RBMO

REVIEW

Impact of chronic endometritis in infertility: a SWOT analysis

BIOGRAPHY

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KEY MESSAGE

Pending new evidence, it would be advisable not to include chronic endometritis in the initial baseline study before assisted reproduction in order not to delay other assisted reproduction treatments.

ABSTRACT

Chronic endometritis is a pathology often associated with reproductive failure, but there are still no clear recommendations on whether its inclusion in the initial study of infertile couples is necessary. In this discussion paper, based on a SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis, the different aspects of the repercussions of chronic endometritis in fertility are evaluated. To avoid possible subjectivity in the analysis and results of this study, the researchers followed the Oxford criteria for the evaluation of evidence. The results from the evaluation of the reviewed literature seem to indicate that, pending new evidence, it would be advisable not to include chronic endometritis in the initial baseline study before assisted reproduction in order not to delay other assisted reproduction treatments. However, it would be advisable in cases of repetitive implantation failure and pregnancy loss after having undergone IVF with viable embryos and before continuing with costly reproductive processes, since results could be improved. The development of randomized studies assessing the impact of antibiotic treatment as a possible therapeutic option in infertile women with chronic endometritis, as well as the possible impact on endometrial microbiota and receptivity/implantation, would allow for the establishment of more precise clinical guidelines in this regard.

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KEYWORDS

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INTRODUCTION

In recent years, there has been a substantial increase in publications focused on chronic endometritis and infertility (71 between 2010 and 2015, and 140 between 2015 and 2020) (*PubMed, 2020*). This increase is related to the appearance of data suggesting a possible involvement of chronic endometritis in reproductive results, indicating an increase in its prevalence in women with unexplained infertility (*Cicinelli et al., 2018*; *Liu et al., 2018*) and in patients who have suffered recurrent miscarriage (*Kitaya, 2011*; McQueen et al., 2005; *Zolghadri et al., 2011*) or repeated implantation failure (RIF) (*Bouet et al., 2016*; *Cicinelli et al., 2005*; *Johnston-MacAnanny et al., 2010*; *Song et al., 2018*; *Tersoglio et al., 2015*; *Yang et al., 2014*).

Chronic endometritis is defined as localized inflammation of the endometrial mucosa characterized by the presence of oedema, increased stromal cell density, dissociated maturation of the stroma and epithelium, as well as the presence of a plasma cell infiltrate in the stroma (*Bayer-Garner and Korourian, 2001*; *Greenwood et al., 1981*; *Kasius et al., 2011*; *Kitaya et al., 2011*; *Smith et al., 2010*). A pathophysiological model for chronic endometritis (*Liu et al., 2018*) has been proposed in which a possible microbial infection of the endometrial cavity or dysbiosis would induce aberrant expression of pro-inflammatory molecules, triggering unusual immune responses in the human endometrium. Such immune responses provide an abnormal microenvironment for the recruitment of circulating B cells into the endometrial stromal compartment and the gravitation of these lymphocytes to glandular areas. Furthermore, a fraction of the accumulated endometrial B cells can differentiate into endometrial stromal plasma cells (ESPC) *in situ*. This event translates into an increase in the presence of antibodies in the mucosa (*Kitaya et al., 2014*), which has a potentially negative impact on the embryo implantation process (*Kitaya et al., 2011*; *Kushnir et al., 2016*).

Previously, clinical concern regarding chronic endometritis was non-existent as women with chronic endometritis were often asymptomatic, and in cases where clinical symptoms were present, they were not specific to this pathology (*Romero et al., 2004*). This attitude has led to a lack of importance being given to chronic endometritis in the field of gynaecology. However, reproductive medicine has begun to consider that its diagnosis could be essential as it has been closely related to unexplained infertility (*Cicinelli et al., 2018*; *Liu et al., 2018*), repeated miscarriages (*Kitaya, 2011*; McQueen et al., 2005; *Zolghadri et al., 2011*) or RIF (*Bouet et al., 2016*; *Cicinelli et al., 2005*; Johnston-MacAnanny et al., 2011; *Song et al., 2018*; *Tersoglio et al., 2015*; *Yang et al., 2014*).

The diagnosis of chronic endometritis is based on hysteroscopy of the uterine cavity and endometrial biopsy, with plasma cells being identified histologically, while specific treatment is determined based on microbial culture. Commonly described hysteroscopic features suggestive of chronic endometritis include focal or diffuse endometrial hyperaemia, micropolyps (<1 mm) and mucosal oedema (*Cicinelli et al., 2005*); however, the diagnostic accuracy of hysteroscopy is modest.

The detection of abnormal plasma cell infiltration in the endometrial stroma is the most commonly used diagnostic parameter to define this pathology (*Akopians et al., 2015*; *Greenwood et al., 1981*; *Kitaya et al., 2015*; Michels et al., 2005). Using conventional haematoxylin and eosin staining, it is difficult to distinguish the plasma cells from the monocytes and fibroblasts of the endometrial stroma, and the success rate of accurate diagnosis is not very high (*Greenwood et al., 1981*; *Kitaya, 2011*). However, immunochemical detection of transmembrane heparan sulphate proteoglycan syndecan-1 (CD138), which is a specific marker of plasma cells, has been shown to increase the success rate of accurate diagnosis (*Cicinelli et al., 2018*). Microbiological cultures are used to identify the possible pathogens involved and to direct administration of the most appropriate antibiotic treatment. More recently, the addition of molecular technology techniques in clinical practice, such as next-generation sequencing (NGS) of 16S ribosomal subunits and/or focused real-time polymerase chain reaction (RT-PCR) (*Franasiak et al., 2016*; *Moreno et al., 2016*, *2018*), have unlocked a pathway of knowledge to the possible relationship between an infectious pathology and its involvement in chronic endometritis.

Some publications suggest that treatment with oral antibiotics could improve reproductive results (*Cicinelli et al., 2015*; *Kitaya et al., 2017*; *McQueen et al., 2014*; *Song et al., 2018*). Although there is increasing interest in this field due to the significant impact it could have, no randomized studies that analyse the possible benefit of treatment for chronic endometritis in this population have yet been published (*Kitaya et al., 2018*). For this reason, the current authors planned to carry out a SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis to evaluate the evidence published to date on the possible involvement of chronic endometritis and its treatment in infertility. To avoid possible subjectivity in the results, the evidence was evaluated according to the Oxford criteria (TABLE 1).

