Diagnostic significance of chronic endometritis macrotypes differentiation among women with reproductive losses

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**ABSTRACT**

To evaluate the prognostic value of a comprehensive endometrial study after early reproductive losses (RL). A group of 306 women with early RL (missed abortion \( n = 120 \), spontaneous miscarriage \( n = 120 \), and ineffective in vitro fertilization attempts \( n = 66 \)) were prospectively examined up to 6 months after the discharge of the uterus at the hospital bases of the Department of Obstetrics and Gynecology with the Course of perinatology at the PFUR Medical Faculty. Hysteroscopic macrotypes differentiation – hyperplastic \( (n = 89) \), hypoplastic \( (n = 94) \) and mixed \( (n = 87) \) – was carried out on the basis of features grouping characterizing the thickness, color and structure of the mucosa, the intensity of a vascular pattern in the presence of a chronic endometritis (CE). Evaluation of sonographic accuracy after hysteroscopic CE macrotypes differentiation showed the presence of false-negative conclusions: about unchanged mucosa (65.9%); endometrium polyps (3.5%); intrauterine synechiae (4.2%). Immunohistochemical staining with CD138 isolation showed higher diagnostic accuracy in CE detecting in comparison with the morphological method: in a hyperplastic macrotype (90.5% and 84.1%, respectively), hypo- (93.7% and 89.8%) and mixed (81.6% and 79.4%). Great diagnostic value is shown in identifying histopathic CE features in the context of hysteroscopic macrotypes differentiation in groups of women with RL.

**Introduction**

Chronic endometritis (CE) is an inflammatory process with a violation of endometrium structure and function [1]. The variability of its frequency can be explained by diagnostic difficulties. The diatrical opposite of the results of instrumental studies – from indisputable authenticity to the necessity of differentiated application – makes a full-fledged treatment of an endometrial defect, associated with a current loss of pregnancy, improbable. The risk of reproductive losses recurrence on the background of unrecognized and untreated CE cases justifies the need to analyze the informative value of the methods for diagnosing morphology-functional changes in the endometrium from the current position with the aim of optimizing the algorithms for examining women with miscarriage.

The objective is to evaluate the prognostic value of a comprehensive endometrial study after early reproductive loss.

**Material and methods**

In a prospective study, 306 women of reproductive age who were referred for examination to the hospital bases of the obstetrics and gynecology department with a course of perinatology at the PFUR medical faculty due to early reproductive losses between January 2014 and December 2016 were randomly selected.

Written informed consent for participation in the study was obtained from all patients.

Criteria for inclusion in the study: age 18–45 years, the presence of reproductive losses in anamnesis (not more than 6 months after the emptying of the uterus), missed abortion (MA), spontaneous miscarriage (SM), ineffective IVF attempts.

Exclusion criteria: gynecological and extragenital diseases in acute and subacute stage, genital organs malformation, antiphospholipid syndrome, systemic diseases and endocrinopathies.

The age of the patients ranged from 19 to 42 years old (on average, 28.6 ± 5.3 years).

The following groups were formed:
I – after a spontaneous miscarriage \( (n = 120) \),
II – missed abortion \( (n = 120) \),
III – ineffective IVF attempts \( (n = 66) \).

According to the results of a transvaginal pelvic organs’ study in the above-mentioned groups (on the 5th–9th day and the 22nd–24th day of the menstrual cycle), the following CE signs were detected: widening of the uterine cavity, heterogeneity of the endometrium structure, hyperoechoic inclusions in the basal layer, deformation of the middle part of the M-echo, in the luteal phase – ‘thin endometrium’ (less than 7 mm), its structural mismatch to the current phase of the menstrual cycle (homogeneity, ‘immaturity’).

Hysteroscopic examination of the uterine cavity was carried out on the 7th–9th day of the menstrual cycle with a panoramic observation and subsequent evaluation of the endometrium. Diagnostic CE criteria were stromal edema, focal or diffuse hyperemia, micropolyps.
Hysteroscopic CE macrotypes differentiation (hyperplastic \( n = 89 \)), hypoplastic \( n = 94 \), mixed \( n = 87 \) was performed on the basis of features grouping characterizing thickness, color and structure of the mucosa and vascular expression.

