NARRATIVE REVIEW

Correlations between hysteroscopy and histopathology to consider for the diagnosis of impaired inflammatory states of the endometrium: a narrative review.

Short title: *Hysteroscopy and histopathology correlations in IISE.*

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Abstract
Endometrial inflammatory disorders are histologically characterized by a number of features which to date, are not fully taken into consideration in our practice of diagnostic hysteroscopy. A part of the current clinical and hysteroscopic consensual approach is in contradiction with many basics of histopathology and immunology, ultimately biasing research.
Objective: Analysis of the histopathological features of endometrial inflammation which provide a ground for correlations with hysteroscopy in order to improve the endometrial sampling and to standardize the diagnosis of inflammatory disorders for the benefit of practice and research.
Methods : A narrative review via a search in MEDLINE, EMBASE, Global Health, The Cochrane Library and Web of Science. Pertinent book chapters, original and review articles, published in English until December 31st, 2021 were selected, focusing on the changes of endometrial glands and stroma during inflammatory disorders. Those which can be correlated with hysteroscopy have been selected in order to define a list of well founded diagnostic criteria, serving as guidelines for an optimal visually-guided biopsy.
Results: A list of correlations between hysteroscopy and histopathology is established, with a particular focus on the morphological patterns to guide the hysteroscopist during diagnosis. The histopathological changes to be screened by the pathologist are also defined.
Conclusion: growing awareness of the well established features of the endometrial histopathology provides the right basis for a standardized well-founded practice of diagnostic hysteroscopy in inflammatory disorders, which is a sine qua none prerequisite for evidence-base and interpretable clinical trials.

Keywords: Impaired Inflammatory State of the Endometrium; targeted biopsy; non shed endometrium; inflammatory vs dysfunctional disorders.

Introduction:

The new concept of impaired inflammatory state of the endometrium (IISE) acknowledges chronic inflammation as a crucial component of normal endometrium and defines impairment as whatever disrupts the physiological inflammatory process involved therein [1]. Unlike chronic endometritis (CE) which always reflects excessive inflammation caused by germs, IISE could result either from immune suppression or disproportionate inflammatory response to whatever perturbs homeostasis [1,2]. Consequently, IISE is a more proper terminology than CE as it separates physiological inflammation from pathological; excessive from deficient and transient from chronic [3]. For this reason and in this paper, we will refer to CE with the term chronic IISE (C-IISE). The latter is susceptible of causing various obstetrical and gynecological conditions such as infertility, repeated miscarriage, placenta related complications, endometrial polyps, hyperplasia and carcinoma [1,4-8].

In terms of endometrial inflammation however, the major problem research is facing today is the absence of well-founded consensual definitions and diagnostic criteria. Some of those which continue to be used today are in violation of the basics of immunology and histopathology. They have been severely criticized for a long time, presented as seriously hindering our understanding of this disorder, as they unavoidably result in biased studies and hence, in a wronged interpretation of data [9-11].

Among the contradictory statements, the current definition of CE reflects a limited vision of endometrial inflammation. In the literature, it is still considered as a histopathological entity whose diagnosis requires the presence of plasma cells within the endometrium. Ironically, this approach has been seriously questioned by pathologists themselves, since 1911 [10]. Moreover, in hysteroscopy, the international working group on CE has defined 5 hysteroscopic patterns suggestive of C-IISE: micropolyps, strawberry aspect, hyperemia, edema and hemorrhagic spots [12]. However, the three last ones are also typical signs of the very first stages of acute inflammation [3].

The absence of a consensus to guide endometrial sampling in case of inflammatory or dysfunctional disorders is another essential problem we face in our practice. In a uterine cavity free of organic anomalies like polyps, fibroids or malignancies, there are to date no specific guidelines for a targeted biopsy allowing optimal sampling. Only the technique is stressed, not the morphological patterns of the biopsy site [13-15]. In an “empty uterine cavity”, hysteroscopy is usually conducted in a “come in – come out” fashion, and blind biopsies with Pipelle or Novak continue to be used [16]. Even in symptomatic patients suffering from Abnormal Uterine Bleeding (AUB) or unexplained infertility, blind sampling continues to be recommended [17]

Meanwhile, many authors have been urging the scientific community to look into more consistent criteria, both hysteroscopically and pathologically [1,3,11,18]. Defining pertinent diagnostic criteria is essential to start consistent multicenter studies where a standardized medical terminology and diagnostic approach are adopted.

In this paper, we aim at defining diagnostic hysteroscopic patterns based on a histopathological basis. The analysis of the histopathological features of C-IISE provides precious fundamentals for an improved practice of diagnostic hysteroscopy, hopefully contributing to improving the quality of diagnosis and research.

Methods

A non-systematic review was done via a search in the following databases: MEDLINE, EMBASE, Global Health, The Cochrane Library and Web of Science. Pertinent book chapters, original and review articles, published in English until December 31st, 2021, focusing on the changes of

endometrial glands and stroma during inflammatory disorders, were selected. Those which can be correlated with hysteroscopy in order to define a list of well founded diagnostic criteria, serving as guidelines for an optimal visual-guided biopsy were determined.

Results

The already described histopathological features other than plasma cells:

Even in the last century, pathologists were attributing endometrial inflammation to other possible causes than germs, such as prior biopsy, intrauterine contraceptive device, cervical stenosis, and the presence of an organic lesion such as polyps, leiomyomas, hyperplasia or carcinoma [19,20].

However, the use of plasma cells as the sole criterion was first introduced in 1907 but has continuously been criticized since then. In fact, in addition to inflammatory cells, there is a constellation of histological changes that facilitate recognition of endometrial inflammation [20]. The importance of implementing these additional criteria has been stressed mostly by pathologists because, on the one hand, the presence of sporadic plasma cells can be identified in histologically normal endometrium [11,20]. On the other hand, if C-IISE reaches a disease state, this would logically imply stromal and/or glandular changes within the mucosa [10,21]. In the absence of these additional morphological changes of the endometrium, an exhaustive search for plasma cells is even thought to be unnecessary [10,21]. This approach has recently been recommended by McQueen et al, additionally stressing the cost savings when CD138 staining is only used for the cases where endometrial stromal changes are identified and no plasma cells are detected via hematoxylin and eosin (H&E) staining [11]. Although the quantity of the required changes still remains to be defined, most pathologists agree that the diagnosis of C-IISE should not rest on the finding of an apparent plasma cell in an endometrium that otherwise appears normal, because the background pattern is as important as the quantity of plasma cells for establishing the diagnosis of C-IISE [10,11,20].

