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Role of endothelial dysfunction in reducing ovarian reserve in women with chronic salpingophoritis

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ABSTRACT

Chronic salpingophoritis is a critical inflammatory disease of the pelvic organs and is a risk factor of diminished ovarian reserve. Notably, chronic salpingophoritis is accompanied by decreased blood supply in the uterus. Circulation in the peripheral bloodstream of pathological inflammatory factors and immune complexes in the blood contributes to the development of oxidant stress, which damages the endothelium vessels and leads to impairment of its functions. Against the background of long-term pathological reactions in the inflammation center forms a vicious circle, wherein endothelial dysfunction plays a crucial role in the development of sclerotic processes in the ovarian tissues and endocrine function of the organ. These persistent morphofunctional disorders contribute to the delay of follicle maturation, which leads to decreased ovarian reserve. The result of the study reveals that, in women, during the peak of reproductive function, having chronic salpingophoritis and reduced ovarian reserve, blood flow in the ovarian arteries deteriorates. Pronounced changes in the dopplerometric blood flow parameters in the ovarian arteries are caused by damage to the vascular wall such as distortion of its tone and disorders in the production of vasoconstrictors and vasodilators (NO and ET-1). This is exacerbated by blood vessel endothelial thrombogenicity and results in long-term endothelial dysfunction, which contributes to impaired hormonal function of the ovaries. Notably, a persistent disorder of vasodimotor and thrombogenic endothelial function leads to a decrease in recruitment of follicles in the ovaries and reduction in ovarian reserve in the selected patient population.

Keywords: pelvic inflammatory disease; chronic salpingo-oophoritis; endothelial dysfunction; ovarian reserve; flow-mediated dilation.

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Роль эндотелиальной дисфункции в снижении овариального резерва у женщин с хроническим сальпингоофоритом

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АННОТАЦИЯ

Среди воспалительных заболеваний органов малого таза особое место занимает хронический сальпингоофорит, который является одним из факторов риска снижения овариального резерва яичников. Известно, что хронический сальпингоофорит сопровождается ухудшением кровоснабжения в придатках матки. Циркуляция в периферическом кровотоке патологических провоспалительных факторов и иммунных комплексов в крови способствует развитию оксидантного стресса, что повреждает эндотелий сосудов и ведёт к нарушению его функций. На фоне длительно протекающих патологических реакций в очаге воспаления формируется порочный круг, в котором эндотелиальная дисфункция играет важную роль в развитии склеротических процессов в тканях яичников и нарушении эндокринной функции органа. Эти стойкие морфофункциональные нарушения способствуют задержке созревания фолликулов, что приводит к снижению овариального резерва.

В результате проведённого исследования выявлено, что у женщин, имеющих хронический сальпингоофорит и сниженный овариальный резерв, в период расцвета репродуктивной функции ухудшается кровоток в артериях яичников. Выраженные изменения допплерометрических параметров кровотока в яичниковых артериях обусловлены стойким повреждением сосудистой стенки в виде извращения её тонуса, нарушения выработки вазоконстрикторов и вазодилататоров (оксида азота и эндотелина-1). Это усугубляется тромбогенностью эндотелия сосудов и приводит к длительной эндотелиальной дисфункции, что способствует нарушению гормональной функции яичников. Доказано, что стойкое расстройство сосудодвигательной и тромбогенной функций эндотелия приводит к снижению рекрутинга фолликулов в яичниках и сокращению овариального резерва у выбранного контингента больных.

Ключевые слова: воспалительные заболевания органов малого таза; хронический сальпингоофорит; эндотелиальная дисфункция; овариальный резерв; поток-опосредованная вазодилатация.