Verification of CE diagnosis was carried out by histological examination of mucosal samples obtained by pipelle biopsy during hysteroscopy on the 7th–10th day of the menstrual cycle.

Additionally, in case of necessity to clarify the mucosal state in the luteal phase, an aspirational pipelle biopsy with subsequent morphological examination was performed on the 22nd–24th day of the menstrual cycle.

Histological preparations were made according to a standard procedure with the staining of paraffin sections with hematoxylin and eosin, also with picrofixin according to Van Giesen method.

Immunohistochemical staining was performed using a two-step polymer imaging system called EnVision + Dual Link System-HRP from Dako Cytomation (Denmark). Primary antibodies CD138 (Type Moab, Isotype IgG1, kappa, RTU dilution) were used.

When evaluating the staining results with CD138 antibodies, the positive staining of the cell cytolemma was taken into account. The results obtained were expressed as an average number of immunocytes with the corresponding immunophenotype in the field of vision as \( \times 400 \) increased. The expression level was semi-quantitative: ‘weak’, ‘moderate’, in the corresponding morphological element.

Morphological criteria for CE setting were the following: lymphoid infiltration of the endometrial stroma, focal or diffuse, with plasma cells in the follicles; fibroplastic changes in the stroma, thickening of the vessel wall due to sclerosis and hyperplasia of smooth muscle cells.

Complete (with the mandatory presence of plasma cells in lymphoid infiltrates) and incomplete (some of the listed characteristics) CE morphological forms were identified.

Mathematical processing of the obtained data was carried out using standard SPSS software for Windows version 20 (SPSS Inc., Chicago, IL). Statistical processing of the study material included descriptive statistics, analysis of relationships and differences. To assess the significance of the differences in the quantitative characteristics, the Student’s t-test and F-Fisher criteria were applied, the differences were considered significant at \( p < .05 \).

**Results**

A set of sonographic CE signs made it possible to assume its presence among 77% of women with ineffective IVF attempts, 80% with missed abortion (MA), 70.8% with spontaneous miscarriage (SM). The inflammatory process in the uterine mucosa against the background of the remains of placental tissue was defined among 6.1% of women with IVF failures and 7.5% with SM. Echographic detection of endometrial polyps (EP) occurred among 9.2% of women with SM, 6.6% of women with MA, and least of all with ineffective IVF attempts (1.5%, \( p < .05 \)). Intrauterine adhesions was found among 6.7% of women with RL.

The detailed study of sonographic markers occurrence in groups with reproductive losses showed that endometrial structure mismatch to the phase of the menstrual cycle in the group with SM was found among 33.3% of women with SM, 1.5 times more often with MA compared with IVF failures (40.8% and 28% respectively, \( p < .05 \)) (Table 1). The presence of hyperechoic patterns on the background of heterogeneous M-echo was noted among 42% of women with MA and IVF failures, 28.3% of women with SM (\( p < .05 \)). Hyperechoic inclusions in the basal layer of the endometrium as a manifestation of focal fibrosis were observed among 12.5% of women with SM (\( p < .05 \)), 21.7% with MA (\( p < .05 \)) and 28.8% with IVF failures. Expansion of the uterine cavity was more common in the presence of MA anamnesis (10%), thinning of the endometrium (less than 7 mm) – among 40% of women with MA and a third of the remaining women (31.8%). The combination of the hypechoic contour around the M-echo and varicose veins of the myometrium against the background of sonographic CE signs (one or several) occurred among 41.4% of women.

The conclusion about the absence of CE signs was made among 35% of women with SM, 54.5% - with IVF failures and 21.7% with MA.

Hysteroscopic CE signs were found among 74.3% of women with reproductive losses, the remains of placental tissue – among 17.5% with NUP and 10.7% in the other groups. Visualization of intrauterine adhesions predominated in cases of SM and MA (10%) and occurred among only 3% of women with IVF failures. The frequency of endometrial polyps was greatest in cases with SM and IVF failure (10.7%). Unchanged endometrial mucosa was defined predominantly among women with IVF failures (15.1%), within SM and MA groups – 2.9%.

