% vs. 63.38% [$p = 0.025$]).	(19) Liu Y. et al. 2019 [32]	130 infertile women. Endometrial biopsy and fluid collected exactly 7 days after the LH surge.	<i>L. crispatus</i> was less abundant with endometritis. <i>Anaerococcus</i> and <i>Gardnerella</i> correlated negatively in terms of relative abundance.

Table 1. Cont.

Article	Sample	Results	Article	Sample	Results
(10) Cicinelli et al. 2022 [33]	A multicentre, retrospective, observational study on 193 consecutive women of childbearing age treated with hysteroscopy, to evaluate the diagnostic accuracy of IHC for MUM-1 in endometritis, compared to IHC for CD-138.	IHC demonstrated equal diagnostic accuracy for MUM-1 and CD-138. MUM-1 allowed the identification of a greater number of plasma cells/HPF than CD-138 (6.50 [SD 4.80] vs. 5.05 [SD 3.37]; $p = 0.017$).	(20) Zargar et al. 2019 [34]	A cross-sectional study, hysteroscopy performed on the 3rd to 5th day after the end of the menstrual cycle and a subsequent biopsy on 85 patients.	Hysteroscopy is a reliable diagnostic tool in patients with RIF and RPL. The sensitivity, specificity, and positive and negative predictive values were 86.36%, 87.30%, 70.37%, and 94.82%, respectively.

Legend: Chronic endometritis, CE; number of patients, n=; recurrent miscarriage, RM; recurrent implantation failure, RIF; high-power fields, HPF; recurrent pregnancy lost, RPL; recurrent spontaneous abortion, RSA; artificial intelligence, AI.

3.2. Natural Killer CD56+

Natural Killer (NK) cells are potentially linked to reproduction in a significant way [35]. The literature provides varied data regarding the connection between Natural Killer cells, endometritis, and infertility (Table 2) [36–50].

Uterine NK cells represent the major leukocyte population in the normal endometrium and also play a fundamental role in angiogenesis and trophoblast invasion [51]. Their presence varies physiologically during the different phases of the menstrual cycle, likely due to the recruitment of NK cells from peripheral blood or their proliferation in the uterus. They represent 40% of total leukocytes during the proliferative phase and increase to 60% during the secretory phase [52].

There are two subgroups of CD56+ NK cells, depending on the density of CD56 on the cell surface, which can be distinguished into CD56bright (high expression) and CD56dim (low expression) cells. CD56bright cells are primarily immunomodulatory and cytokine-producing, while CD56dim cells are highly cytotoxic and represent the mature and predominant phase in peripheral blood [53].

In peripheral blood, 90% of NK cells are CD56+/CD16+ and CD56−/CD16+ cells. CD56+/CD16− cells constitute 70–90% of lymphocytes present in the secretory phase of the endometrium and are less cytotoxic [54,55]. Both peripheral blood NK cells (pNKs) and uterine NK cells (uNKs) display CD56 on their surface but differ in both phenotype and function. A total of 90% of pNK cells are CD56dim/CD16+, while 80% of uNK cells are CD56bright/CD16+.

Several studies have attempted to correlate pNK levels with recurrent miscarriages, but the literature to date has yielded conflicting results (Table 2).

The study by Azargoon et al. observed a significantly higher mean percentage of CD56+ cells in infertile women compared to fertile women (p -value 0.007). However, no significant differences were found in the total number of CD56+ cells between women with recurrent miscarriages and the control group [56].

The study by Fukui et al. showed, using immunophenotypic analysis, a higher percentage of CD16+/CD56dim cells and a lower percentage of CD16−/CD56bright cells in women with infertility who miscarried following in vitro fertilization, compared to women who carried their pregnancies to term [57].

Lachapelle et al. also observed a prevalence of CD16+/CD56dim cells and a reduction in CD16−/CD56bright cells in women with recurrent miscarriages compared to controls [58].

The study by Junovich et al. found an increase in the number of CD16+ endometrial NK cells in patients with unexplained infertility, correlated with a reduction in IL-6 and VEGF levels in the endometrium [59].

It can therefore be hypothesized that an increase in CD16+ NK cells may create an unfavourable environment for implantation, likely by producing pro-inflammatory cytokines and secreting cytotoxic factors in response to trophoblast cells [59].

Repeated implantation failure is typically defined as three failed Intra-Cytoplasmic Sperm Injection (ICSI) cycles, although this definition varies, and the literature often uses a number of failed cycles of ≥ 2 . The IVF success rate is 40.1% in women under 35 years of age, while it is 20.6% in women over 40 years of age. Pregnancy failure is due to implantation failure in more than 50–75% of cases [60].