METHODS

In this study, a SWOT analysis was carried out to discern the perceived strengths and weaknesses of the diagnosis and treatment of chronic endometritis in infertile patients, to identify the possible opportunities available and the key threats of this strategy according to the reviewed bibliography, and to discern the experts' point of view. The SWOT method has only recently been applied in fertility medical research to assess the possible applicability of a particular clinical approach or technique when scientific evidence is insufficient, to highlight specific issues and to weigh the possible pros and cons (*Bellver et al., 2019*; *Blockeel et al., 2016*; *Bosch et al., 2020*; *Checa et al., 2018*; *Engmann et al., 2016*; *Esteves et al., 2017*; *Streuli et al., 2018*).

Initially, a bibliographic search aimed at "Chronic endometritis AND infertility" was undertaken. Two independent investigators carried out the bibliographic assessment and a third investigator was consulted if there was lack of agreement. A second manual bibliographic search was then carried out to complete those matters of relevance important issues included by the researchers in the clinical outline of the SWOT analysis that had not been resolved in the first general search. The total number of references was divided among the researchers and an Excel spreadsheet was created for each of the sections of the SWOT analysis, which was available on the SISGtool.org (Ediciones Mayo S. A, Spain) platform along with the corresponding references. In each of the tables, the

TABLE 1 OXFORD CENTRE FOR EVIDENCE-BASED MEDICINE LEVELS OF EVIDENCE, MARCH 2009

Levels of evidence	Type of study
1a	Systematic reviews (with homogeneity) of randomized controlled trials
1b	Individual randomized controlled trials (with narrow confidence interval)
1c	All or none randomized controlled trials
2a	Systematic reviews (with homogeneity) of cohort studies
2b	Individual cohort study or low-quality randomized controlled trials (e.g. <80% follow-up)
2c	'Outcomes' research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

Note: A minus sign "–" may be added to denote evidence that fails to provide a conclusive answer because it is either (a) a single result with a wide confidence interval; or (b) a systematic review with troublesome heterogeneity.

Available at: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/]

ideas/phrases identified for each section were noted, and each researcher added to each of them the studies classified by the degree of evidence. The quality of the selected articles was assessed using the Oxford Centre for Evidence-Based Medicine levels of evidence, which rank the validity of evidence in a hierarchy of levels, with systematic reviews as level 1 (strong evidence) and expert opinions as level 5 (weak evidence) (Oxford CEBM, 2009) (TABLE 1).

RESULTS

The initial literature review revealed 211 articles and classified 93 as relevant. A second manual bibliographic search was then carried out to complete those relevant issues that were included in the SWOT clinical scheme but not resolved in the first general search.

Strengths

A high prevalence described in infertility

Some authors estimate that up to 56.8% of women with infertility (*Cicinelli et al., 2015*) present a diagnosis of chronic endometritis, the prevalence in these women being twice as high as that observed in fertile women (*Liu et al., 2018*; evidence level 2b) and higher than that described in the general population (*Puente et al., 2020*).

This prevalence is even higher in women with RIF, with estimates of up to 67.5% (*Kitaya et al., 2018*), and in women with recurrent miscarriage, where it has been described in up to 67.6% (*Zolghadri et al., 2011*).

It has also been noted that, in women with endometrial polyps, the prevalence of chronic endometritis increases significantly in those with an unexplained history of infertility compared with those with no prior history of infertility (22.6% versus 8.6%, $P = 0.001$) (*Volodarsky-Perel et al., 2019*; evidence level 2b) and that women of reproductive age with chronic endometritis have a 60% higher risk of future infertility than those without chronic endometritis (*Wiesenfeld et al., 2012*; evidence level 2b).

Plausibility of a pathophysiological link

A pathophysiological model for chronic endometritis has been proposed in which a microbial infection of the endometrial cavity could induce aberrant expression of chemokines and adhesion molecules (CD62E, CXCL1 and CXCL13) in epithelial, stromal and vascular endothelial cells of the endometrium; this would then lead to the migration of a large number of B cells to the endometrial epithelium and the glandular lumen, and to the extravasation of B cells into the stroma (*Kitaya et al., 2010*; *Resta et al., 2012*; *Tabibzadeh et al., 1986*). The former would lead to a delay in endometrial receptivity, and the latter cells would differentiate into plasma cells, decreasing the expression of genes associated with endometrial receptivity (evidence level 5).

In-vitro studies demonstrate that bacterial lipopolysaccharides can induce the expression of E-selectin, which promotes the expression of CXCL13, activates B-cell adhesion molecules and increases the expression of CXCL1 in the glandular endometrium (*Franasiak et al., 2016*). This results in an abnormal immune response with migration of circulating B lymphocytes towards the stroma (*Franasiak et al., 2016*); the stromal plasma cells express many immunoglobulins (IgA1, IgA2, IgM, IgG1, IgG2) at the endometrial level, and the excess of these antibodies could adversely affect implantation (*Kushnir et al., 2016*).

Di Pietro and colleagues used RT-PCR to analyse the expression of genes involved in the inflammation, proliferation and apoptosis processes in the endometrium during the implantation period in women with and without chronic endometritis, and found a specific profile of gene aberration in those with chronic endometritis. In particular, *IGFBP1*, *BCL2*, and *BAX* were up-regulated, while *IGF1*, *IL11*, *CCL4* and *CASP8* were down-regulated (*Di Pietro et al., 2013*). This has been associated with unfavourable conditions for embryonic implantation and development (*Kitaya et al., 2014*; *Vaskivuo et al. 2002*; *Vatansever et al., 2005*; *Wu et al., 2017*), and explains the histological changes frequently present in these women, such as the presence of polyps.

An increase in the expression of oestrogen and progesterone receptors as well as in Ki-67 markers for cell proliferation in both epithelial and stromal cells has also been reported. This increase, together with the expression of antiapoptotic genes such as *BCL2* and *BAX*, indicates a change in the proliferative phenotype of the endometrium (*Kitaya et al., 2015*) and a modification of the decidualization of endometrial cells of the human stroma through a disruption of the functions of sex steroid hormone receptors with increased expressions of *ERα* (also known as *ESR1*), *ERβ* (also known as *ESR2*), *PRA* and *PRB* (*Di Pietro et al., 2013*; *Wu et al., 2017*: evidence level 3b). These

TABLE 2 EFFECT OF ANTIBIOTIC THERAPY ON CHRONIC ENDOMETRITIS CURE RATES AND REPRODUCTIVE OUTCOMES IN THE PUBLISHED STUDIES