Reports of the often inconsistent hysteroscopic and pathomorphological conclusions against the background of separate attempts to identify various CE morphotypes make it possible to propose the concept of reducing macroscopic signs of the inflammatory process to a visually dominant endoscopic type.

The basis for endoscopic CE variants differentiation was a number of macroscopic features: in a mixed type mucosa is pale pink, uneven in color (50.6%) and thickness (77.8%), with alternating visually unchanged zones with thinning sites (27.6%) and a combination of micropolyps with edema and endometrial hyperemia (73.6%).

In a hyperplastic CE variant, mucosa is also pale pink, hypertrophied (65.5%), with more distinct vascular pattern, increased edema of the stroma (31.5%) and polypoid growing areas (71.9%), the combination of which (83.1%) was the most significant ‘stigma’ of the given macrotype.

Endoscopic CE characteristics in a hypoplastic macrotype: pale (85.1%), thinned mucosa of dull whitish color (78.7%), rare vascular patterns (33.0%) up to their absence, intrauterine synechiae (61.7%).

Further research to differentiate hysteroscopic macrotypes with morphological and immunohistochemical CE verification revealed a number of diagnostic errors.

Detailing of sonographic CE signs within the macrotypes showed incompliance of the endometrium with normal echographic criteria among more than half of patients with greater occurrence of individual ‘inflammatory’ stigmas in each variant.

Distinctive features in a hypoplastic CE macrotype were the presence of increased echogenicity areas of different magnitude and shape (48.9%) in the middle M-echo region (\( p < .05 \)); thinning of the endometrium (less than 7 mm) (56.4%) (\( p < .05 \)). The endometrial structure mismatch to the menstrual cycle was more common in hypo- and hyperplastic macrotypes (48.9% and 40.4%, respectively) than in the mixed ones (28.7%, \( p < .05 \)). The combination of a hypechoic contour around the M-echos and varicose veins of the myometrium against the background of other CE signs was less often detected in a hyperplastic macrotype (38.2% vs. 47.9%, \( p < .05 \)).
The absence of sonographic CE stigma in cases with reproductive losses – among 36.5% of women with SM, 21.7% – with MA, 54.5% – IVF failures (25% of women with hyperplastic, 47.1% in other types) – raises the issue of the diagnostic value of the study (81.2–83.1%).

Extrapolation of CE macrotypes in a group with reproductive losses allowed us to verify the greater specificity of hysteroscopic study and to point out the cases of hypodagnosis of diseases.

Some states hiding CE are defined: unchanged mucosa (6.1% – in a hyperplastic macrotype, singly (0.85%) - in the rest); micropolyps of endometrium (focal hyperplasia) – in hyperplastic and mixed types (2.6% and 0.9%, respectively); intruterine adhesions (in hypo – and mixed variants (3.3% and 0.9%, respectively)).

CE detection on the background of the remains of placental tissue did not correspond to the true frequency due to the difficulties in recognizing small particles of placental tissue, visualized in the form of a spongy structure of increased echogenicity, predominantly rounded. The observation of unrecognized CE episodes in making conclusions about endometrium micropolyps or focal hyperplasia was based on a shift in emphasis towards microfocal growth of the mucosa with hypodagnosis of mild signs of inflammation – puffiness and hyperemia.

CE indicator was the smallest in the group with IVF failures (83.3%), with comparable numbers among women after SM and UP (90.0% and 91.7%, respectively).

Morphological CE verification was determined by significant inflammatory infiltration of its stroma with lymphocytes: focal – predominantly in a hyperplastic macrotype (69.1%) (p < .05), diffuse – in hyperplastic (80.9%) (p < .05) and mixed ones (69%) (p < .05) (Table 2).

The refutation of the fact of plasma cells isolation, which is mandatory for chronic inflammation of the endometrium, is confirmed by their detection among 51.1% of women with a hyperplastic macrotype and 71.6% of the rest (p < .05). Dystrophic-atrophic cell damages in the basal and glandular layers of the endometrium, reflecting the intensity of apoptosis of integumentary epitheliocytes and glandulocytes, were found in 85.1% of mucosal samples in a hyperplastic macrotype, 37.9% in a mixed one (p < .05).