The morphological changes that have already been retained in the literature as diagnostic criteria for C-IISE are listed in table1 and their relevance was ascertained by studies [10,11,20,23]. It is important to note that pleomorphic inflammatory infiltrates are physiologically observed in late secretory and menstrual phases [20,22].

The notion of “non shed endometrium” in chronic inflammation:

In some references of histopathology, it is highlighted that endometritis becomes chronic only if a part of the endometrium is not shed during menstruation [24]. To better understand this notion, it is important to recall the mechanism of endometrial shedding during menses, where the duet progesterone-endometrial inflammation plays a pivotal role. In fact, under the effect of progesterone, uterine natural killer (µNK) cells considerably increase during secretory phase, yet with an inhibited cytotoxic effect [25]. Progesterone is well known for its anti-inflammatory properties [26]. Its withdrawal at the end of the menstrual cycle causes activation of some pro-inflammatory mediators, neutrophils recruitment and resumption by µNK cells of their cytolytic activity, all leading to glandular and stromal breakdown [25-28]. Progesterone is also in charge of the predecidualization of stromal cells which do contribute to this process as well. At the lysis of the corpus luteum, progesterone’s drop causes the predecidual cells to free the cytolytic enzymes of their granules into the mucosa, additionally contributing to the shedding process [29].

In case of luteal insufficiency and/or progesterone-resistance, these physiological self-limiting inflammatory mechanisms are variably impaired, depending on the severity of the disorder [27]. Areas within the endometrium will not benefit from the cyclical changes orchestrated by progesterone, thus resulting in a lack of predecidualization of stromal cells as well as an impaired recruitment and activity of the inflammatory cells (mainly µNK cells and neutrophils). On the other

hand, the cytolytic activity of the recruited µNK cells will not be sufficiently inhibited. Consequently, irregular bleeding, with stromal and glandular breakdown, will coexist with areas of poorly predecidualized non shed endometrium, containing stromal cells which remain spindle- shaped, not plump as they normally become in an optimal progesterone environment.

Chronic inflammation is already known to induce a progesterone-resistant state [20,21,26,27,30]. Conversely, plasma cells have been observed in hormonally mediated endometrial disorders, in association with gland architectural changes [23]. IISE and hormone imbalances both have common consequences on the endometrium. Impaired inflammation provokes impaired expression of hormone receptors by glandular and stromal cells. Meanwhile, hormonal anomalies directly impact the recruitment and activity of the endometrial inflammatory cells and cytokines. The two protagonists do thus very closely interfere with one another in a vicious circle whose starting point could be any of the two. This is why the new concept of IISE acknowledges hormone imbalances as one of the etiologies to endometrial inflammatory disorders, unlike the entity CE which is described to be only caused by germs [1].

Non shed endometrium is presented as a sine qua non criterion for C-IISE, be it non specific or specific [24]. The areas where the endometrium does not shed display spindled-shaped stromal cells, as well as glandular changes. In fact, glands present as atrophic, resting, insufficiently proliferated, irregularly proliferated or hyperplastic. These 5 terms have each one a specific signification in pathology and are described to be very relevant of C-IISE [24,31]. In table 2, the main features of stromal and glandular changes of a non-shed endometrium are listed. Quite interestingly, many of them offer the possibility of being correlated with hysteroscopy.

Authors report presence of plasma cells in the majority of disordered proliferative endometria and stromal breakdown [23]. However, the spindled-stroma seems to need revision. In fact, this criterion seems pertinent when a biopsy is performed during the secretory phase, when predecidualization is one of the capital parameters to assess. At this stage, progesterone has caused transformation of Endometrial Stromal Cells (ESC) from spindle shape (typical of proliferative phase) to a plump rounded one (typical of luteal phase). However, hysteroscopy is nowadays performed during proliferative phase for many reasons. Among these reasons, plasma cells are easier to identify at this stage of the menstrual cycle [32]. This is why it is pertinent to recall that a spindled stroma cannot stand as a diagnostic criterion unless the sampling is performed during secretory phase, not the proliferative one. However, the presence of spiral arterioles during a proliferative stage could be considered as another sign for non shed endometrium, since these vessels are typically present in the late luteal phase (table 3).

Pathologists need to be aware of all the histological criteria so far described for C-IISE as their presence needs to be meticulously reported especially in symptomatic patients (table 4). However, one of the main problems encountered in practice is that not all of them are aware therof. It is of utmost importance to spread information in this area and train both pathologists and gynecologists on the basics of endometrial histopathology to warrant an optimal collaboration between the two protagonists. Quite interestingly, many of these criteria offer the possibility of being correlated with hysteroscopy and thus are particularly interesting to study.

The histological criteria that can be correlated with hysteroscopy

The analysis of the histopathological features of C-IISE provides precious fundamentals for an improved practice of diagnostic hysteroscopy. The following parameters appear relevant and can be correlated with hysteroscopy.

1- The cyclical changes of the endometrium

The endometrial mucosa is a cyclical changing tissue displaying characteristic features in a time-dependent fashion, which allows endometrial dating. This phenomenon is impaired in C-IISE,

causing focal or diffuse “out of cycle” areas [20,21,31]. Obviously, distinction between normal and impaired maturation is only possible by precise statement of the phase of the menstrual cycle. Distinction on morphologic grounds alone is not possible [31]. Consequently, it is mandatory to specify the day of the menstrual cycle in all diagnostic hysteroscopies. The length of the menstrual cycle is obtained by noting the first day of the upcoming menses, in order to retrospectively determine the precise phase where hysteroscopy was performed. This allows a more optimal histopathological correlation. Moreover, any hormonal treatment or disturbances have to be reported and more interestingly avoided before diagnostic hysteroscopy.

Conclusion: specification of day and the length of the menstrual cycle is mandatory. Histological dating of the endometrium reflects either a synchronous normal endometrium or an out of date one: deficient or disordered proliferation; atrophic, resting or hyperplastic endometrium. Distinction on morphologic grounds alone is not possible and precise statement of the phase of the menstrual cycle.

2- Proliferative phase

The secretory phase is well known to be particularly rich in physiological and histological details, especially those related to the post-ovulatory changes of the endometrium, which is why it has long been the preferred one for subfertile patients [33].