Study	Study design	Number	Antibiotic treatment	Cure rate of CE	Reproductive outcomes
Cicinelli et al. (2015)	Retrospective cohort study (evidence level 2b)	*n* = 106 CE and RIF	T1. Doxycycline (200 mg/day for 14 days) T2. Ciprofloxacin and metronidazole (500 mg of each for 14 days)	OCR 75%	Significantly higher PR and LBR in patients cured compared with women with persistent CE (PR 65.2% versus 33.0%, *P* = 0.039; LBR 60.8% versus 13.3%, *P* = 0.02, respectively)
Kitaya et al. (2017)	Observational cohort study using prospectively collected data (evidence level 2b)	*n* = 438 RIF *n* = 142 RIF/CE *n* = 279 RIF/non-CE	T1. Doxycycline (200 mg/day for 14 days) T2. Ciprofloxacin and metronidazole (500 mg of each for 14 days)	OCR 99.1% (92.3% with T1 and 99.1% with T2)	LBR in the first ET cycle (*P* = 0.031, RR 1.48, 95% CI 1.03–0.12) and three cumulative ET cycles (*P* = 0037, RR 1.39, 95% CI 1.02–1.90) following antibiotic treatment in the cured RIF/CE group (32.8% and 38.8%, respectively) was significantly higher than in the RIF/non-CE group (22.1% and 27.9%, respectively)
Johnston-MacAnanny et al. (2010)	Retrospective chart review (evidence level 3b)	*n* = 33 RIF *n* = 10 RIF/CE *n* = 23 RIF/non-CE	T1. Doxycycline (200 mg/day for 14 days) T2. Ciprofloxacin and metronidazole (500 mg of each for 14 days)	OCR 99.1% (92.3% with T1 and 88.9% with T2)	The CE/RIF group had lower implantation rates (11.5%) in the IVF cycle following treatment (resolution not confirmed) than the non-CE/RIF and RIF/undetermined CE (32.7% and 20.3%) groups CPR (20.0%, 52.1% and 40.6%, *P* = NS) and OPR (10.0%, 52.1% and 34.4%, *P* = NS) were similar among all groups
Tersoglio et al. (2015)	Prospective study of a model-based control with analogue abductive methodology (evidence level 2b)	75 patients with RIF in ovodonation and 12 controls	Doxycycline 200 mg/day for 14 days, continuing in association with metronidazole 1 g/day and ciprofloxacin 1 g/day for 14 days If no remission of the inflammatory process is achieved, the above scheme is repeated, in association with linezolid 600 mg/day orally for 10 days + All the patients received corticosteroid therapy in doses meprednisone orally 4 to 8 daily mg; Glycine 100 mg/day associated with Vit. E 300mg, Vit. B6 100mg and Vit. A 10.000 UI/day orally	9/14 OCR 64%	Implantation rate 75.7% versus 36.6%, *P* = 0.05 OR 6.75 (0.64–61.1) (NS) for LBR when the endometrium was normalized after treatment compared with persistent CE
Vitagliano et al. (2018)	Meta-analysis of five observational studies (evidence level 2a)	*n* = 796 Infertile women RIF undergoing one or more IVF cycle(s)	Different antibiotic regimen	OCR (n.a.)	Patients with cured CE showed higher OPR/LBR (OR 6.81), CPR (OR 4.02), and IR (OR 3.24) in comparison with patients with persistent CE IVF outcomes were comparable between women with and without CE (OPR/LBR, CPR and IR) Miscarriage rate was not significantly different between groups
Cicinelli et al. (2018)	Retrospective study (evidence level 2b)	95 patients with unexplained infertility	Antibiotic regimen (n.a.)	OCR 82.3%	Significantly higher PR and LBR in patients cured of CE compared with women with persistent CE and women without a CE diagnosis (PR 76.3% versus 20% versus 9.5%, *P* < 0.0001; LBR 65.8% versus 6.6% versus 4.8%, *P* < 0.0001)
McQueen et al. (2014)	Observational cohort study using prospectively collected data (evidence level 3b)	395 women with CE and with a history of two or more pregnancy losses *n* = 35 CE/RPL	T1. Ofloxacin (800 mg) and metronidazole (100 mg) for 2 weeks T2. Doxycycline alone, doxycycline and metronidazole, or ciprofloxacin and metronidazole	OCR 100% (94% with T1 and 100% with T2)	LBR 88% (21/24) for the treated CE group versus 74% (180/244) for the group without CE Per-pregnancy LBR for the treated CE group 7% (7/98) before treatment versus 56% (28/50) after treatment

CE, chronic endometritis; CI, confidence interval; CPR, clinical pregnancy rate; ET, embryo transfer; IR, implantation rate; LBR, live birth rate; n.a., not available; NS, not significant; OCR: overall cure rate; OPR, ongoing pregnancy rate; OR, odds ratio; PR, Pregnancy rate; RIF, repeated implantation failure; RPL, recurrent pregnancy loss; RR, relative risk; T1, T2, T3, first, second and third courses of antibiotic therapy.

findings support the idea that, in chronic endometritis, the endometrium would not typically or correctly respond to the action of hormones that favour the endometrial changes characteristic of a receptive endometrium (*Burney et al., 2007*).

Moreover, alterations in uterine contractility in both the mid-luteal and peri-ovulatory phases affect fertility, may cause symptoms and are more frequent in chronic endometritis (*Pinto et al., 2015*), with a reduction in the retrograde contractility of the Fallopian tubes (*Coughlan et al., 2014*). This alteration of peristalsis induced by the presence of chronic endometritis could, at least in part, affect fertility and favour the appearance of symptoms such as dysmenorrhoea and pelvic pain.

Simplicity of diagnostic techniques

The diagnostic techniques for chronic endometritis that are included in routine practice are of low complexity. Sampling of the endometrium is usually performed using an endometrial suction biopsy device, which is inserted through the cervix to obtain a small piece of endometrial tissue. This is generally a simple, well-tolerated and easy to perform procedure (*Du et al., 2016*; *Utida et al., 2019*) that is carried out in the doctor's office on an outpatient basis. All the diagnostic techniques used (hysteroscopy, culture, anatomical study, NGS), including immunohistochemical techniques, continue to be simple compared with the complexity of assisted reproduction techniques.

Treatable pathology

In the clinical treatment of chronic endometritis, broad-spectrum antibiotics are established as standard treatment, since a culture is not standard procedure to identify the micro-organisms involved. Several studies have analysed the effects of antibiotic therapy on chronic endometritis, pointing to a definite improvement in results after treatment, with high resolution rates (TABLE 2) (*Cicinelli et al., 2015*; *Johnston-MacAnanny et al., 2010*; *Kitaya et al., 2017*, *2018*; *McQueen et al., 2014*; *Tersoglio et al., 2015*; *Vitagliano et al., 2018*), with the possibility of including adjuvant therapies such as anti-inflammatory medications or probiotics that would act on the inflammatory process itself or regulate the endometrial microbiome.