During the implantation window, the number of endometrial NK cells increases significantly, from 30% in the proliferative phase to 70% in the secretory phase [39]. The increase in NK cells is likely involved in preparing the endometrium for embryo implantation, angiogenesis, trophoblast invasion, decidualization, and immunological tolerance through the production of various cytokines [61].

Several studies have investigated the impact of NK cells on the success or failure of IVF procedures (Table 2).

Interestingly, some research has observed a paradoxical association between normal uNK cell counts and poor reproductive outcomes, leading to functional hypotheses of exhaustion or inappropriate receptor–ligand interactions. Killer Cell Immunoglobulin-like Receptors (KIRs) and their interactions with HLA-C ligands on trophoblasts could potentially determine the immunological “compatibility” between mother and embryo, influencing implantation success [30,52,62].

The study by Mardanian et al. demonstrated a significantly higher level of CD56dimCD16+ cells in peripheral blood in the IVF-failure group compared to the IVF-successful group ($p < 0.0001$), while the level of CD56brightCD16– cells did not show statistically significant differences ($p = 0.28$) [63].

Other data have found a higher percentage of CD56dim NK cells in the peripheral blood of women with repeated implantation failure compared to fertile controls, such as the study by Sacks et al. ($p < 0.001$) [64].

The relationship between NK cells in the peripheral blood and implantation failure remains highly controversial. It is believed that increased NK cell activity may be involved in the immune response of “fetal rejection” by preventing invasion of the trophoblast in the endometrium [65].

However, updated studies evaluating the presence and impact of endometrial NK cells on infertility are few or with a small sample size and are not always conclusive.

Chen et al. [66] showed a significantly higher percentage of CD56+ cells in the endometrium in cases of repeated implantation failure (p -value < 0.001). A more in-depth investigation of the NK cell population showed a significantly higher percentage of both CD56+CD16+ and CD56+CD16– cells in women with repeated implantation failure compared to the control group.

In the retrospective study by Ekemen et al. [36], endometrial samples were collected during the secretory phase of the cycle. In 74.3% of cases with two or more IVF failures, elevated CD56+ cells were found in patients. These patients were then treated with cortisone and intralipid therapy. In 85.5% of cases, a successful pregnancy was achieved following treatment.

Functional profiling of uNK cells at the transcriptomic level reveals a dual phenotype. While CD56bright uNK cells express angiogenic factors, aberrant populations exhibit increased transcripts for cytotoxic mediators. Research using single-cell RNA sequencing has identified uNK subpopulations with divergent roles, supporting implantation or mediating immune rejection. At the proteomic level, excessive activation correlates with the secretion of granzyme B, perforin, and IFN- γ , which can disrupt trophoblast invasion and endometrial vascular remodelling [30,57]. CD56bright CD16– endometrial NK cells are present in large numbers at the implantation site where they come into contact with trophoblast cells, and transcriptomic studies suggest that this cell phenotype expresses proangiogenic factors [53,67].

The mechanism by which trophoblast cells escape endometrial NK cells is unclear. It is hypothesized that increased NK cell activity may lead to trophoblast cell suppression and thus miscarriage [68].

A new area of interest is the interaction between CD138+ plasma cells and endometrial NK cells. Some studies, such as that of Kitaya et al. in 2018, suggest that chronic inflammation and an altered innate immune response may together create a uterine environment unfavourable to implantation [69].

Preliminary studies suggest altered levels of metabolites involved in oxidative stress, which could alter immune tolerance and local cytokine production. These alterations could modulate the cytotoxic threshold of NK cells and plasma cell survival, compromising embryo implantation [70].

CD138+ plasma cells and NK cells have shown a particularly important role in IVF, where the lack of endogenous immunomodulation by the corpus luteum could increase susceptibility to immune dysfunction. This is a possible explanation why antibiotic therapy for chronic endometritis and/or corticosteroid and intralipid therapy in cases of high numbers of cytotoxic NK cells in the peripheral blood are associated with increased implantation success [67].

Table 2. Literature review about Natural Killer CD56+ and infertility.

