# Chronic endometritis in women with recurrent pregnancy loss and recurrent implantation failure: prevalence and role of office hysteroscopy and immunohistochemistry in diagnosis

Q3 Pierre-Emmanuel Bouet, M.D., M.Sc.,[a,b] Hady El Hachem, M.D., M.Sc.,[a,b] Elise Monceau, M.D.,[a,b] Gilles Gariépy, M.D.,[c] Isaac-Jacques Kadoch, M.D.,[a,b] and Camille Sylvestre, M.D.[a,b]

[a] Department of Reproductive Medicine, Ovo Clinic; and [b] Department of Obstetrics and Gynecology and [c] Department of Pathology, University of Montreal, Montreal, Quebec, Canada

**Objective:** To determine the prevalence of chronic endometritis (CE) in patients with recurrent implantation failure (RIF) after IVF and unexplained recurrent pregnancy loss (RPL).
**Design:** Prospective observational study between November 2012 and March 2015.
**Setting:** University-affiliated private IVF clinic.
**Patient(s):** Women with RIF after IVF (group 1) and unexplained RPL (group 2).
**Intervention(s):** Office hysteroscopy followed by an endometrial biopsy was performed as part of the workup for RIF and RPL. The diagnosis of CE was histologically confirmed using immunohistochemistry stains for syndecan-1 (CD138).
**Main Outcome Measure(s):** The prevalence of CE in each group and the sensitivity/specificity of office hysteroscopy in the diagnosis of CE.
**Result(s):** Ninety-nine patients were included (46 in group 1 and 53 in group 2). The mean age was 36.3 ± 4.9 years in group 1 and 34.5 ± 4.9 years in group 2. Five biopsies were uninterpretable (three in group 1 and two in group 2) because of insufficient specimen. The prevalence of CE was 14% (6/43) in group 1 and 27% (14/51) in group 2. The sensitivity and specificity of office hysteroscopy in the diagnosis of CE were 40% (8/20) and 80% (59/74), respectively.
**Conclusion(s):** We found a high prevalence of immunohistochemically confirmed CE in women with RIF and RPL. Office hysteroscopy is a useful diagnostic tool but should be complemented by an endometrial biopsy for the diagnosis of CE.
**Clinical Trial Registration No.:** www.clinicaltrials.gov, NCT01762098. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
**Key Words:** Chronic endometritis, recurrent pregnancy loss, implantation failure, plasma cells, office hysteroscopy

**Discuss:** You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/bouetpe-chronic-endometritis-rpl-rif/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

The endometrial factor in recurrent implantation failure (RIF) after IVF and recurrent pregnancy loss (RPL) is under constant scrutiny. One of the etiologies is chronic endometritis (CE), which is defined as a chronic inflammation of the endometrial lining (1). Patients are usually asymptomatic but can present with chronic pelvic pain, dyspareunia, abnormal uterine bleeding, or persistent vaginal discharge (1). Office hysteroscopy can help diagnose CE with direct visualization of mucosal edema, focal or diffuse endometrial hyperemia, and micropolyps (<1 mm) (2). However, the gold standard for the diagnosis of CE is histological identification of plasma cells in the endometrial stroma (3). The use of immunohistochemistry

Received July 27, 2015; revised September 2, 2015; accepted September 17, 2015.
P.-E.B. has nothing to disclose. H.E.H. has nothing to disclose. E.M. has nothing to disclose. G.G. has nothing to disclose. I.-J.K. has nothing to disclose. C.S. has nothing to disclose.
Reprint requests: Dr. Pierre-Emmanuel Bouet, M.D., M.Sc., Department of Reproductive Medicine, Ovo Clinic, 8000 Boulevard Decarie, Montréal, Quebec H4P 2S4, Canada (E-mail: pebouet@hotmail.com).

Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.09.025

(IHC) stains for syndecan-1 (CD138), a proteoglycan found on the cell surface of plasma cells and keratinocytes, provides a more accurate diagnosis (4).

Various reports suggest an infectious etiology of CE (5–7). Cicinelli et al. reported positive cultures in 75% of women with histologically confirmed CE, with common bacteria (*Escherichia coli, Enterococcus faecalis, Streptococcus agalactiae*) most frequently found (77.5%), followed by *Mycoplasmae/Ureaplasma* (25%) and *Chlamydia* (13%) (5).

The impact of CE on reproductive capacity is controversial, but reports suggest it may negatively affect fertility outcomes since endometrial receptivity is altered by an abnormal infiltration of plasma cells and secretion of IgM, IgG, and IgA antibodies (8). Moreover, an altered endometrial expression of genes encoding for proteins involved in the inflammatory response, proliferation, and apoptosis has been found in women with CE (9). Various studies have found an increased prevalence of CE in women with RPL (13%) (10) and RIF (30%) (11).