Point hemorraghes in the stroma were noted in the part of biopsy specimens with hyperplastic and mixed CE macrotypes (38.2% and 31%, respectively). Focal hyperplasia of the basal layer and smooth muscle cells was a characteristic feature of the hyperplastic CE macrotype (79.8%), which is somewhat more frequent than in the mixed type (62.1%) (p < .05).

Fibroblastic reconstruction of the stroma and spiral vessels walls was determined among 38.6% of women with mixed and hyperplastic CE macrotypes against the background of predominance in a hypoplastic one (74.5%, p < .05). Focal fibrosis was expressed in the densification of the fibrous tissue around vessels, diffuse one – in fibrosing of the vast endometrium areas, mainly around deep layers. Observations of endometrial dyskinesia and phase of the cycle, the absence of decidual-like metamorphosis and reduction on the background of sclerosis of the vascular zones, in combination with individual CE features, were determined among 72.3% of women with a hypoplastic type and 34% among the rest.

Histological verification made it possible to identify focal fibrosis of the stroma in the group with RL (7.6% in the group with IVF failures, 4.8% in MA, 1.7% in SM, p < .05) and endometrium micropolyps (focal hyperplasia) (3% – in cases of IVF failures, 6.1% – conclusion about morphologically unchanged mucosa).

The result of a comprehensive study of women with reproductive losses in amenorrhea was the vacuum aspiration of the remains of placental tissue (a group of women who had reproductive loss of pregnancy in the interval no more than two months ago) and polypectomy (n = 13 and n = 48, respectively), destruction of intrauterine adhesions.

Immunohistochemical (IHC) study of the presence of plasma cells marker CD138 in samples of biopsy specimens with an incomplete morphological CE pattern (14.9% with a mixed macrotype, 14.9% – hyperplastic, 27.0% – hypoplastic) confirmed CE presence, as well as in the endometrium with undetectable plasma cells originally identified as ‘normal tissue’ (2.8%), synechia/focal fibrosis (2.7%) and endometrial polyps/focal hyperplasia (1.1%).

The higher diagnostic accuracy of IHC syndecan-1 detection in comparison with the morphological method of disclosing

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**Table 1.** Sonographic signs of chronic endometritis.

| Groups | Mixed n = 87 | Hypoplastic n = 94 | Hyperplastic n = 89 | p  |
|--------|-------------|-------------------|-------------------|----|
| Endometrium thinning (less than 7 mm) | 20 (23) | 53 (56.4) | 0 (0) | p1,2 < .05 |
| Endometrial structure mismatch to the phase of the menstrual cycle | 25 (28.7) | 46 (48.9) | 36 (40.4) | p1,2 < .05 |
| Uterine cavity expansion | 7 (8) | 14 (14.9) | 3 (3.4) | p1,2 < .05 |
| Hyperechoic patterns on the background of heterogeneous M-echo | 38 (43.7) | 46 (48.9) | 37 (41.6) | p > .05 |
| Hyperechoic inclinations in the endometrium basal layer | 21 (24.1) | 21 (22.3) | 27 (30.3) | p > .05 |
| The combination of the hypoeochic contour around the M-echo and varicose veins of the myometrium | 39 (44.8) | 48 (51.3) | 34 (38.2) | p > .05 |
| Absence of CE signs | 41 (47.1) | 24 (25.5) | 41 (46.1) | p1,2 < .05 |

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**Table 2.** Morphological signs of chronic endometritis.