Article	Sample	Results	Article	Sample	Results
(1) Chen et al. 2025 [66]	Three groups: RM, RIF and the controls, with 56 women in each group.	CD56+ NK cells were higher in patients with RM or RIF compared to controls.	(9) Marron et al. 2019 [44]	A total of 612 patients underwent endometrial biopsy. A control group was used for comparison purposes [n = 35]	RIF patients have increased uNK (53.2 vs. 45.2 and 42.9%, $p < 0.0001$). All sub-fertiles had a higher % of peripheral-type NK cells ($p = 0.001$) and greater CD69+ activation ($p = 0.005$), higher B-cell levels ($p < 0.001$), elevated CD4:CD8 ratio ($p < 0.0001$), lower T-regs ($p = 0.034$), and a higher proportion of CD4 Th1+ cells ($p = 0.001$).
(2) Ekemen et al. 2023 [36]	Retrospective study on endometrial biopsy from 76 women with unexplained infertility (UI) and recurrent IVF failures.	Significant correlation between CD56+ and BCL-6; CD138+ was an independent parameter. After antibiotic, pregnancy rates increased from 58.5% to 61.6% and 73.8% in CD56 positive, and CD56, BCL-6 or CD138 positive cases, respectively.	(10) Yang et al. 2019 [45]	A total of 183 women, of which 75 were in natural cycles and 108 were in hormone replacement therapy cycles. All endometrial biopsies were collected exactly on the expected day of implantation.	No significant difference ($p > 0.05$) was found in uNK cell density between natural cycles (median 2.28%, range 0.99–4.78%) and HRT cycles (median 2.55%, range 0.69–5.02%) in IVF-ET treatment.
(3) Cuadrado-T. et al. 2023 [37]	A total of 39 women with RM who had IVF cycles with donated eggs and 21 healthy egg donors with proven fertility.	A higher % of CD56dimCD16+ NK cells was observed in patients compared to healthy donors.	(11) Donoghue et al. 2019 [46]	Pipette endometrial biopsies were collected 6–8 days after the LH surge in natural cycles of women with: RIF (n = 14), IS (n = 11), and women with potential RIF at the time of the study (n = 9).	No difference in CD56+ or CD16+ uNK cells. In all groups, a higher % of uNK cells was present in the distal regions compared to those closer to the arterioles. A significant reduction in uNK cell was observed in women with a previous pregnancy.

Table 2. Cont.

Article	Sample	Results	Article	Sample	Results
(4) Mousavi-Salehi et al. 2023 [38]	A total of 54 women, in three groups: 18 subjects with RIF, 21 with spontaneous abortion and 15 healthy women.	The mean ratio of NK cells and IFN- γ levels was increased in women with RM compared to the healthy control group [$p < 0.018$] and [$p < 0.031$], respectively]. RIF and control groups showed no significant differences.	(12) Li et al. 2020 [43]	A total of 524 patients with RRF, 324 women with RM, and 200 women with RIF. Peripheral blood and endometrial samples were collected in the mid-luteal phase.	The excessive presence of endometrial immune cells in patients with CE may be involved in reduced endometrial receptivity and RRF. CD56+ NK cells, CD163+ M2 macrophages, and CD1a+ endometrial dendritic cells were not altered between non-CE and CE patients.
(5) Kanter et al. 2023 [39]	A total of 51 subjects: 20 from natural cycles and 31 from IVF cycles stimulated 7 days after pick.	There was a reduction in the density of endometrial CD56+ uNK cells ($p < 0.05$), as well as in the uNK3 subpopulation ($p = 0.025$) in particular (CD103+ NK cells).	(13) Adib Rad et al. 2018 [47]	Unexplained recurrent cases were assigned to the case group, and 40 fertile women were assigned to the control group.	A cut-off value of $\geq 5.25\%$ ($p < 0.001$) and $\geq 3.4\%$ ($p < 0.015$) for an increase in the % of CD56+ CD16+ and CD56+ CD16- cells is predictive of RSA.
(6) Vomstein et al. 2023 [40]	A total of 46 healthy controls, 28 RPL patients, and 11 uINF. Endometrial biopsies and menstrual blood collected during the first 48 h of menstruation in 7 controls were evaluated.	RPL patients showed higher CD56+ NK cell counts in menstrual blood (mean $\pm$ SD: $31.13 \pm 7.52\%$ vs. $36.73 \pm 5.4\%$, $p = 0.002$). RPL and uINF patients had higher peripheral CD56+ NK cell counts ($11.42 \pm 4.05\%$, $p = 0.021$; $12.86 \pm 4.29\%$, $p = 0.009$ vs. $8.4 \pm 3.5\%$).	(14) Kofod et al. 2017 [48]	Four groups: hydrosalpinx, salpingectomy, unexplained infertility, and a fertile group.	Increased CD56+ uNK cells and elevated HLA-G expression were predictors of positive pregnancy outcomes.