Yet and just as interestingly, hysteroscopic examination is preferably indicated in the proliferative phase by most authors [33,34]. At this stage, the mucosa is thinner, thus avoiding misinterpretation with polypoid or hyperplastic endometrium. Moreover, the increased tonicity of the cervix caused by progesterone is avoided, hence facilitating the technique, especially in office settings.

In the specific case of inflammatory disorders of the endometrium, luteal phase is additionally interesting to avoid because of the physiological presence of inflammatory infiltrates at this stage [21,22]. Moreover, despite the contradictory available data, most studies revealed increased prevalence of C-IISE, up to 50% higher, when the sampling is performed during the follicular phase as compared to the secretory one [32]. The stage of the menstrual cycle is presented as a major confounder to take into consideration when assessing this condition. The usual presence of plasma cells in the deeper layers of the endometrium is a potential explanation for this difference, as a thicker mucosa during luteal phase can cause a reduced portion of deeper tissue during sampling [32].

Consequently, both follicular and luteal phases have advantages and disadvantages and can both be interesting to study. However, given the above-mentioned advantages of the proliferative phase in the particular context of hysteroscopy and inflammatory disorders, our analysis is centered thereupon. Consequently, only the histological and hysteroscopic features of the proliferative phase will be focused in this paper.

Proliferative phase is usually divided in 3 sub-phases: early, mid and late proliferative. The main features are summarized in table 3 and most of them can be correlated with hysteroscopy. These features should be particularly targeted by pathologists and described in the report.

If out of date areas are seen within the mucosa, this will be suggestive of a perturbed endometrial maturation. Altered or ambiguous gland phase –in addition to stromal changes– are already known to be associated with C-IISE [10,11,21,22,36].

Conclusion: diagnostic hysteroscopy is to be scheduled during proliferative phase.
The **histological** features to be searched for are:

- Height of the endometrium
- Regular distribution of glands
- Form and size of glands: narrow and straight, curved or tortuous.
- Epithelial and glandular cells: cuboid, columnar or pseudostratification
- loose stroma of spindle-shaped cells
- Stromal edema: physiological in mid-proliferative phase
- Absence of spiral arterioles

Some of these histological criteria can be correlated with hysteroscopy

3- Distribution of glands – Regular inter-glandular spaces

In all the references of histopathology, evenly distributed endometrial glands represent a key feature of a normal proliferative phase [20,21,29,36]. Quite interestingly, this criterion can also be evaluated via hysteroscopy, which offers the possibility to see gland orifices as white dots, regularly distributed throughout the mucosa (figure1).

The presence of areas where gland orifices are not equally distant from one another needs to be considered as an additional marker for a targeted biopsy, especially if redness and irregular thickness are associated (figure1). In fact, unequal inter-glandular spaces represent one of the features of irregular disordered proliferation and hyperplasia, both listed among the additional histopathological criteria of C-IISE (table 4). A visually-guided biopsy performed within an endometrial area displaying this hysteroscopic glandular pattern provides increased odds of histopathological correlation.

Conclusion: irregular distribution of endometrial glands is a hysteroscopic pattern to consider for a targeted biopsy, especially when associated with edema, hyperemia and micropolyps.
Histopathological correlation: irregular disordered proliferation and hyperplasia: irregular distribution, shape and width of glands.

4- Localized stromal edema

Stromal edema is another histological criterion which can be correlated with hysteroscopy. It appears as a swollen area compared to the surrounding endometrium (figure2). Although it can be physiological in mid-proliferative phase [29,36], it is still presented as one of the hysteroscopic criteria of CE [12]. In all cases, its presence needs to be considered as a marker for the targeted-biopsy site, especially if micropolyps or unevenly distributed glands are associated (fig2). Histologically, if edema is seen within tortuous glands without pseudo stratification, mid proliferative pattern is more likely and hence physiological. If edema is concomitant with pseudostratification or a deficient proliferation, it is considered outdated, and hence more relevant of an IISE, especially if associated with the other criteria (table 3).

Meanwhile, it is very important to recall that edema is one of the cardinal signs of acute inflammation, and can develop during hysteroscopy because of mechanical effect [3] (see criterion 9)

Conclusion: stromal edema is a hysteroscopic pattern to consider for a targeted biopsy, especially when associated with redness, micropolyps or unevenly distributed glands.
Histopathological correlations: physiological mid-proliferative phase; iatrogenic edema (transient IISE); out of date stromal edema of C-IISE.

5- Micropolyps, strawberry pattern, hyperemia and hemorrhagic spots

These criteria, in addition to stromal edema, consist of the five hysteroscopic patterns described as relevant of CE by the international working group on this condition [12] (figure3)

Micropolyps have already been the subject of a study by Cicinelli et al. Their rich content in inflammatory cells – including plasma cells– was histologically demonstrated [37]. For this reason, this pattern provides an interesting indicator for the targeted biopsy site, offering increased odds of histopathological correlation.

However, hyperemia, edema and hemorrhagic spots lack specificity in terms of chronic inflammatory disorders, as they are primarily typical signs of acute inflammation [3]. Their presence in a C-IISE can be explained by the fact that chronic inflammation predisposes to repeated acute inflammatory episodes and vice versa. Another explanation is their potential histological correlation with glandular and stromal breakdown. The latter, one of the additional histological criteria of C-IISE, causes a mixture of acute and chronic bleeding patterns. It is also accompanied with areas of stromal collapse, glandular breakdown, stromal fibrosis, macrophages, and hemosiderin deposition [20].

Conclusion: micropolyps is a hysteroscopic pattern to consider for a targeted biopsy and is histologically correlated with inflammatory infiltrates rich in plasma cells

Hyperemia and hemorrhagic spots are inflammatory patterns encountered both in transient and C-IISE.

6- Areas of irregular endometrial thickness:

Uniformity of the histological changes induced by hormones in the endometrium depends on factors such as the distribution of estrogen and progesterone receptors, the local blood supply as well as various metabolic factors [21,29,35]. In a normal follicular phase, the height of the endometrium is regularly thin. If there are focal areas of irregular thickness, this could be suggestive of an underlying disorder: stromal edema; focal atrophic, deficient or resting endometrium; stromal breakdown; irregular proliferation and/or focal hyperplasia (table 4). In fact, when a C-IISE reaches disease state, disturbance of stromal and glandular maturation and shedding can result in areas of unequal endometrial growth [20,21,24,35,36].
This criterion, interestingly, can be correlated with hysteroscopy. Depending on the surface of the affected areas, unequal thickness is susceptible of causing different hysteroscopic patterns of an irregular surface: corrugated surface as well as embossed or debossed patterns, whose limit with the surrounding endometrium is marked by a slope or a stairstep-like elevation (figure4).