| Groups | Mixed n = 87 | Hypoplastic n = 94 | Hyperplastic n = 89 | p  |
|--------|-------------|-------------------|-------------------|----|
| Focal inflammatory infiltration in the basal layer and other areas | 25 (28.7) | 65 (69.1) | 11 (12.4) | p < .05 |
| Diffuse inflammatory stroma and endometrial cells infiltration | 60 (69.0) | 25 (26.6) | 72 (80.9) | p < .05 |
| Focal fibrosis of the stroma and spiral vessels walls | 35 (40.2) | 70 (74.5) | 33 (37.1) | p < .05 |
| Dystrophic-atrophic cell damages in the basal and glandular endometrium layers | 33 (37.9) | 80 (85.1) | 15 (16.9) | p < .05 |
| Focal hyperplasia of the basal layer and smooth muscle cells | 54 (62.1) | 16 (17) | 71 (79.8) | p < .05 |
| Dyschronosis of glandular epithelium proliferation | 27 (31.0) | 68 (72.3) | 33 (37.1) | p < .05 |
| Point hemorrhages in the stroma | 27 (31.0) | 0 (0) | 34 (38.2) | p > .05 |
| Plasma cells in the lymphoid infiltrates of the endometrium | 60 (69) | 48 (51.1) | 66 (74.2) | p1,2 < .05 |

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*Note:* p1,2 < .05 indicates statistically significant differences between the groups.
plasma cells for all macrotypes – hyperplastic (90.8% and 83.9%, respectively), hypo- (93.3% and 89.9%, respectively) and mixed (81.9% and 79.8%, respectively) – agrees with the data of other authors [2,3].

Taking into account final CE verification for each macrotype, the effectiveness of the method for recognizing the chronic inflammatory process in the uterine mucosa has been evaluated. The echographic research method does not have sufficient resolving power in CE detecting: the diagnostic value for revealing macro-types varies within the limits of – 81.2–83.1%. The hysteroscopic method is more informative, its potential being varied in higher limits (87.5–94.2%). The morphological research method should be considered highly specific and diagnostically accurate. However, we demonstrated the possibility of obtaining more detailed information when using the immunohistochemical technique in CE diagnosis.

Discussion

According to our study, the acceptability of individual sonographic signs for screening the chronic inflammatory process in the endometrium is questionable, which proves the erroneous opinion about the prevalence of unchanged uterine mucosa among infertile patients [2].

The need to search for any consistent patterns of certain CE signs prevalence explains the tendency to group the ‘stigma’ identified by various research methods aiming to differentiate histopathological features of the inflammatory process in the uterine mucosa. The effectiveness of hysteroscopy in the detection of endometrial damage against the background of chronic inflammation has been repeatedly proved [4–6], but the detection of micropolyps in some cases, in others – thinned hyperemic mucosa, as well as the discrepancy of endoscopic and morphological characteristics, confirm the need for correction of the traditional visual picture interpretation.

The diagnostic value of an isolated hysteroscopic assessment is challenged by the facts of detecting CE ‘masks’ – masking the process with intrauterine adhesions and visually unmodified mucosa.

Insignificant indices of the divergence in hysteroscopic and morphological conclusions about chronic uterus inflammation in hyperplastic and mixed CE macrotypes are half as much as in hypoplastic ones, according to the data of other authors. There are reports of histological CE confirmation in 57.5% of those detected with hysteroscopy and 66%, as well as of the inverse ratio (43.6% and 66.3%, respectively) [6,7].

The statements about the higher hysteroscopy diagnostic accuracy (89.4%), in comparison with the histological method, are based on restrictive criteria for the diagnosis, which require the presence of plasma cells in the lymphoid infiltrates of the endometrium [8,9].

The detection of such a symptom in only two-thirds of women with hyperplastic and mixed CE macrotypes and a half – with a hypoplastic one allows to refute the fact of their constant presence in the inflammatory process. Background processes of inflammatory stromal infiltration of lymphocytes – focal (pre-dominantly with a hypoplastic macrotype) and diffuse (with the remaining) – exclude the probability of CE overdiagnosis. Isolated plasma cells detection is associated with a number of non-CE-related conditions: a predecidual reaction in the late secretory endometrium, mononuclear inflammatory cell infiltration, proliferation of stromal cells and plasmacytid reaction of stromal cells [1]. False informative results in the groups were determined by the overdiagnosis of endometrium polyps – with the morphological prevalence of CE signs on the background of placental tissue remains.