Improvement of reproductive results with treatment in a population with a poor prognosis (implantation failure, recurrent miscarriage)

As seen from a pathophysiological point of view, chronic endometritis can affect the implantation process, and recovery through the use of antibiotics seems to improve pregnancy rates in women with chronic endometritis and RIF (evidence level 2a) (*Cicinelli et al., 2015*; *Kitaya et al., 2017*; *Tersoglio et al., 2015*; *Vitagliano et al., 2018*), unexplained infertility (*Cicinelli et al. 2018*: evidence level 2b) or recurrent miscarriage (*McQueen et al., 2014*: evidence level 3b). Furthermore, patients with chronic endometritis resolved by antibiotic treatment and prior RIF seem to show better live birth rates and pregnancy and implantation rates than those with recurring chronic endometritis (*Vitagliano et al., 2018*: evidence level 2a); in addition, the results of IVF are comparable to those of women without chronic endometritis (*Vitagliano et al., 2018*: evidence level 2a). In women with RIF, polyvalent treatment of the inflamed endometrium can reverse histological damage, and this normalization leads to a doubling of the implantation rate and the live birth rate in oocyte donation programmes (*Tersoglio et al., 2015*: evidence level 2b). Also, in cases of recurrent miscarriage, an improvement has been noted in the rates of live birth (7% before versus 56% after treatment) and the cumulative rate of live births (*McQueen et al., 2014*: evidence level 3b) (TABLE 2).

Weaknesses

Scarce knowledge of the aetiology

In the general population, the aetiology of chronic endometritis has been related to the presence of foreign bodies or structural pathology of the endometrial cavity, such as the presence of an intrauterine device, retained products of conception, submucous myomas, polyps, incomplete abortion or infectious agents. In sterile patients, the current leading established cause of chronic endometritis is a microbial infection in the uterine cavity. This is supported by the fact that some antibiotic therapies are effective in eliminating ESPC in affected patients (*Cicinelli et al., 2015*, *2018*; *Kitaya et al., 2017*; *McQueen et al., 2014*; *Tersoglio et al., 2015*; *Vitagliano et al., 2018*), but there is still no evident causal agent involved. With the diagnostic techniques used (culture, PCR, NGS) an infectious agent is not always identified, so other causes could also be implicated.

The micro-organisms frequently detected in the endometrium with chronic endometritis are common bacteria (*Streptococcus* species, *Escherichia coli*, *Enterococcus faecalis* and *Staphylococcus* species), *Mycoplasma/Ureaplasma* species (*Mycoplasma genitalium*, *Mycoplasma hominis* and *Ureaplasma urealyticum*), *Proteus* species, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Gardnerella vaginalis*, *Corynebacterium* species and fungi (*Saccharomyces cerevisiae* and *Candida* species) (Cicinelli et al., 2008, *2009*; *Kitaya et al., 2017*). In contrast, several studies indicate a very low detection rate of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (Cicinelli et al., 2008; *Haggerty et al., 2004*; *Polisseni et al., 2003*), and antibiotic treatment aimed at their eradication does not allow for the preservation of future fertility in women with chronic endometritis (*Wiesenfeld et al., 2012*). It has also been noted that an altered proportion of the anaerobic species of lactobacilli, the predominant bacterium in the female reproductive system (*Moreno et al., 2016*), could generate dysbiosis and contribute to the appearance of chronic endometritis. However, the results are contradictory between the different studies (*Kitaya et al., 2017*).

Human immunodeficiency virus (*Johnstone et al., 1994*; *Pitsos et al., 2009*) and cytomegalovirus (*Frank et al., 1992*) have also been implicated in chronic endometritis, but the association between these viral infections and chronic endometritis remains uncertain. It is essential to highlight that the micro-organisms detected in endometrial tissue are often inconsistent with those detected in endocervical tissue or vaginal discharge (Cicinelli et al., 2008, *2009*), suggesting that microbial examinations of samples from the lower genital tract cannot predict the presence of pathogens causing chronic endometritis (evidence level 3b). Also, endometrial tissue culture and conventional PCR have failed to identify micro-organisms in more than half of infertile women with chronic endometritis (*Kitaya et al., 2017*), and similar pathogen detection rates have been reported in women with and without chronic endometritis (*Moreno et al., 2016*). These findings indicate an inconsistency in the detection of chronic endometritis-causing micro-organisms within the uterine cavity, as well as the limitations of traditional microbial examinations in the diagnosis of chronic endometritis. As a consequence, some authors consider that the primary pathophysiological basis of chronic endometritis would be the interaction between micro-organisms and endometrial immunity, and would not be limited solely to the presence of micro-organisms in the endometrium (*Eckert et al., 2003*; *Puente et al., 2020*).

Apparently asymptomatic pathology and a lack of analytical markers

The clinical manifestations of chronic endometritis, such as dyspareunia, pelvic pain, vaginal discharge and abnormal vaginal bleeding, are not specific to

this pathology. Moreover, around 25% of women with chronic endometritis are asymptomatic (Song et al., 2018; Zolghadri et al., 2011). Despite being an inflammatory disease, the presence of peripheral blood inflammatory markers, such as C-reactive protein, leptin, interleukin-6 and leukocytosis, cannot predict the presence of chronic endometritis (Cicinelli et al., 2005; Liu et al., 2018).

Inconsistent definition and discrepancy of diagnostic criteria

Chronic endometritis has been defined as an unremitting and subtle inflammatory disease characterized by the infiltration of plasma cells into the endometrial stroma area (ESPC) (Crum et al., 1983). Although ESPC are considered the hallmark for the diagnosis of chronic endometritis, studies have not shown that they are specific to this pathology since they are also present in hormone-mediated endometrial disorders in association with changes in gland structure (disordered proliferative and anovulatory patterns) and stromal rupture processes (Gilmore et al., 2007: evidence level 3b).

Furthermore, no internationally accepted diagnostic criteria have to date been established for chronic endometritis, and the diagnostic criteria proposed in the studies are chosen quite arbitrarily. At least seven different diagnostic criteria have been described in the literature regarding plasma cell density (plasma cell count in limited areas) (Liu et al., 2018). To make progress in the definition and identification of chronic endometritis, a consensus on the quantification method and diagnostic criteria is essential.

A lack of standardization in diagnostic techniques

Although immunohistochemical staining for CD138 has been found to improve the sensitivity and accuracy of identifying the plasma cells, the technique is not, however, standardized (Liu et al., 2018). The diagnosis seems to vary depending on the laboratory tests and the quality control used (Torlakivic et al., 2015), the dilution (Kasius et al., 2011; Torlakivic et al., 2015), the incubation time, the temperature, the thickness of endometrial sections, the number and area of sections examined (Adegboyega et al., 2010; Bayer-Garner et al., 2004; Eckert et al., 2002) as well as the menstrual cycle phase in which the biopsy is performed (Punnonen et al., 1989).

