Comparison of the prevalence of chronic endometritis as determined by means of different diagnostic methods in women with and without reproductive failure

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Objective: To compare the prevalence of chronic endometritis (CE) when different diagnostic methods are used.
Design: Prospective observational study.
Setting: University-affiliated hospital.
Patient(s): Four groups of women were studied, including women with proven fertility (Fertile; n = 40), unexplained recurrent miscarriage (RM; n = 93), recurrent implantation failure (RIF; n = 39), and infertile subjects undergoing endometrial scratch in a natural cycle preceding frozen-thawed embryo transfer (Infertility; n = 48).
Intervention(s): Endometrial biopsy was performed precisely 7 days after LH surge (LH+7). Plasma cells were identified by means of traditional hematoxylin and eosin (HE) staining and by means of immunohistochemistry (IHC) for Syndecan-1 (CD138).
Main Outcome Measure(s): Prevalence of CE.
Result(s): The use of CD138 epitope was more sensitive than HE staining in identifying plasma cells. The use of plasma cell count per unit area had the lowest observer variability compared with cell count per ten randomly chosen high-power fields and cell count per section. Using this method, the prevalence of CE in women with RM, RIF, and Infertility were 10.8%, 7.7%, and 10.4%, respectively, not significantly higher than that of Fertile subjects (5.0%).
Conclusion(s): Using what may be a new method of plasma cell assessment, it appears that the prevalence rates of CE reported in many earlier studies may have been overestimated.
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Key Words: Chronic endometritis, plasma cell, prevalence, reference range, reproductive failure

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Chronic endometritis (CE) refers to local persistent inflammation of the endometrium. CE has been reported to be associated with various subgroups of reproductive failure, including infertility (1–3), recurrent miscarriage (RM) (4–8), and recurrent implantation failure (RIF) (4,9–11).

The presence of plasma cells in endometrial stroma has been accepted as the criterion standard method to establish a diagnosis of CE (12).

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Nevertheless, the reported prevalence of CE in endometrial biopsy specimens has varied considerably, ranging from 3% to 60% (Table 1). There are several possible explanations to account for the wide variation reported. First, there are two different methods used to identify plasma cells. Traditionally, plasma cells are identified in hematoxylin and eosin (HE)–stained specimens. However, the identification of plasma cells in HE sections requires experience coupled with diligent search, without which they can be easily missed. A more recently introduced method is immunohistochemistry (IHC) staining for Syndecan-1 (CD138), a proteoglycan found on the cell surface of plasma cells and keratinocytes. This has been found to improve the sensitivity and accuracy for identifying the plasma cells essential for the diagnosis of CE (13–15).

Second, various investigators have used different approaches to quantify the CD138+ cell count (Table 1). In the first approach, the number of plasma cell per whole section was measured. In the second approach, the plasma cell count per a defined number of (e.g., ten) randomly chosen high-power fields (HPFs) was measured. There are rationales behind each of these two approaches. Some investigators have advocated scrutinizing the entire specimen because they thought that plasma cells are not normally present in the endometrium and the finding of one or more plasma cells is indicative of a diagnosis of CE (12, 16, 17). One shortcoming of such an approach is that it does not take into account the size of the specimen. One would expect that, other things being equal, the larger the specimen size, the more likely it is to find plasma cells, and vice versa. Consequently, other authors introduced the concept of plasma cell density to correct for the size of the specimen examined; they advocated examining ten or more chosen HPFs and expressing the number of plasma cells detected per HPF or per ten HPFs, because each HPF is equivalent to a defined area (4, 6, 10, 11, 15, 18, 19). To avoid bias in selecting the HPFs to be examined and to improve objectivity, it is desirable to have randomly chosen fields. However, the potential disadvantage of such an approach is that plasma cells are usually present in low numbers, so the inclusion of only ten selected HPFs may not be sufficient to produce a consistently reproducible result. We postulate that a new method of plasma cell assessment that combines the positive attributes of the two above-mentioned methods would be to count all CD138+ cells in the entire section, then measure the area of the examined tissue section and express the result as plasma cell count per unit area. In this way, it would overcome the problem of local fluctuation of plasma cell count as well as correcting for the variation in results due to sample size difference.

There is also no consensus on the diagnostic criteria used to define what constitutes CE. At least seven criteria have been reported in the literature, including at least one plasma cell per section (20), at least one plasma cell per HPF (10), at least one plasma cell per ten HPFs (3), at least five plasma cells per ten HPFs (4), at least five plasma cells per 20 HPFs (22), the presence of one to five plasma cells per HPF or discrete clusters of <20 plasma cells (7), and an endometrial stromal plasmacyte density index (the sum of the stromal CD138+ cell counts divided by the number of the HPFs evaluated) of ≥0.25 (11) (Table 1). The proposed criteria are all rather arbitrarily chosen and not based on reference ranges derived from normal fertile populations.

In the present study, our aim was to establish a reference range of plasma cell count in the endometrium of fertile subjects with the use of two different methods of identification and three different methods of quantification, as discussed above, followed by a comparison of the performance of these methods. The prevalence rates of CE so derived among women with reproductive failure was then determined, using this methodology, with a view to determining the optimal strategy to identify and quantify plasma cells and to diagnose CE.

TABLE 1

Prevalence of chronic endometritis reported in the literature among three groups of women (infertility, recurrent miscarriage, and recurrent implantation failure) in relation to inclusion criteria, diagnostic criteria, and timing of endometrial biopsy.

Reference	Inclusion criteria	Diagnostic criteria (plasma cell count)	Timing of endometrial biopsy	Prevalence
Infertility				
Cicinelli et al., 2005	Unexplained infertility	≥1/section	Follicular phase	30% (45/150)
Kitaya and Yasuo, 2010	Unexplained infertility	≥1/10 HPFs	LH+6–8	29% (22/76)
Kasius et al., 2011	Infertility	≥1/section	Follicular phase	3% (17/606)
Kitaya et al., 2012	Infertility	≥5/20 HPFs	Follicular phase	44% (23/52)
Recurrent miscarriage				
Kitaya, 2011	≥3 miscarriages	≥1/10 HPFs	LH+6–8	9% (5/54)
Zolghadri et al., 2011	≥3 miscarriages	≥1/section	Follicular phase	43% (61/142)
Cicinelli et al., 2014	≥3 miscarriages	≥1/section	Follicular phase	53% (190/360)
McQueen et al., 2015	≥2 miscarriages	1–5/HPF or discrete clusters <20	Not mentioned	56% (60/107)
Bouet et al., 2016	≥2 unexplained miscarriages	≥5/10 HPFs	Follicular phase	27% (14/51)
Recurrent implantation failure				
Johnston-MacAnanny et al., 2010	≥2 failed ET cycles or >10 failed ETs	≥1/HPF	Not mentioned	30% (10/33)
Kitaya et al., 2017	≥3 failed ETs	ESPDI ≥0.25	Follicular phase	34% (142/421)
Cicinelli et al., 2015	≥3 failed ET cycles	≥1/section	Follicular phase	57% (61/106)
Bouet et al., 2016	≥3 failed ETs	≥5/10 HPFs	Follicular phase	14% (6/43)

Note: ESPDI = endometrial stromal plasmacyte density index; ET = embryo transfer; HPF = high-power field, ×400 magnification; LH+6–8 = 6 to 8 days after LH surge.

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