Uterine mucosa thinning because of intrauterine adhesions in more than half of women with hypoplastic CE macrotypes changed the inflammatory process into the focal fibrosis typical of Asherman’s syndrome.

The resolution of doubtful cases, with incomplete morphological CE pattern, took place during immunohistochemical study with CD 138, which effectiveness in making a decision to diagnose the disease by pathomorphologists is undeniable [3,8].

Analysing the detailed correlation of the basic changes in the hysteroscopic structure of the endometrium makes it possible to define specific CE features within each macro-type.

The correlation between the endometrium thickness and changes in its echosstructure (hyperechoic inclusions in the basal layer), the chronological inconsistency of the menstrual cycle with the hypoplastic macrotype corresponded to the ideas about a significant violation of stromal–epithelial relationships with a reduced volume of vessels and a distinct fibroplastic transformation of the stroma [10].

It is logical to assume that the dystrophic changes in integumentary epithelial cells and gland cells can be the final phase of chronic inflammation, as well as a consequence of the primarily emerging and progressive degeneration of the epithelium parallel to the sclerosis of the stroma and the reduction of the vessels of the microcirculatory bed. The essence of discussions about the genesis of this pathomorphosis is to ascertain the change in the receptivity of the endometrium in a hypoplastic macrotype, which is most appropriately considered within the histopathological features of endometrial damage.

Indications for a significant edema of the stroma in combination with hyperemia and polyloid formations of not more than 1 mm with hyperplastic CE macrotype allow us to regard them as diagnostic markers. Similar conclusions are consistent with reports on the detection of micropolyps in 93.7% against the background of the inflammatory process and the possibility of assessing the severity of histological damage in liquid hysteroscopy [11].

Morphological markers of a hyperplastic CE macrotype were the following: focal hyperplasia of the basal layer and smooth muscle cells, which, according to separate reports, turned out to be a consequence of activation of the proliferative activity of the epithelial structures of the inflamed endometrium. The diagnostic value of hysteroscopy in a hyperplastic CE macrotype was not only in visualization of the pathological process, but also in the possibility of controlling the rational removal of altered tissue sites.

A variegated pattern of alternation of hypoplastic pale mucosa with zones of edematous stroma and micro-polyloid growing areas in a mixed CE macrotype conformed to structural mosaicism of the mucosa (fibrosis and atrophy), probably due to weakened regeneration on the background of endometrial injury.

Dyschronosis observations of endometrium and phase of the cycle, the absence of decidual-like metamorphosis and inadequacy of angiogenesis combined with certain CE features did not contradict the data on luteal phase insufficiency being caused by the slow inflammatory process in the uterine mucosa [12]. This fact allows to refute the opinion about the isolated role of progesterone deficiency conditions in the genesis of miscarriage, directing research thought along the way of emphasis on the change in receptivity as a cause of implantation failure in cases of CE.

A prolonged course of timely undiagnosed CE with its inflammatory infiltration and fibrosis is accompanied by mucosal
architectonics remodeling and aberrant expression of extracellular matrix molecules.

The change in the intercellular interaction extends to the endometrial receptor apparatus, determining the hormone-conditioned disruption of the ‘dialogue’ with the embryo during the ‘implantation window.

Conclusions

The heterogeneity of data on CE frequency among patients with RL is determined by the complexity of interpreting the results of various research methods.

The feasibility of an integrated approach to CE diagnosing in a group of patients with reproductive failures increases with differentiating macrotypes of the inflammatory process.

We believe that the concept of reducing macroscopic characteristics to a visually dominant type allows to improve the tactics of managing CE patients, emphasizing various histopathic features of the inflammatory process.

Summarizing the data of CE pathomorphism, we should point out the variability of phenotypic expression of epithelial cells in response to endometrial inflammation, the degree of which is determined by microbial infection and the degree of local autoimmune aggression.

The change in the uterine receptivity of the inflamed endometrium interferes with its full reactivity to a certain gene expression by the production of ‘competent’ molecular mediators that provide hormone-mediated feto–mother interaction.

Disclosure statement

No potential conflict of interest was reported by the authors.

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