With respect to the histological diagnosis, the suggestion to include both conventional pathological study and CD138 inmunohistochemical examination is crucial, since there is still a lack of consensus on a universal definition of chronic endometritis. Most authors believe that the plasma cells are necessary for a diagnosis of chronic endometritis, but the presence of chronic endometritis promotes different stromal and glandular findings, including superficial stromal oedema, increased stromal density, spindled stroma and polymorphic inflammatory cells, generally related to plasma cells as detailed by Greenwood and Moran in 1981 (Greenwood and Moran, 1981). Precise techniques used to single out plasma cells (CD138) may overestimate the incidence of chronic endometritis if the presence of these cells is used as the only basis for a diagnosis of chronic endometritis. Apart from standardization of the number of plasma cells per unit area, other major issues include the timing and method of endometrial sampling. In the secretory phase, 15% of the samples taken show plasma cells only in the basal layer of the stroma, which can go unnoticed if this is not included in the biopsy. Many other studies have shown a greater prevalence of chronic endometritis in the proliferative phase than in the secretory phase. The day within the menstrual cycle and the volume of the endometrial biopsy specimens should be taken into account by examiners for better diagnosis of chronic endometritis (Eckert et al., 2002; Kitaya et al., 2018; Song et al., 2018)

As mentioned above, there is still a significant lack of randomized studies evaluating the reproductive impact of antibiotic treatment. Most of the studies are retrospective or prospective observational studies, although it is noteworthy that some studies that have analysed treatment for chronic endometritis have not included a test of cure in their protocol (Yang et al., 2014) and the latter should be encouraged for a better evaluation of their clinical results.

Significant differences in chronic endometritis frequency

The lack of a consensus in the definition and the absence of criteria and standardized diagnostic methods could explain the high inconsistency in the prevalence of chronic endometritis (2.8–56.8% in infertile women, 14–67.5% in women with RIF and 9.3–67.6% in women with recurrent miscarriage) reported in the literature, both in studies that used the same diagnostic method and in those that used different diagnostic methods (Cicinelli et al., 2015; Liu et al., 2018; Zolghadri et al. 2011: evidence level 3b).

Discrepancies in detection results depending on the diagnostic method used

Discrepancies have been found between plasma cell detection results using conventional staining methods and immunohistochemical results with CD138 staining in the same endometrial samples. Of the cases initially diagnosed with classical staining, 25% did not detect $CD138^+$ cells, while CD138 immunostaining identified plasma cells in 35% of the cases initially diagnosed as normal endometrial tissue (Vicetti et al., 2011: evidence level 2b).

Other techniques used, such as hysteroscopy, show contradictory results in 58.46% of cases diagnosed by histology, observing that, in all inconsistent cases, histopathological evaluation usually underdiagnoses chronic endometritis while hysteroscopy overdiagnoses (Moreno et al., 2018: evidence level 2b).

The sole use of diagnostic techniques for chronic endometritis (histology, hysteroscopy, and microbial culture) has shown poor diagnostic accuracy (46.15%, 58.46% and 66.15%, respectively) (Moreno et al., 2018). Although it has been speculated that the concomitant use of all three techniques could have a significant impact on diagnostic precision, consistent results only appear in 20% of cases (Moreno et al., 2018) and would considerably increase the complexity and cost of diagnosis.

At present, the inclusion of both CD138 immunohistochemical studies and conventional pathology studies are recommended to increase diagnostic precision (Bayer-Garner et al., 2004; Song et al., 2019: evidence level 3b), as interobserver correlation improves when both techniques are used (Kasius et al., 2012: evidence level 3b). RT-PCR could also be useful for detecting intrauterine pathogens when histology is negative,

as well as for deciding on target therapy when histology is positive (*Moreno et al., 2018*).

An invasive and time-consuming method

In the diagnosis of chronic endometritis, the detection method (hysteroscopy and visualization, endometrial study), sample collection approach (hysteroscopy with guided biopsy, blind biopsy) and sample analysis process (histological study of plasma cells using conventional staining or CD138 immunohistochemistry, culture) must first be differentiated. On many occasions, the need for invasive endometrial biopsy and tedious histopathological examinations makes clinicians reconsider the need to carry out an evaluation for chronic endometritis as, clinically, it is considered a benign and frequently asymptomatic pathology. Furthermore, endometrial biopsy (hysteroscopy with guidance or blind) is an invasive method that presents risks for patients such as bleeding for several days, cramping, uterine perforation, pain, pelvic infection and bacteraemia (*Will et al., 2020*).

Operator-dependent diagnostic method

Among the diagnostic techniques used for detecting chronic endometritis, histology and hysteroscopy are two highly subjective, non-specific techniques that depend on the pathologist's and endoscopic surgeon's individual observations (*Kitaya et al., 2015*). The results are determined mainly by the clinician's experience in analysing the sample, and results are less consistent when different operators analyse the same sample (*Smith et al., 2010*: evidence level 2b).

Sample contamination

Characterization of the uterine microbiome is particularly tricky, mainly due to the low bacterial abundance in the human uterus and the possible contamination occurring during trans-vaginal sampling. Even working under strict sterile conditions, contaminants are still evident, and possible sources of contamination described in the literature include solutions, reagents, instrumentation and the molecular biology kits used in the analysis (*Baker et al., 2018*; *Benner et al., 2018*; *Peric et al., 2019*; *Winters et al., 2019*). Furthermore, must be remembered that the incidence of contaminants becomes even more relevant when the analysis is carried out with high-sensitivity techniques such as NGS (*Laurence et al., 2014*).

Bypassing hysteroscopy does not worsen reproductive outcomes (inSIGHT, TROPHY studies)

The results of the inSIGHT (Hysteroscopy Before In-Vitro Fertilisation) study showed that the routine implementation of hysteroscopy did not improve birth rates in infertile women with a normal transvaginal ultrasound scan of the uterine cavity who were scheduled for a first IVF treatment, and concluded that hysteroscopy should not be routinely offered to women with normal transvaginal ultrasonography results (*Smit et al., 2016*: evidence level 1b). The TROPHY (Hysteroscopy in Recurrent In-Vitro Fertilisation Failure) study confirmed that outpatient hysteroscopy before IVF in women with a normal ultrasound of the uterine cavity and a history of unsuccessful IVF treatment cycles did not improve the rate of live births (*El-Toukhy et al., 2016*: evidence level 1b); therefore in these cases, hysteroscopy, if performed, should be accompanied by an endometrial sample.