Table 2. Cont.

Article	Sample	Results	Article	Sample	Results
(7) Yu et al. 2023 [41]	A total of 113 fertile and 79 RRF, including 40 RM patients and 39 RIF patients.	The reference ranges (RIs) of endometrial immune cells in infertiles were as follows: CD56+ uNK cells, 1.785–8.712%, Foxp3+ Tregs (forkhead box P3), 0.041–0.154%, CD163+ M2 macrophages, 0.298–1.492%, CD1a+ dendritic cells (DCs), 0.006–0.081%, and CD8+ T cells, 0.674–2.504%. CD56+ uNK cells, CD163+ M2 macrophages, CD1a+ DCs, and endometrial CD8+ T cells were significantly increased in patients with RRF.	(15) Chen et al. 2017 [49]	A total of 215 patients, of whom 97 with recurrent spontaneous abortion, 34 with recurrent failure and 84 fertile women.	The recurrent reproductive failure groups had a significantly higher percentage of uterine NK cells than controls (RM: median 3.2%, range 0.6–8.8%; RIF median 3.1%, range 0.8–8.3%).
(8) Lapedes et al. 2022 [42]	A total of 256 RIF, habitual abortion and idiopathic sterility.	There is a correlation (0.233 with p -value 0.01) between uNK cell number and activation status. Patients with higher uNK cell counts were more frequently diagnosed with endometriosis (p -value 0.05, correlation 0.130).	(16) Elabd et al. 2016 [50]	Two groups of 30 women each, one with previous implantation failure vs. a control group. CD3-CD56+dim and CD3-CD56+dimCD69+ NK cells were analyzed by flow cytometry.	A higher % of CD3-CD56+dim and CD3-CD56+dimCD69+ cells was observed in the study group ($p = 0.0001$ and $p = 0.003$, respectively). The increased % of CD56+dim and CD56+dimCD69+ NK cells may be related to infertility.
Legend: Chronic endometritis, CE; recurrent miscarriage, RM; recurrent implantation failure, RIF; recurrent pregnancy lost, RPL; in vitro fertilization, IVF; unexplained infertility, Uinf; recurrent reproductive failure, RRF; implantation success, IS.					

3.3. Endometrial Sampling Methods

Regarding different diagnostic methods, hysteroscopy is still the gold standard, but the 2025 study by Falahy et al. showed no statistically significant differences between hysteroscopic curettage and the Pipelle probe sampling [71].

An innovative and less invasive diagnostic tool still under investigation is the aspiration of uterine fluid (“endometrial lavage”) as a method to assess the immune status of the endometrium through the search for immune markers. Some preliminary studies suggest that soluble forms of CD138 and NK cell-associated cytokines (e.g., IL-15, IFN- γ) can be quantified in endometrial secretions and may correlate with endometrial tissue findings [72].

These blind techniques would facilitate repeated monitoring of the immune profile over time and in response to potential treatment [30,72].

As shown in Tables 1 and 2, several studies highlight the potential clinical utility of tools such as pipettes in outpatient settings.

3.4. Treatment

The treatment of chronic endometritis is predominantly antibiotic, given the primarily bacterial etiology of the disease. In recent years, several studies have shown that adequate treatment of chronic endometritis is associated with significant improvements in in vitro fertilization outcomes [51,67].

Currently, antibiotic therapy represents the gold standard for the treatment of this condition, often combined with the use of prednisone [73] or, in more experimental settings, supported by immunoglobulin treatment [74].

The study by Cicinelli et al. [51] compared the pregnancy rate and live birth rate between patients undergoing antibiotic treatment with subsequent histological confirmation of disease resolution and patients with persistent endometritis after treatment. The results showed a significantly higher live birth rate in group 1 compared to group 2 (61% vs. 13%, p -value 0.02).

Similarly, Cheng et al. [75], through a systematic review and meta-analysis, evaluated the impact of antibiotic therapy on IVF outcomes. The results showed a statistically significant increase in several outcomes, such as implantation rate, ongoing pregnancy rate, and live birth rate in patients with successfully treated chronic endometritis, compared to both patients with persistent CE and those without an initial diagnosis of chronic endometritis. This benefit was demonstrated exclusively in cases where histological confirmation of endometritis resolution was present.