These patterns can be associated with redness, micropolyps and unevenly distributed glands and need to be meticulously searched as the irregularities can be quite subtle (figure5). They need to be considered as an indicator for a targeted biopsy because they can be correlated with the above cited histopathological changes which need to be particularly investigated by pathologist.

Conclusion: irregular endometrial surface is a hysteroscopic pattern to consider for a targeted biopsy, especially when associated with redness, micropolyps or unevenly distributed glands: slope, stairstep, embossed or debossed patterns.

Histopathological correlation: stromal edema, focal atrophic, deficient or resting endometrium; stromal breakdown; irregular proliferation and/or focal hyperplasia

7- IISE: more commonly focal than diffuse.

One of the overlooked capital features of inflammatory and dysfunctional disorders is their focal character, although they can also be diffuse [20,22] (figures 1-5).

This fact stresses the impertinence of blind biopsy which increases the odds of missing the diagnosis if the specimen is not sampled within the inflammatory site itself [33]. Unfortunately, the available studies on CE continue to use blind sampling with Pipelle, curette or Novak, even when hysteroscopy is performed, thus biasing the evaluation of hysteroscopy-histopathology correlations [16,32,33].

Conclusion: in histopathology, inflammatory disorders are well known to be more commonly focal. Correlation with hysteroscopy: superiority of targeted biopsy to blind sampling.

8- Isthmic region of the uterus:

The uterine isthmus, or lower uterine segment (LUS), is about 6 to 10 mm and connects the cervix to the uterine corpus. Its anatomical limits have been defined both in anatomy and in hysteroscopy, namely the *internal histological and anatomical ostia of the uterus* [38] (figure6). Histologically, the isthmic endometrium is well known to be poorly responsive to hormones and hence does not participate in cyclical changes of the mucosa [21,29,35,36,38]. It is rather flat, with an inactive low columnar surface and glandular epithelium, containing slender, often horizontally directed glands, surrounded by a dense, fibrous stroma of small spindle-shaped cells. Ciliated cells are normal in the lower uterine segment and should not be interpreted as ciliated metaplasia [21,35,36].

These characteristics stress the importance of giving a particular attention to the anatomic limits of the isthmus during a diagnostic hysteroscopy. If the sampling is performed within the isthmic region, a note has to be made to the pathologist for a proper interpretation.

Conclusion: The endometrium lining the LUS is poorly responsive to hormones and does not display the usual cyclical changes allowing a proper endometrial assessment.

Correlation with hysteroscopy: visualization of the internal histological and anatomical ostia of the uterus whenever possible to permit precise delimitation of this region; sampling should be avoided therein and if necessary, a mention should be made to the pathologist in order to prevent overdiagnosis of out of date dysfunctional endometrium.

9- Iatrogenic acute inflammation:

Hysteroscopy, uterine distension and deflation, as well as the contact of the instruments with the mucosa, cause an inflammatory response, displaying some of the cardinal signs of acute inflammation namely edema, hyperemia and hemorrhagic spots [3] (figure7). However, these patterns can also be expressed in C-IISE, as the latter provides a predisposing ground for acute inflammatory episodes.

This highlights the importance of paying particular attention to the iatrogenic inflammatory patterns during hysteroscopy, as these sites do not have to be sampled. Their presence is increased by intrauterine manipulation.

Conclusion:
Iatrogenic acute inflammation stresses the importance of the following precautions:

- Use of small diameter instruments
- No dilation before diagnostic hysteroscopy.
- Determination of the endometrial sites to sample: preferably at the first passage of the scope.
- At the second passage, the additional iatrogenic inflammatory lesions can be misleading and in all case do not have to be sampled.
- Avoid getting out of the uterus before finishing the procedure

10- Histopathological artifacts correlated with hysteroscopy: improving biopsy technique.
In addition to iatrogenic inflammation and the pitfall of the isthmic region, it is capital to grow the awareness of gynecologists regarding the technical difficulties pathologists face when examining an improper endometrial sample. Some of the main characteristics of a good sample from the point of view of pathologists are sufficient amount of tissue; presence of surface epithelium; avoiding endometrium from lower uterine segment or basalis; avoiding tangential sectioning or compression of the sample; avoiding late secretory phase as lymphoid infiltrates become prominent; correct manipulation and conservation of the specimen [33,34].

From here, it becomes clear that a biopsy is best performed under visual control, thus targeting the suggestive hysteroscopic patterns, and allowing a proper sampling, avoiding the isthmus, and respecting the surface epithelium (figure8). Very importantly, the volume of the sample has to be significant. For this reason, among the validated hysteroscopic techniques of endometrial sampling, the punch biopsy technique which consists of removing the sample with the 5Fr grasping forceps through the working channel, unavoidably results in a small volume of tissue [39,40]. It requires multiple sampling, which implies more manipulation of the endometrium ultimately adding iatrogenic inflammation. The grasp biopsy however allows larger amount of tissue compared to the punch technique [13,39,40].

In post menopausal patients, scissors and bipolar electrodes are preferred due to the fibrotic stroma in this context especially in case of atrophy, making the grasping technique difficult to perform [13].

Conclusion: blind biopsy with a Pipelle or Novak are impertinent in inflammatory disorders because in addition to their commonly focal character, these tools could blindly sample the isthmus, the basalis or a scratched endometrium without a surface epithelium, thus compromising the histopathological examination.

Visual guided biopsy is capital: ideally at first passage, taking sufficient amount of tissue covered by a surface epithelium, with a particular attention to the isthmic bias and a proper conservation.

The information related to the patient has to be reported, with all the previously mentioned criteria.

Inflammatory versus dysfunctional disorder: two sides of a single coin.

The term “dysfunction” is etymologically the combination of “dys” (bad or difficult) and “function”. It designates failure or impairment of normal function. A uterus free from visually diagnosable malformations, synechiae, polyps, fibroids, malignancy or retained products of onception is considered organically normal. However, if there are abnormalities in the functions of the cells or tissues composing the organ, the term dysfunctional is commonly used.