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内皮功能障碍在患有慢性输卵管炎妇女的卵巢储备功能下降中的作用

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摘要

在盆腔器官炎症疾病中，慢性输卵管炎占有特殊地位，它是卵巢储备功能下降的危险因素之一。众所周知，慢性输卵管炎伴有子宫附件血供恶化。血液中的病理性促炎因子和免疫复合物在外周血中循环，导致氧化应激的产生，从而损害血管内皮，导致其功能受损。在炎症病灶长期病理反应的背景下，形成恶性循环，其中内皮功能障碍在卵巢组织硬化过程和器官内分泌功能失调的发展中起着重要作用。这些持续的形态功能障碍导致卵泡成熟延迟，从而导致卵巢储备功能下降。

研究显示，患有慢性输卵管卵巢炎和卵巢储备减少的女性在生殖功能鼎盛时期卵巢动脉的血流会恶化。卵巢动脉血流多普勒测量参数的明显变化是由血管壁持续受损造成的，具体表现为血管张力失常、血管收缩剂和血管舒张剂（一氧化氮和内皮素-1）的生成受阻。血管内皮的血栓形成加剧了这种情况，并导致长期的内皮功能障碍，从而导致卵巢激素功能受损。事实证明，血管内皮的血管运动和血栓形成功能持续失调会导致卵巢中的卵泡募集减少，并降低部分患者的卵巢储备功能。

关键词：盆腔炎；慢性输卵管炎；内皮功能障碍；卵巢储备；血流介导的血管扩张。

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BACKGROUND

Pelvic inflammatory diseases (PIDs) persist in their relevance to women of reproductive age and exert an adverse impact on their quality of life and reproductive health. These diseases experienced a 1.8-fold increase in prevalence during the initial decade of the 21st century alone [1]. Reproductive potential deteriorates with each exacerbation of PIDs, resulting in a twofold increase in the frequency of infertility [2, 3]. Chronic salpingoophoritis (CSO) occupies a unique position within this group of diseases, with a prevalence of 60–85% among all PID patients [4] and more than 30% among all women of reproductive age [5].

The chronic inflammatory process in the uterine appendages is accompanied by inadequate vascularization of tissues, which results in structural and functional disorders. These disorders lead to delayed follicular growth, atresia, and a subsequent decrease in ovarian endocrine function, impaired folliculogenesis, and occasionallymass death of the follicular apparatus [6–9].

Among couples with infertility, the frequency of low ovarian reserve reaches 35% [10]. The efficacy of IVF is six times lower, and the efficiency of overcoming infertility in such patients is 2.5 times lower [11]. Furthermore, women in this demographic exhibit an increased risk of reproductive losses when the long-awaited first pregnancy occurs [12]. The ovarian reserve of women of reproductive age is known to be diminished in association with CSO [13]. In female infertility, the incidence of CSO reaches 45% [14]. The duration of infertility and hormonal dysfunction is prolonged because of the intensification of apoptotic mechanisms in the ovary due to chronic inflammatory processes [15]. Therefore, it is imperative to identify novel pathogenetic mechanisms that account for the decline in ovarian reserve and to develop methods to restore ovarian function.

Endothelial dysfunction (ED) is presently a significant factor in the development of various chronic inflammatory diseases [16–20]. The regulation of vascular tone and leukocyte adhesion is influenced by chronic inflammation, which impairs the anticoagulant and anti-inflammatory properties of the vascular wall [17, 18]. The synthesis of the primary vasodilator, nitric oxide, is suppressed by the production of cytokines, vasoconstrictors, and oxidative stress, which in turn affect the onset and progression of ED [21]. Prolonged exposure to hypoxia, toxins, and proinflammatory agents in the pathological focus also causes vascular wall damage, gradually depleting and modifying endothelium's compensatory abilities, because of which vasoconstriction becomes the predominant response of endothelial cells [22, 23]. Ovarian dysfunction is exacerbated, and the chronic course of the pathological process is perpetuated by the deterioration of blood supply to the uterine appendages in conjunction with CSO [24–26].

The current search for methods to enhance fertility and preserve ovarian reserve is highly relevant, as the demographic issue is becoming more prevalent. The study of the role of ED in reducing ovarian reserve in CSO patients of reproductive age will enable the development of novel approaches to pathogenetic therapy to enhance follicle recruitment in the ovaries and, therefore, the restoration of fertility.

Aim. This study aimed to evaluate endothelial function and hemodynamic features in ovarian arteries in CSO patients with reduced ovarian reserve.