A lack of consensus on treatment regimens

To date, from observing the different antibiotic regimens, there is no agreed-upon treatment for chronic endometritis (TABLE 2). In clinical practice, the micro-organism causing the infection is frequently not identified, so broad-spectrum antibiotics are usually prescribed, which can lead to a high rate of recurrent infections after treatment, as well as side effects derived from the clearance of endogenous off–target microbiota in the uterine cavity and other body sites (*Bradshaw et al., 2006*). If identification of micro-organisms were carried out, antibiotic guidelines could be adapted to the pathogen found and to any possible allergy the patient might have to the antibiotics used (*Cicinelli et al., 2015*, *2018*). In patients with negative endometrial microbial examinations, some authors propose a treatment based on the Centers for Disease Control (CDC) guidelines (available online at https://www.cdc.gov/std/tg2015/pid.htm) (ceftriaxone 250 mg intramuscularly in a single dose plus doxycycline 100 mg orally twice daily for 14 days plus metronidazole 500 mg orally twice a day for 14 days). In patients with a positive result after the first treatment, some authors propose the option of repeating the same protocol up to three times (*Cicinelli et al., 2015*). Nevertheless, significantly better outcomes result with antibiogram-guided antibiotic treatment than with treatment based on standard CDC guidelines (live births 78.4% versus 50%) (*Cicinelli et al., 2014*).

Absence of randomized studies evaluating the reproductive impact of antibiotic treatment

The data on the impact of antibiotic treatment as a possible therapeutic option for improving reproductive results in infertile women with chronic endometritis come from retrospective or prospective observational studies (see TABLE 2, Study design). Given the lack of conclusive evidence on the treatment of chronic endometritis, some international societies such as the *Royal College of Obstetricians and Gynaecologists (2011)* and the American Society for Reproductive Medicine (2012) have recommended that endometrial biopsy does not need to be included in the infertility evaluation.

Opportunities

Greater diagnostic accuracy

Several aspects must be considered to improve and personalize the diagnosis of chronic endometritis. The use of adequate protocols that jointly analyse representative hysteroscopy findings in chronic endometritis such as endometrial micropolyposis and strawberry appearances (*Cicinelli et al., 2005*: evidence level 2b), and the incorporation of new technological advances could make hysteroscopy increasingly efficient, precise and safe, and less painful for patients (*Vitale et al., 2020*). Clinicians' ability to recognize and diagnose this disease would greatly benefit from established and agreed-upon hysteroscopic diagnostic criteria for chronic endometritis, as reflected in an international randomized study carried out by Cicinelli and colleagues. In their study, observers from different countries participated, five different diagnostic criteria were agreed upon through a Delphi poll, and the consensus of the physicians for diagnosing chronic endometritis following these criteria was 80% (*Cicinelli et al., 2019*: evidence level 1b).

Specifically, narrow-band imaging hysteroscopy – narrow-band imaging – is

a real-time endoscopic imaging technique created to improve visualization of the vascular network and the texture of the mucosal surface by improving tissue characterization and diagnosis. This technique has a high specificity and a low number of false-negative results, which would reduce the number of biopsies that were unnecessary or performed in the wrong areas. Furthermore, compared with hysteroscopic observation with white light, narrow-band imaging hysteroscopy showed a significantly higher sensitivity for the detection of chronic endometritis and significantly increased the concordance rate between hysteroscopy and histological diagnoses in more than 95% of patients (*Cicinelli et al., 2010*, *Ozturk et al., 2016*: evidence level 2b).

The use of possible chronic endometritis markers has also been investigated. These include proinflammatory cytokine concentrations (*Tortorella et al., 2014*: evidence level 3b), metalloproteinases (*Soboleva et al., 2006*; *Yoshii et al., 2013*: evidence level 3b) or microRNAs targeting protein-coding genes in chronic endometritis (such as miR-27a-3p and miR-124-3p) (*Di Pietro et al., 2018*: evidence level 2b), and could represent non-invasive markers of chronic endometritis with the ability to assess endometrial quality in IVF in the near future. The introduction of microbiology techniques such as NGS and/or RT-PCR into clinical practice, which are quick, minimally invasive and inexpensive tools, will allow the identification of cultivable and non-cultivable pathogenic micro-organisms associated with chronic endometritis (*Moreno et al., 2016*, *2018*). Furthermore, it has been proved that the pathogens involved in chronic endometritis that were detected by molecular techniques could be the cause of RIF in women with a supposedly normal endometrium, and these pathogens could therefore be treated before the pathology manifested itself; however, there is currently a lack of evidence to support this screening and treatment option (*Bellver and Simon, 2018*: evidence level 5).

Possibility of treating many cases reducing cost, time and other diagnostic or therapeutic tests

In the event of a high level of the confirmed prevalence of chronic endometritis in an infertile population, treatment would be an opportunity for improvement in many patients. The inability to accurately diagnose and treat chronic endometritic could become the underlying factor that would lead to an excessive use of assisted reproductive techniques for a significant percentage of patients with the objective of conceiving. RIF associated with untreated chronic endometritis can lead to frustration, stress, psychological and financial uncertainty and, subsequently, an increased risk of complications for patients (*Slade et al., 1997*; *Verhaak et al., 2005*). In these cases, the detection and treatment of chronic endometritis would avoid the excessive use of unnecessary diagnostic or therapeutic tests, and would shorten the time and reduce costs.

Kuroda and colleagues (*Kuroda et al., 2020*) concluded that patients with chronic endometritis show a result of 15% receptive after endometrial receptivity testing, while in patients with non-chronic endometritis or cured chronic endometritis over 50% of endometria are rated as receptive. This outcome suggests that appropiate treatment of chronic endometritis could favour recovery from an altered window of implantation. Therefore, in RIF, chronic endometritis should be diagnosed and treated prior to performing an endometrial receptivity analysis test or any other kinds of test, thereby reducing costs and time to pregnancy.

This is an expected finding as chronic endometritis promotes delayed differentiation of the endometrium in the mid-secretory phase. During the secretory phase, endometrium with chronic endometritis often presents with pseudostratification and mitotic nuclei in both the glandular and surface epithelial cells. The expression of antiapoptotic genes (*BCL2*, *BAX*), proliferation associated nuclear marker (Ki-67) and ovarian steroid receptors is up-regulated, and by contrast, the expression of genes potentially associated with embryo receptivity (*IL1*, *CCL4*, *IGF1*, *CASP* [also known as *CUX1*]) and decidualization (*PRL*, *IGFBP1*) is down-regulated during this phase of the menstrual cycle (*Di Pietro et al., 2013*; *Wu et al., 2017*).