In the hormone-sensitive female reproductive system, dysfunctional disorders are usually linked to hormone-imbalances. However, sex hormones have anti-inflammatory properties on the endometrium. In fact, progesterone’s action is crucial in decreasing inflammation in the endometrium and disturbed progesterone functioning results in pro-inflammatory phenotypes [27]. Conversely, chronic inflammation induces a progesterone-resistant state [27,30,41]. In other terms, despite hormones being normally secreted by the ovaries, their impact on the endometrium is insufficient due to the impaired expression of hormone receptors caused in an inflamed endometrium, subsequently resulting in the dysfunctional anomalies which are already described for chronic inflammatory processes.
This explains why the limit between dysfunctional and inflammatory states is blurred, as both are interrelated.

The formerly termed “dysfunctional bleeding” is only to be considered after exclusion of pregnancy-related disorders, medications, iatrogenic causes, obvious genital tract pathology and systemic conditions [42]. Since 2012, the PALM and COEIN terminology has abandoned the use of the term dysfunctional AUB and recommend the term AUB– E, the letter “E” standing for “Endometrial” factor [43,44]. This new classification separated endometrial from adenomyotic, dyscoagulative, iatrogenic and hyperplastic conditions. AUB-E means the function of the endometrium itself is impaired.

In terms of histopathology, the entity “dysfunctional endometrium” is still used and defines alterations in the normal cyclical changes of the endometrial mucosa [31]. However, in the studies where “dysfunctional bleeding” was investigated via blind sampling, histopathological correlations were very limited, as “normal proliferative or secretory endometrium” was prevalent irrespective of all groups of age [42,45]. Hyperplasia, in its different forms, is another predominant finding, in addition to inadequate sampling. In conclusion, histologically dysfunctional endometrium represented the least frequent finding, thus highlighting the bad correlations between these blind sampling methods and histopathology. All this highlights the superiority of visual biopsy.

Future therapeutic perspective in correlation with the notion of “non-shed endometrium” in C-IISE: cold resection of inflammatory lesions?

The entity of “non shed endometrium”, presented as a sine qua none prerequisite for a chronic inflammatory disorder to develop [11,22,24], stresses the importance of rethinking our therapeutic approach to this issue. In fact, superficial cold resection of the inflammatory lesions appears pertinent to consider in this context, especially in case of persistence after medical treatment. Micropolyps and areas of unequal thickness, especially if associated with edema and unevenly distributed glands, seem to deserve a particular attention, as they are highly correlated with histological signs of non-shed endometrium, as previously addressed. Some authors have already reported eradication of inflammatory lesions in approximately 80% of patients after biopsy or curettage [22].
Taking these facets into consideration would open new therapeutic doors for clinical trials. We propose that the inflammatory lesions be removed mechanically, either with scissors, grasping forceps or the cold loop of a mini-resectoscope. In case of relatively large areas to remove, and if the 5Fr grasping forceps is used, we propose to mimic the polypectomy technique introduced by Bettocchi et al [46]: place the open jaw of the forceps at the base of the biopsy site, gently push toward the fundus, reposition the grasper as many times as necessary until the endometrial area is detached (figure9). This gentle “grasp-push & repeat” technique allows gentle mechanical removal of larger surfaces. Scissors and cold loop can also be used.

Conclusion
Today, in our approach to endometrial inflammation, we deplore the use of consensual criteria which partly violate the very basics of histopathology, immunology and hysteroscopy. This is causing multiple diagnostic and therapeutic biases, explaining the heterogeneous data related to this disorder, as it is greatly dependent on each team’s practice setting [20]. No interpretable studies can come to fruition in the absence of pertinent definitions of the problem.

Going back to basics leads to a well-founded standardized practice, a capital prerequisite to uniform clinical trials and thus to exploitable data. Establishing well-grounded hysteroscopic and histopathological diagnostic criteria is of utmost necessity for evidence-based research.

It is very important to recall that C-IISE is not only incriminated in fertility issues, but is a well known risk factor of life-threatening diseases like endometrial neoplasia.

It is big time for hysteroscopists to grow their knowledge on endometrial histopathology and to conduct diagnostic hysteroscopy in a meticulous fashion, with particular attention to the above explained correlations.

We propose that IISE be diagnosed as follows:

Hysteroscopically: the presence during proliferative phase of one or more of the following morphologic patterns suggestive of inflammatory disorders: micropolyps, irregular thickness (slope or stairstep corrugated surface; embossed or debossed patterns), unevenly distributed glands and strawberry pattern. Edema, hyperemia and hemorrhagic spots are to be cautiously considered as they can reflect a transient IISE. These signs should stand as markers for the targeted biopsy site. The sampling has to be performed under visual control, within the inflammatory lesions, using small diameter instruments without prior dilatation. The good technique is the one allowing a sufficient amount of tissue from the inflammatory site, with respect to the surface epithelium, without compression and with a proper conservation. The isthmic localization needs to be specified as well as the menstrual phase. The lesions to biopsy need to be determined at the first entry of the scope.
Iatrogenic inflammatory patterns are not to be sampled. The notion of non shed endometrium needs further studies, as it would imply resection of the localized inflammatory lesions, especially if they persist after medical treatment.

Histologically: our conclusions support the recently recommended diagnostic strategy by pathologists [11]. Additionally, we propose to consider the presence of at least one epithelial/stromal change from table 4 in the absence of artifacts, in addition to a polymorphic inflammatory infiltrate containing at least one or more plasma cells by H&E staining. CD138 and MUM1 staining are to consider in the failure of H&E staining to identify plasma cells in the setting of stromal/glandular changes.

Compliance with Ethical Standards

Authors contribution: AD: Conceptualization, Data curation, Methodology, Project administration, Original draft, Editing. BvH: Critical review, Data curation, Supervision, Validation. MG: Critical review & Validation. All authors commented on previous version, read and approved the final manuscript

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Figure legend

Figure 1. Inter-glandular spaces: evenly distributed around the left tubal ostium (A); unevenly distributed: lateral view (B); associated with focal edema (C); associated with hyperemia (D).

Figure 2. F**ocal stromal edema at hysteroscopy: with hyperemia (A); with unevenly distributed glands and a micropolyp (B)**.

Figure 3. H**ysteroscopic patterns of C-IISE by the international working group on CE (in addition to stromal edema): micropolyps (A); strawberry aspect (B); hyperemia (C); hemorrhagic spots (D)**.

Figure 4. Irregular endometrial thickness at hysteroscopy: corrugated surface with a stairstep separating limit from the surrounding endometrium (A); embossed and debossed patterns with a slope separating limit from the surrounding endometrium (B & C) : 1, seen from a distance; 2: close view; 3: mechanical resection; white arrows: embossed surface; black arrows: debossed surface.