On the basis of these data, we decided to study the link between CE and RIF/RPL. Our primary objective was to determine the prevalence of immunohistochemically diagnosed CE in women with RIF after IVF and RPL. Our secondary objective was to assess the value of office hysteroscopy in the diagnosis of CE.

## MATERIAL AND METHODS

We undertook a prospective observational study at Ovo Clinic, a private IVF center affiliated with the Université de Montréal, Canada. Between November 2012 and March 2015, all patients between 18 and 43 years of age with a history of RIF afterIVF (group 1) or RPL (group 2) were included.

RIF was defined as failure to achieve a clinical pregnancy after transfer of at least three good-quality embryos in fresh or frozen cycles in women <35 years of age and four good-quality embryos in fresh or frozen cycles in women ≥35 years. Biochemical pregnancies were included in RIF. RPL was defined as ≥2 consecutive early pregnancy losses (<14 weeks gestation) and was considered unexplained after a negative workup (12).

Our initial workup for RIF and RPL included serum levels of fasting glucose, TSH, and PRL; karyotypes (patient and male partner); a thrombophilia screen (antiphospholipid antibodies, lupus anticoagulant, anti$\beta$2glycoprotein, factor V Leiden); and a thorough evaluation of the uterus to rule out uterine malformations (three-dimensional ultrasound followed by a hysterosonography [HSSG] or a hysterosalpingography [HSG]). We also performed a diagnostic hysteroscopy as part of our initial workup for RIF and RPL, even in cases of normal HSG/HSSG. Indeed, studies have shown that a significant percentage of intrauterine abnormalities remain undiagnosed even after HSG in patients with a history of failed IVF attempts (13). Office hysteroscopy enables us to rule out primarily cervical abnormalities, endometrial polyps, and submucosal leiomyomas, as well as uterine septums and synechiaes that are sometimes missed by HSG/HSSG.

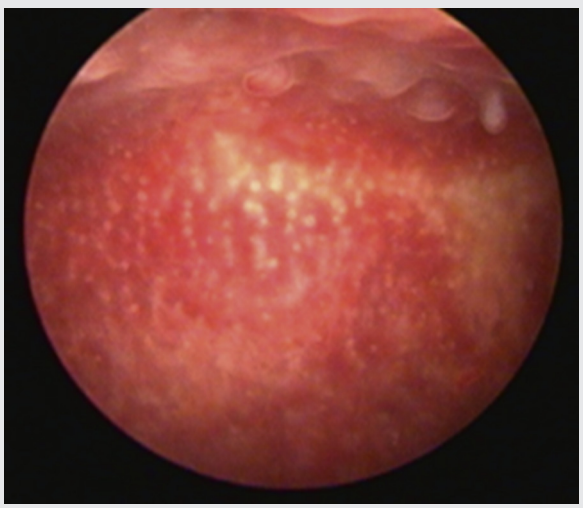
The study was approved by our Institutional Review Board, and all patients signed an informed consent before inclusion. There were no known conflicts of interest associated with this study, and there was no significant financial support for this work that could have influenced its outcome.

We excluded from the study all patients with a positive pregnancy test, unexplained uterine bleeding, a history of antibiotic treatment in the month preceding the biopsy, a uterine malformation, a cavity-deforming submucosal myoma, or a polyp >5 mm. Patients with an incomplete or a positive etiologic workup were excluded as well.

Patients meeting the inclusion criteria were referred to a research nurse who scheduled an office hysteroscopy with an endometrial biopsy. A total of 10 different operators performed the office hysteroscopies: seven attending gynecologists specializing in reproductive endocrinology and infertility and three senior reproductive endocrinology and infertility fellows with at least 1 year experience with the procedure. At the start of the study, all participating doctors and fellows attended a 90-minute seminar on CE that included illustrative examples of the visual signs to look for on hysteroscopy. These signs included [1] pedunculated and vascularized micropolyps (<1 mm), most frequently found near the endocervical area (2); and [2] the presence of areas of hyperemic endometrium flushed with a white central point, localized or scattered throughout the cavity, referred to as "strawberry aspect" (Fig. 1) (2, 14).

Office hysteroscopy was scheduled in the follicular phase (between days 6 and 12) of the menstrual cycle. The procedure was performed using a rigid hysteroscope with a 30° foroblique lens-based 3 mm outer diameter and a 3-CCD digital camera system (Karl Storz). A 50-W Hi-Lux light source (Karl Storz) and a 15-inch video color TELE PACK X LED monitor (Karl Storz) were used. Pictures were taken and recorded in digital format.

**FIGURE 1**



Large area of hyperemic endometrium flushed with white central points, a typical aspect of chronic endometritis called "strawberry aspect."

*Bouet. Diagnosis of chronic endometritis. Fertil Steril 2015.*