Eliminate Spontaneous miscarriage

Recurrent pregnancy loss has been associated with the results of subclinical infection and inflammation in the endometrium, the abnormal endometrial microenvironment resulting from an atypical pattern in the lymphocyte population in chronic endometritis and its negative impact on normal endometrial decidualization. Very recently, the group of Kaku Shoji (*Kaku et al., 2020*) have considered that all these pathological characteristics seen before pregnancy may continue even after pregnancy. In their study, plasma cell counts in miscarriage tissue specimens were examined by immunohistochemistry (CD138) in a control group with no chronic endometritis before pregnancy and in another group diagnosed with chronic endometritis who became pregnant and suffered miscarriage within a year after the diagnosis of chronic endometritis without having received antibiotic treatment. The presence of moderate or severe inflammation in the decidua according to the Gilmore classification (*Gilmore et al., 2007*) was seen only in women with chronic endometritis. This finding may provide a suggestion of the presence of chronic endometritis before pregnancy, which may be beneficial for future fertility treatment.

New treatments in patients who do not respond to antibiotics

Several studies have reported that some anti-inflammatories (*Samodelkin et al., 2017*; *Sekulovski et al., 2019*) and progestins (*Bayer-Garner et al., 2004*) are another treatment option for chronic endometritis, but the data demonstrating their effectiveness and safety are insufficient. Intrauterine treatment with autologous platelet-rich plasma has the potential to be used as a successful therapeutic tool for chronic endometritis, especially for those women who do not respond to conventional antibiotic regimens. This approach has been successful on two levels as it first improved chronic endometritis, which then allowed the successful implantation of donated embryos that led to subsequent clinical pregnancies and live births (*Sfakianoudis et al., 2019*: evidence level 4).

New treatments could improve reproductive results

Reproductive results could be improved by the application of new treatments such as low-intensity intravascular laser irradiation of blood (Konoplya et al., 204: evidence level 4), microbiota regulators (pro- and pre-biotic administration, microbiota transplants) (*Molina et al., 2020*: evidence level 3b) or intrauterine

antibiotic infusion (*Sfakianoudis et al., 2018*: evidence level 3b) that include not only a systemic approach to the infection, but also a local one and the regulation of the immune and inflammatory response.

Threats

Risk of over- and under-diagnosis

In the diagnosis of chronic endometritis, the identification of plasma cells in endometrial biopsy samples is still considered as the gold standard method. However, when analysing the prevalence of chronic endometritis in the literature, it can be seen that there is considerable variability in the prevalence figures related to the different methods of quantification and different diagnostic criteria used. A risk of underdiagnosis has been reported when histological methods are used (*Moreno et al., 2018*: evidence level 2b) and a risk of overdiagnosis when CD138 immunostaining is used (*Inki et al., 1997*: evidence level 4). CD138 immunostaining is a more sensitive and precise method to identify plasma cells compared with the conventional haematoxylin and eosin staining method (*Bayer-Garner et al., 2004*; *Kitaya et al., 2013*). However, the manner in which sections and immunoreactivity are assessed may occasionally cause errors in the identification of the endometrial epithelial cells for ESPC, resulting in a possible overdiagnosis of chronic endometritis (*Inki et al., 1997*). An assessment that combines counting all $CD138^+$ cells in an entire section and expresses the result as plasma cell count per unit area could overcome the problem of local fluctuations in plasma cell count as well as correcting for the variation in results due to sample size differences (*Liu et al., 2018*).

In addition to the identification of plasma cells in endometrial biopsy samples, hysteroscopy has been proposed as an alternate method of diagnosis for chronic endometritis, but a risk of overdiagnosis has also been described (*Moreno et al., 2018*; evidence level 2b). This is attributed to the fact that hysteroscopic diagnosis is based on the presence of oedema, hyperaemia and/or micropolyps, all of which are symptoms that could be due to other pathophysiological conditions or a non-infectious inflammation of the uterine cavity (Cicinelli et al., 2008; *Song et al., 2018*).

False expectations and high demand in patients with reproductive failure

In a study by Kitaya and colleagues, initially planned randomization of infertile women with RIF/chronic endometritis in the active treatment arm and the placebo arm was not possible because more than 95% of infertile couples with RIF requested antibiotic treatment if they had chronic endometritis (Kansai Medical University, Osaka, Japan) (K. Kitaya, unpublished observation, 2019) (evidence level 2b). This demonstrates the high demand for and possible false expectations of treatment generated in these patients with reproductive failure.

Risk of indiscriminate treatment without proven effect

There are isolated case data showing that a lack of treatment after chronic endometritis detection does not affect reproductive outcome (*Fatemi et al., 2009*; evidence level 4). In addition, a case-control review noted that women with RIF who received antibiotics (without histological confirmation that chronic endometritis was cured) showed no improvement in clinical pregnancy rates compared with untreated control groups, and treatment did not modify the miscarriages rates (*Johnston-MacAnanny et al., 2010*; evidence level 3a). Therefore, indiscriminate use of antibiotics should be avoided until evidence corroborates the findings of detailed studies.

Appearance of antibiotic resistance

The search for the ideal treatment of chronic endometritis is still underway as several aspects need to be considered, such as the administration and intensity of the antibiotic regimen, the treatment duration and time, and the method of evaluating the effectiveness (*Sfakianoudis et al., 2019*). Professionals may have a difficult time selecting the optimal treatment as current data are still confusing. The dangers associated with the generation of resistance to antibiotics must be taken into account, especially in those cases in which patients undergo inadequate and repetitive treatments for chronic endometritis (*Llor and Bjerrum, 2014*). On one hand, increased antimicrobial resistance has been associated with an increased risk of severe infections, complications, more extended hospital stays and increased mortality, and, on the other hand, antibiotic overprescribing has been related to an increased risk of adverse complications, more repeat visits and increased medicalization of self-limiting conditions (*Melkumyan et al., 2015*).

Microbial imbalance

The disturbance of healthy uterine bacterial microbiomes with the blind, cumulative use of antibiotics is another threat (*Melkumyan et al., 2015*), and some authors suggest that this dysbiosis could even influence negatively reproductive results (*Moreno et al., 2016*; *Ruiz-Alonso et al., 2013*).

Cost-effectiveness

Although there are no cost-effectiveness studies to demonstrate this, the diagnosis and treatment of chronic endometritis could mean an additional cost for any healthcare system.