Figure 5. Focal hyperemia observed from a distance at the entry of the uterine cavity (A); closer view revealing in addition to hyperemia: a corrugated surface with irregular interglandular spaces (B).

Figure 6. Uterine isthmus at hysteroscopy. 1: distal limit, the internal histological os of the uterus; 2: proximal limit, the internal anatomical os of the uterus; 3: the length of the LUS; yellow arrows: intra-isthmic lesions.

Figure 7. Iatrogenic acute inflammation at hysteroscopy. Initial view at the first passage of the scope (A); Focal edema, hyperemia and hemorrhagic spots caused by intrauterine manipulation (B).

Figure 8. Targeted sampling using the 5F grasping forceps. Panoramic view (A), closer view (B), grasp and push technique (C-E); the endometrial sample (F).

Figure 9. M**echanical resection of the entire inflammatory site using the 5F grasping forceps. Irregular thickness and micropolyps (A); gentle grasp-push-repeat until the area is detached (B-D); strawberry pattern (E); removal with the 5F grasping forceps (F)**.

Table legend

Table 1. Additional histopathological criteria for C-IISE.

Table 2. Main histological characteristics of glandular anomalies in C-IISE. In bold character: the criteria which can be correlated with hysteroscopy.

Table 3. The main histological features of early, middle and late proliferative phases.

Table 4. The detailed histopathological criteria for C-IISE.

Stromal changes	Epithelial changes
— Superficial stromal edema — Spindled stroma — Increased stromal density: areas of hypercellularity. — Pleomorphic stromal inflammatory infiltrate dominated by lymphocytes, neutrophils, plasma cells and even eosinophils and histiocytes — stromal pigment deposition	— Abnormal glandular development : underdeveloped glands with less tortuosity and distension; and/or disturbance in maturation of the endometrium, with focal areas that are out of cycle: irregular or retarded maturation, — Glandular and stromal breakdown

Table 1: Additional histopathological criteria for C-IISE

Glandular changes in C-IISE	Histopathological main characteristics
1/atrophic endometrium	**Very low endometrium** with cuboidal surface epithelium, total or subtotal absence of glands and small, spindle-shaped stromal cells. Mitoses are lacking. Spiral arterioles are undeveloped. *** Focal pressure atrophy**: the same features but localized, whereas the surrounding endometrium is different➔ differences in height of the mucosa. Mechanical cause: pressure by a submucosal leiomyoma (response to a prolonged mechanical pressure).
2/ resting endometrium	Atrophic endometrium yet with more glands. They are rather straight and narrow, with a dense stroma
3/deficient proliferation	-Growth of the glands and stroma remains retarded as compared with that of the normal proliferative phase, with **moderate height of the mucosa** and thin/straight glands, small glandular and stromal cells, contrasting with

Figure 1

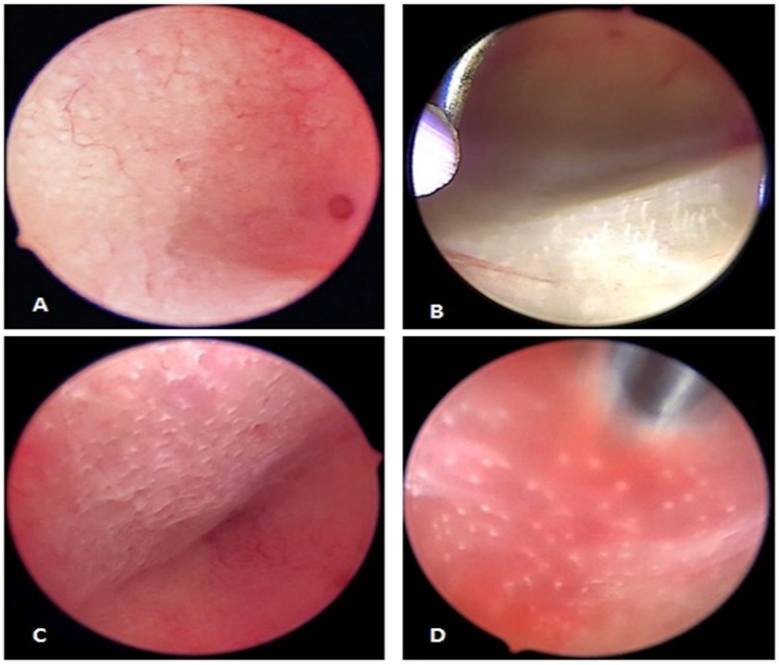
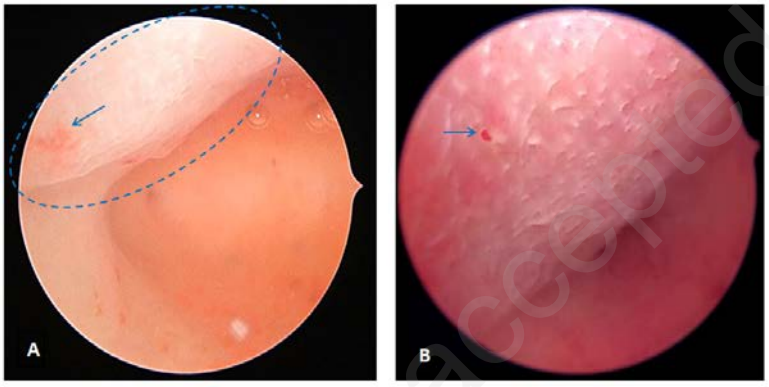


Figure 2



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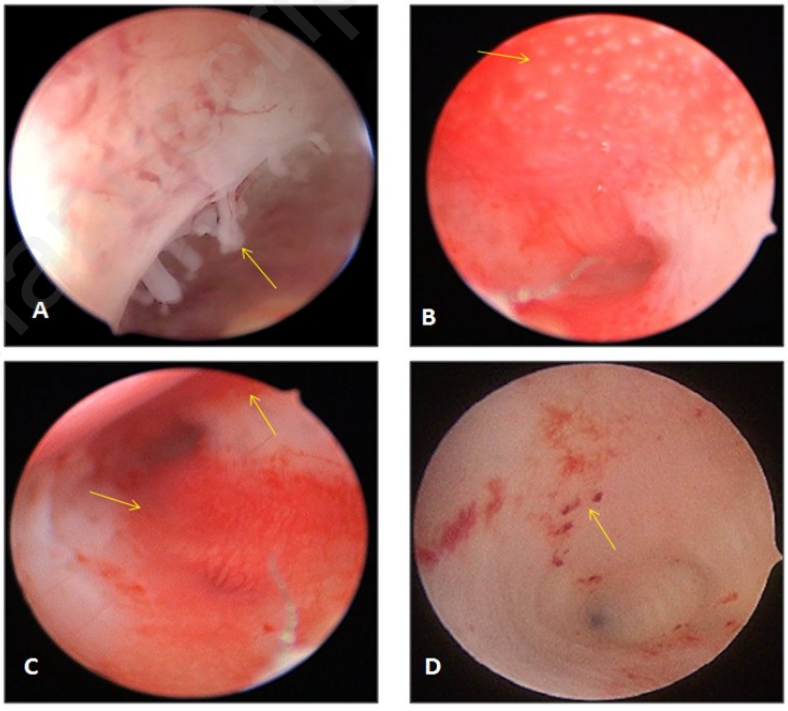