Similar results were also reported in the meta-analysis by Vitagliano et al. [67], which highlighted a significant increase in clinically confirmed pregnancy and live birth rates in patients with histologically confirmed resolved chronic endometritis compared to patients with persistent endometritis after treatment. Conversely, no statistically significant differences were found between patients who did not receive antibiotic treatment and those who did, but without histological confirmation of treatment success.

Several studies have also investigated the role of corticosteroid therapy, given the importance of immunological factors in embryo implantation processes due to the involvement of uterine NK cells in regulating embryo implantation [76].

The 2022 [77] study by Giulini et al., conducted on patients with repeated implantation failure, evaluated the impact of combined therapy with prednisone (10 mg/day) and doxycycline (100 mg twice daily for 14 days) in patients with endometrial biopsies positive for CD138 plasma cells and CD56 cells vs. corticosteroid therapy alone in cases positive exclusively for CD56. The results showed improved reproductive outcomes, with a live birth rate of 22.2% after treatment. Specifically, treatment with prednisone was more

effective in patients with severe endometritis (CD56 > 10%), with a live birth rate of 29.4%, compared to patients with mild forms of endometritis, where the therapy was less effective (live birth rate of 10%). The 2018 study by Lédée et al. [78], conducted on 55 patients with RIF, showed a reduction in CD56+ cell expression in approximately half of the patients after treatment with prednisone.

Cooper et al. (2019) observed a significant reduction in uterine NK cell concentration following prednisone therapy, but did not demonstrate a statistically significant difference in pregnancy outcomes [79].

More recently, the study by Zou et al. [80] reported a significant increase in key reproductive outcomes, such as implantation rate, clinically confirmed pregnancy rate with heartbeat, and ongoing pregnancy rate, in the group treated with the combination of doxycycline and prednisone compared to the group treated with doxycycline alone. Furthermore, treatment with doxycycline alone also showed a significant improvement in reproductive outcomes compared to no treatment, confirming the role of antibiotic treatment.

An emerging area of interest concerns the intrauterine therapeutic approach.

A 2023 [81] study compared pregnancy outcomes between patients treated with oral antibiotic therapy (doxycycline and metronidazole) combined with intrauterine perfusion with gentamicin and dexamethasone and patients treated with oral therapy alone. Comparing the group receiving oral therapy alone with the cohort receiving the combined treatment, significantly higher rates of clinically proven pregnancy (30% vs. 50%, $p < 0.001$), ongoing pregnancy (33.33% vs. 45.45%, $p < 0.0001$), and live births (33.33% vs. 45.45%, $p < 0.0001$) were reported. A statistically significant decrease in the rate of early spontaneous abortions was also observed (6.667% vs. 4.545%, $p = 0.0068$).

The work by Zhang [82] et al. evaluated the efficacy of intrauterine infusion of a targeted antibiotic against the identified microorganism in combination with dexamethasone 5 mg. Patients in whom treatment resulted in resolution of chronic endometritis showed a significantly higher rate of implantation and clinically confirmed pregnancy, both compared to patients with RIF without evidence of chronic endometritis and those with persistent chronic endometritis [82]. Finally, restorative medicine could have a role. Mesenchymal stem cells introduced into the uterus may actively repair damaged endometrial tissue. Regenerative therapies utilize immunomodulation to calm persistent uterine inflammation and tissue damage. Transplanted stem cells secrete critical growth factors to trigger natural cellular healing processes. These cellular approaches stimulate angiogenesis, forming new blood vessels to improve tissue circulation. For example, cell-free therapies utilize exosomes to deliver regenerative genetic material directly to the tissue, and advanced therapies successfully restore lost endometrial glands crucial for early embryo implantation. By reducing fibrosis and boosting lining thickness, these alternatives could restore fertility after chronic infection [83].

4. Discussion

Chronic endometritis is a persistent inflammation of the endometrial stroma. Unlike the acute form, it is often oligosymptomatic or completely asymptomatic, manifesting clinically only through infertility. The role of CE has been linked to miscarriages and recurrent implantation failures. The local balance required for pregnancy establishment is very delicate, and many factors may intervene, albeit in ways that are still unknown. For this reason, the ESHRE guidelines also highlight the evaluation of the endometrium as a potential resource for the diagnosis of CE. Since there are no definitive data, this step is among the suggested ones, which is why it is necessary to increase scientific research in this direction [84].