Delayed start of other reproductive treatments

The complexity related to diagnosis and treatment makes chronic endometritis a pathology that requires time to be addressed and requires negative bacteriology. In the presence of chronic endometritis, some authors defend the need to use antibiotics and control biopsy, with negative bacteriology as a normalization criterion (*Bouet et al., 2016*; *McQueen et al., 2015*). Still others suggest that the normalization of an affected endometrium, a normal cytometric profile and a normal endometrial biopsy are parameters whose regularization occurs in variable periods that sometimes exceed 6 months (*Tersoglio et al., 2015*). The time element is a fundamental factor in patients with infertility problems, and waiting for this amount of time represents a considerable delay in the initiation of other reproductive treatments (*Quaas et al., 2008*).

Imbalance of endometrial fibrosis, increased adhesions, and the possible reduction in the probability of pregnancy

Chronic endometritis has been shown to affect the repair of endometrium and to promote the recurrence of intrauterine adhesions (IUA) (*Chen et al., 2017*; *Liu et al., 2019*). The characteristic features of chronic endometritis include changes in local immunity in the endometrium, blood circulatory disorders in the vessels and increased production of cytokines leading to the development of fibrosis that, in turn, leads to chronic tissue hypoxia and potentiation of inflammation

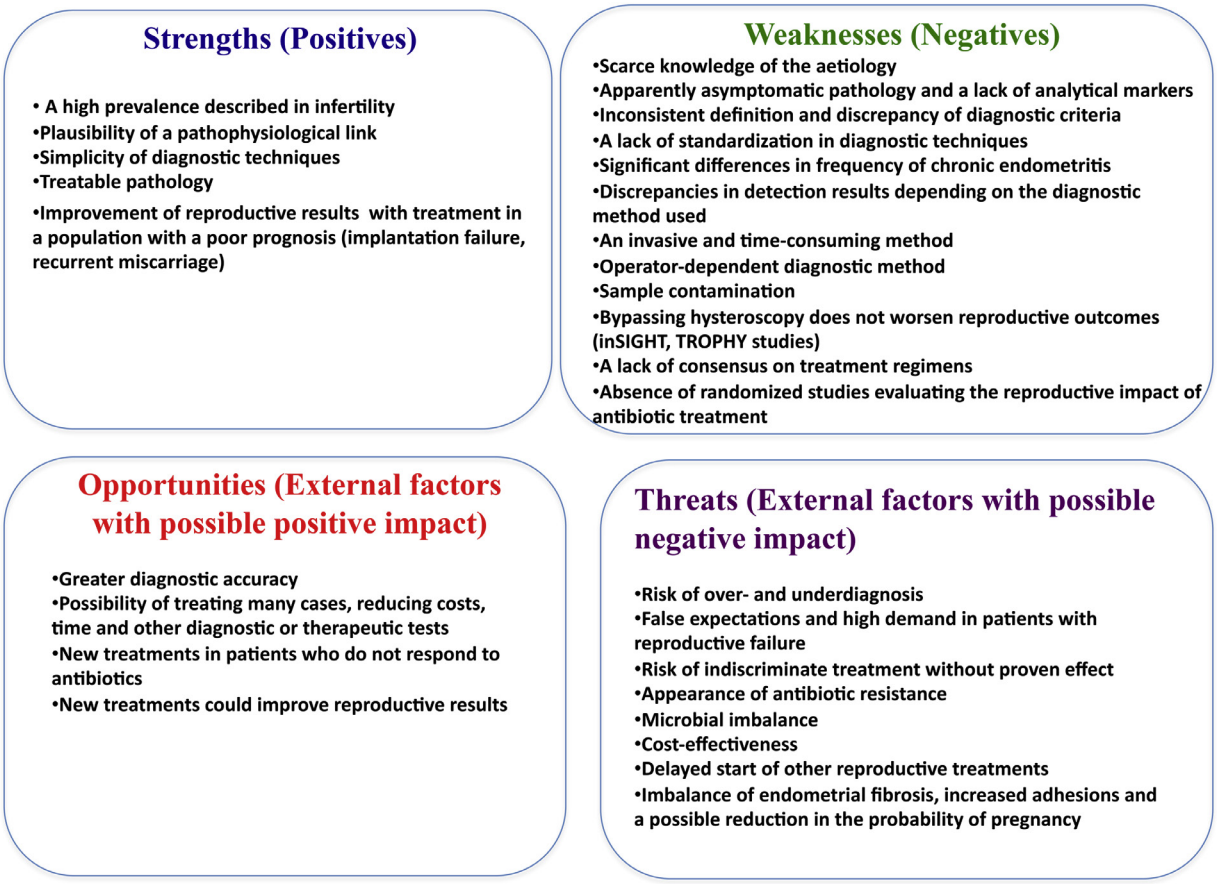

FIGURE 1 A SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis of chronic endometritis in infertility.

(*Kovaleva et al., 2017*; *Liu et al., 2016*). It has been suggested that not treating chronic inflammation in chronic endometritis may affect the steady-state imbalance of endometrial fibrosis, promote the occurrence and recurrence of IUA and affect endometrial receptivity, which could have some impact on the reproductive prognosis (*de Ziegler et al., 2019*). Moreover, the complications of operative hysteroscopy for IUA in these patients include uterine perforation, fluid overload, hyponatraemia, haemorrhage, infection, recurrent adhesions, and uterine rupture in a subsequent pregnancy, which could worsen in women with chronic endometritis (*Chen et al., 2017*; *Liu et al., 2019*).

DISCUSSION

Despite recent innovations, endometrial receptivity remains the 'black box' in assisted reproduction. The implantation process encompasses different stages that are finely regulated by immune cells and cytokines. Recent studies suggest that chronic endometritis could exert a negative effect on implantation by affecting decidualization and altering the expression of proteins involved in endometrial receptivity (such as cytokines, growth factors and apoptotic proteins). In such cases, antibiotic therapy would eliminate the source of infection, restore normal endometrial histology and improve receptivity. In this regard, some observational and retrospective studies have analysed this hypothesis but have yet to be proved by adequate evidence.

In the initial diagnosis of the infertile couple, the evaluation of chronic endometritis should not be implemented until an agreed-upon definition has been accepted, and standardized diagnostic criteria and specific treatment have been established. However, it would be advisable in women with RIF and recurrent pregnancy loss after having undergone IVF with viable embryos and before continuing with costly reproductive processes that are an emotional and financial burden, as results could be improved. The development of randomized studies that assess both the favourable impact of antibiotic treatment as a possible therapeutic option in improving reproductive results in infertile women with chronic endometritis as well as the possible impact on natural microbiota and receptivity/implantation would allow for the establishment of more precise clinical guidelines in this regard (FIGURE 1).

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