Figure 4

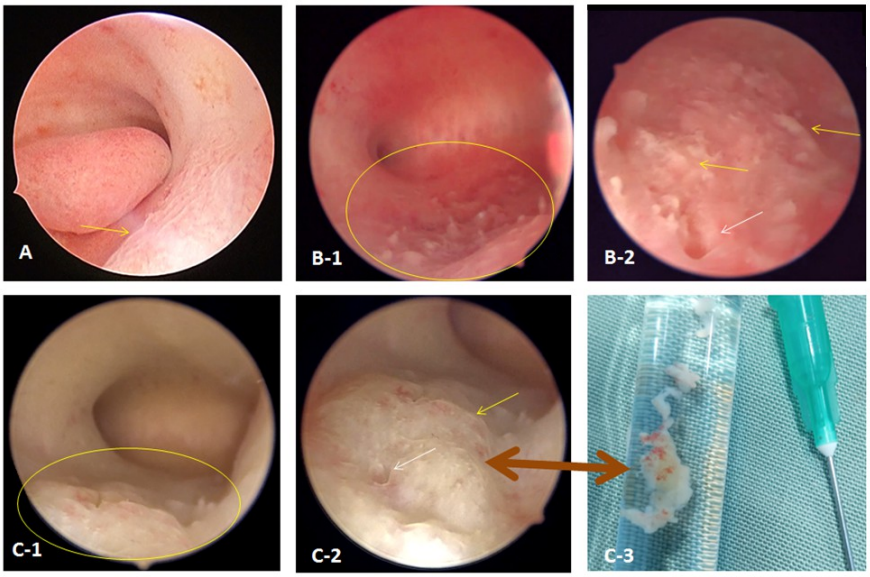


Figure 5

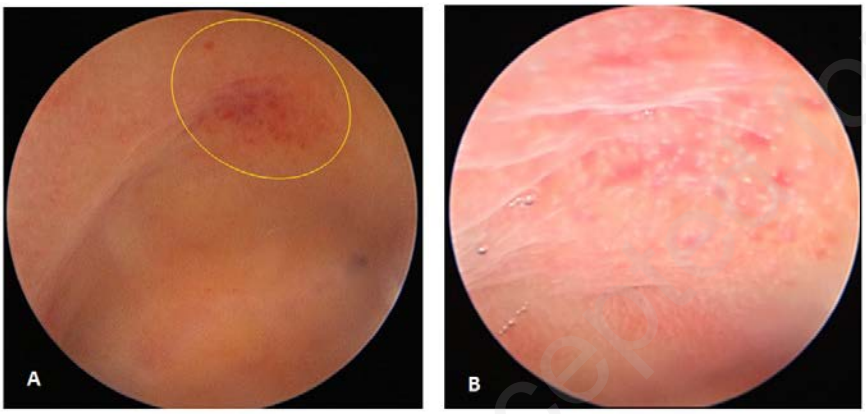


Figure 6

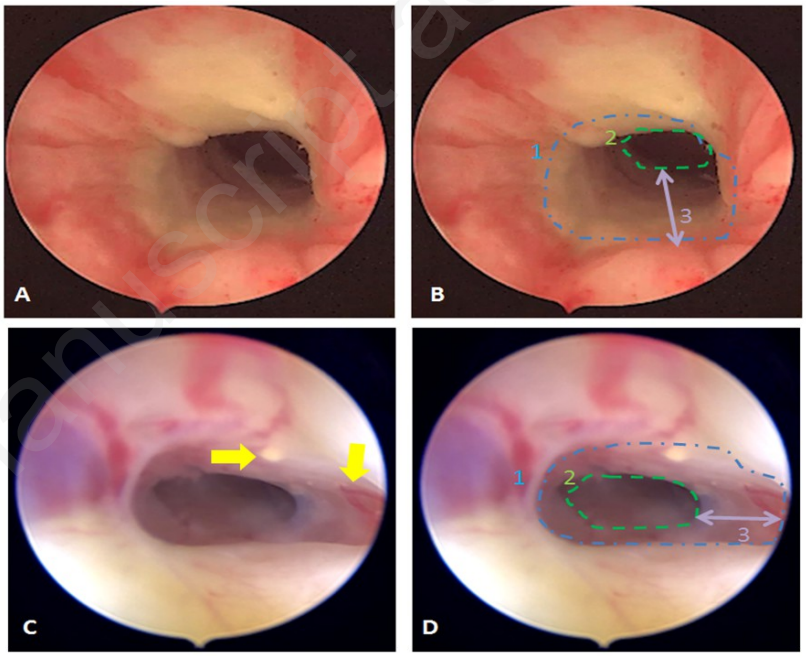


Figure 7

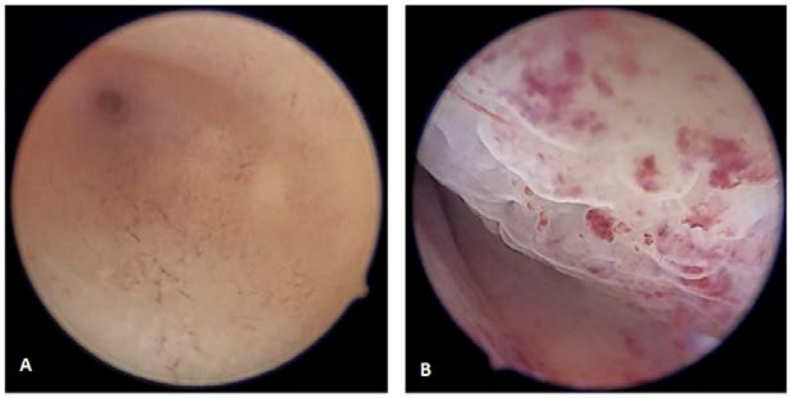


Figure 8

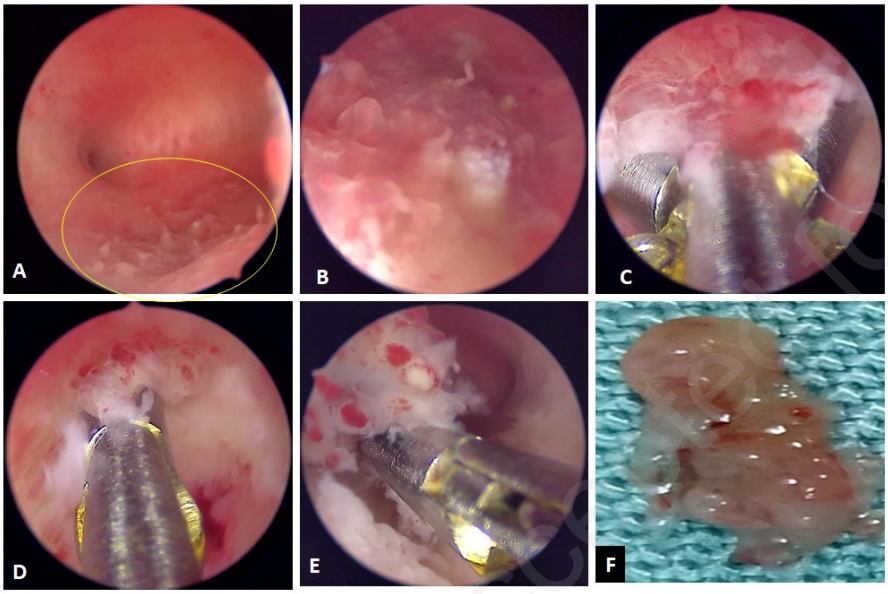
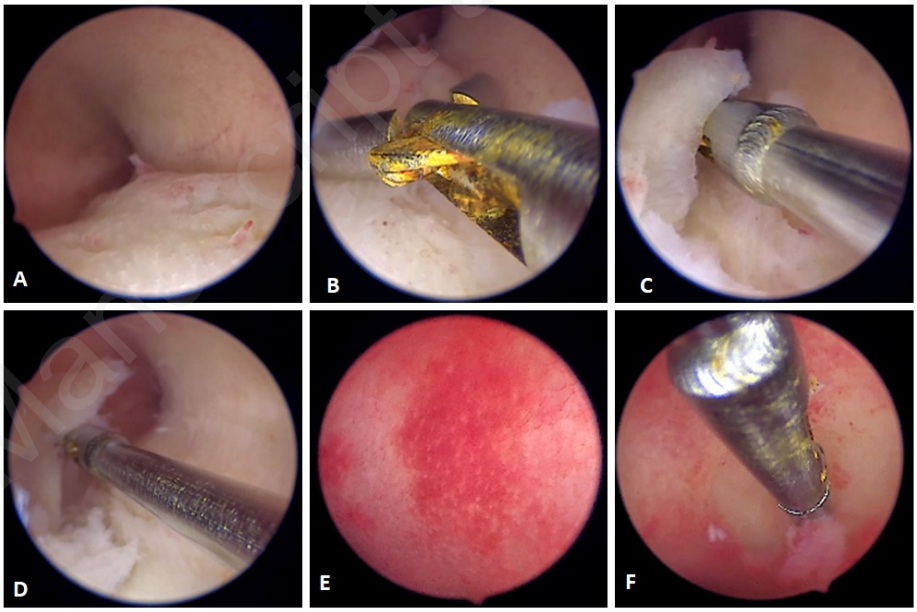


Figure 9



	a usual presence of edema.
4/ irregular (disordered) proliferation	-Growth of glands and stroma exceeds that of the normal proliferative phase. **Variable height of the mucosa** **-Endometrial glands: irregular in shape, width, and distribution**, with pseudostratified epithelial cells plus stromal hypercellularity and focal edema. -Described as a transitional form to simple glandular cystic hyperplasia.
5/ hyperplastic	-Increased ratio of glands and stroma compared with **irregular proliferation.** -Most or all of the endometrial glands are more or less cystically dilated and lined by pseudostratified, highly proliferating epithelium, -Dense undifferentiated stromal cells. * **Focal hyperplasia**: same features but limited to one or a few areas of the endometrium. Due to focal loss of progesterone receptors with normal receptor content of surrounding endometrium ➔ different height of the mucosa
6/ Surface and glandular epithelium changes	- severe long standing inflammation, - squamous and eosinophilic cell changes - A degree of architectural complexity and cytological atypia may also be seen: potential overdiagnosis of hyperplasia or carcinoma
7/Glandular and stromal breakdown	severe long standing inflammation **Irregular haphazard bleeding** leading to **interspersed foci of regenerating and shedding endometrium**, resulting in a **corrugated surface**