Standard histological diagnosis is based on the identification via biopsy of inflammatory infiltrates. Plasma cells should not be abundant in a normal endometrium. The CD138 marker is the surface antigen of choice, identified using techniques such as immunohistochemistry [24]. This dramatically increases diagnostic sensitivity compared to simple hematoxylin–eosin staining, where plasma cells can be confused with stromal fibroblasts. There is still no universal consensus, but the presence of ≥ 5 plasma cells per high-power field (HPF) is commonly used to define positivity (Table 1).

Uterine NK cells are different from peripheral ones. Although they are not direct markers of infection, their count can be crucial. Excessive activation or density of CD56+ cells is often associated with a pro-inflammatory state resulting from endometritis, contributing, for example, to trophoblast rejection.

Hysteroscopy is the visual “gold standard,” but biopsy remains essential for confirmation to study these cell populations.

In addition to direct under vision biopsy, other techniques are available, such as Fluid Biopsy (Uterine Liquid Biopsy) with the analysis of endometrial fluid to detect bacterial DNA or inflammatory cytokines and blind sampling techniques, such as Pipelle, Perma, and Novak [5].

The future of diagnosis is shifting from cellular observation to molecular biology. While CD138+ plasma cell evaluation remains the operational standard, it suffers from high inter-observer variability and epithelial false positives. As CE heavily impacts reproductive success, integrating emerging molecular and microbial approaches could be clinically vital. Other new markers are being studied for their potential diagnostic reliability [30,57], e.g., MUM1 [29], cytokine profile in uterine fluid (IL-6, IL-1 β and TNF- α), and transcriptomic indicators. Molecular techniques, like Real-Time PCR and Next-Generation Sequencing (NGS), provide objective and quantifiable data. Alternative cellular markers like MUM1/IRF4 reduce diagnostic ambiguity by offering cleaner staining with lower background noise [29]. Concurrently, 16S rRNA gene sequencing has redefined CE from a simple infection into a complex microbiome dysbiosis. Mapping the uterine cavity into Lactobacillus-dominated or non-dominated environments allows for personalized, targeted therapies. Techniques are becoming increasingly precise, such as microbiome analysis (Real-Time PCR, NGS), e.g., tests such as ALICE (Analysis of Infectious Chronic Endometritis), allowing the identification of specific pathogens responsible for inflammation, overcoming the limitations of traditional procedures (many endometrial bacteria are difficult to grow in vitro) [85].

Furthermore, evaluating advanced immune biomarkers highlights the true inflammatory burden harming endometrial receptivity. Measuring uterine Natural Killer (uNK) cell density and pro-inflammatory cytokines (IL-6, IL-1 β) maps local immune disruption.

Together, these multi-omic approaches transform CE from a poorly defined finding into a highly characterized condition. Expanding the narrative to include these diagnostic vectors could be essential to optimize treatments and improve reproductive outcomes.

Due to their practicality and ease of use, the outpatient use of other devices (e.g., Pipelles, Perma, etc.) could be beneficial [71]. Despite the lack of visual support, this could streamline waiting lists for hysteroscopic procedures and provide a rapid clinical approach in targeted cases.

The strength of this study is its updated summary of the topic, identifying the most relevant recent literature. This work also attempted to highlight the quantitative aspects of diagnostics in the two most well-known populations in CE and, for the first time, underscored the value of blind endometrial sampling techniques for clinical speed and patient comfort. Limitations include that studies generally involve heterogeneous, limited sample sizes of patients undergoing search for offspring, with different reproductive outcomes.

5. Conclusions

The evolution of various sampling techniques could significantly impact future reproductive outcomes. The diagnosis of chronic endometritis may provide a response to the many implantation failures that still exist in assisted reproduction. It is necessary to further investigate the possibility of increasingly personalized management of the couple seeking pregnancy [29], as well as with some drugs in the context of other infertility disorders [86], with:

- Faster and more painless sampling techniques- even during the gynecological examination (e.g., Perma, Pipelles) [71,87].
- Targeted Antibiotic Therapy—moving from empiric protocols (often based on doxycycline) to therapies guided by molecular PCR results to combat antibiotic resistance.
- Immunomodulation—in addition to antibiotics, the use of vaginal/uterine probiotics to restore a *Lactobacillus*-dominant microbiome and the use of specific anti-inflammatories [88].
- AI in Hysteroscopy—the development of artificial intelligence algorithms capable of recognizing CE patterns during endoscopic examinations in real time, eliminating operator subjectivity.

In conclusion, the diagnosis of chronic endometritis and its treatment in case of a positive result require further scientific studies and investigations to determine the most valid and appropriate strategy for each specific case.

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