Table 2. Main histological characteristics of glandular anomalies in C-IISE. In bold character: the criteria which can be correlated with hysteroscopy.

Early proliferative phase	Flat epithelium; thin endometrium sparse, narrow, and straight glands evenly distributed glands cuboid or low columnar cells loose stroma of spindle-shaped cells undeveloped spiral arterioles
Mid proliferative phase	higher endometrium More numerous glands. Beginning of tortuosity evenly distributed Tall columnar cells. No pseudostratification yet interstitial edema Spiral arterioles: not seen
Late proliferative phase	Slightly less thick endometrium Marked tortuosity of glands evenly distributed pseudostratification Interstitial edema subsided Spiral arterioles: still absent

Table 3. The main histological features of early, middle and late proliferative phases.

Stromal changes	**Epithelial changes**
— Superficial stromal edema — Spindled stroma, — Pleomorphic stromal inflammatory infiltrate dominated by lymphocytes, neutrophils, plasma cells and even eosinophils and histiocytes — Increased stromal density: areas of	Abnormal glandular development : disturbance in maturation of the endometrium, with focal areas that are out of cycle. 1/ atrophic , 2/ resting, 3/insufficiently proliferated,

hypercellularity. The inflamed stroma is dense and less responsive to hormonal changes — stromal pigment deposition	4/ irregularly proliferated, 5/ hyperplastic — Glandular and stromal breakdown

Table 4. The detailed histopathological criteria for C-IISE.