MATERIAL AND METHODS

This prospective, open, comparative study included 65 women of reproductive age who presented to the gynecological clinics in Volgograd. The primary group consisted of 45 CSO patients who have been unable to conceive for one year despite regular sexual activity without contraception. The control group included 20 clinically healthy women whose purpose was pre-pregnancy preparation.

The inclusion criteria for the study were: females in the 25–35 year age group (period of optimal reproductive function) with willingness to conceive; presence of bilateral fallopian tube patency; and those who were willing to provide informed consent to participate in the study. Patients younger than 25 years and older than 35 years with acute PID and extragenital localization, those who had undergone surgical interventions on pelvic organs, as well as women who refused to participate in the study, were excluded.

The levels of follicle-stimulating hormone (FSH) and estradiol were measured in the follicular phase of the cycle for all patients. The ovarian reserve was evaluated using blood anti-müllerian hormone (AMH) levels on days 2–3 of the menstrual cycle, ovarian volume, and antral follicle count (AFC) by ultrasound on days 5–7 of the menstrual cycle.

To evaluate blood circulation in the ovarian arteries, angle-independent indices that characterize peripheral vascular resistance (pulsation index PI and resistance index IR) were assessed.

The endothelial function in patients of both groups was evaluated by serum levels of nitric oxide, endothelin-1, Willebrand factor (WF), thrombomodulin, and the cuff test, which characterizes post-occlusion vasodilation (POVD) of the brachial artery (BA) with reactive hyperemia. This technique was proposed by D.S. Celermajer et al. in 1992 as a non-invasive method to assess vasomotor function and is used as a marker of ED [27]. The BA diameter was determined using ultrasound guidance at rest. A pneumatic cuff was used to constrain the BA for 5 minutes at a pressure that exceeded the systolic blood pressure by 50 mm Hg, thereby inducing reactive hyperemia. The cuff was subsequently deflated, and the BA diameter was remeasured after 1 minute. The formula for POVD was as follows: POVD (%) = (post-test BA diameter – initial BA diameter)/initial BA diameter × 100%. POVD less than 10% and vasoconstriction were regarded as indicators of ED. An expert-class ultrasound device, Mindray DC-70Exp, was employed to conduct the cuff test and to

evaluate ultrasound parameters (ovarian volume, AFC, ovarian artery dopplerometry).

The data were analyzed statistically in the Jupyter Notebook environment using the scipy, numpy, and pandas packages. The program PASS (NCSS) was used to perform the preliminary calculation of the sample, which considered the expected differences between groups, the accepted error of the first kind α=5%, and the statistical power 1–β=80%. Data were tested for conformity to normal distribution using the Shapiro-Wilk criterion. Means (m) and standard deviations (sd) were computed and presented in m±sd format for quantitative data with a normal distribution; 95% confidence intervals (95% CI) were calculated for means. Student's t-test was used to compare the means of the indicators. If the distribution was not normal, the median (me), interquartile range (q3), and lower quartile range (q1) were calculated; the data are presented in the format me [q1; q3]. The means of the analyzed categories were compared using the Mann-Whitney test. The statistical significance level was established at p=0.05.

RESULTS

The mean age of the patients was comparable and was 33.00±2.31 years and 32.40±2.36 years in the primary and control groups, respectively (p=0.34). Statistically significant differences were observed in the hormonal profile indicators of the study participants (Table 1). In the primary group, the estradiol level was 2.7 times lower and the FSH level was 1.6 times higher than in the group of healthy women (p <0.001). The AMH level in the main group was only 2.36±1.54 ng/mL, which was three times lower than that in the control group (p <0.001).

Pelvic ultrasound data analysis (Fig. 1) in the primary group patients revealed that their ovarian volume was 1.5 times smaller than that in the control group (6.26±1.93 cm^3 (95% CI [5.7; 6.8]) vs 9.67±1.14 cm^3 (95% CI [9.1; 10.2]); p <0.001. Notably, ovarian AFC in CSO patients was 5.40±1.52 (95% CI [4.9; 5.9]), which was 1.8 times lower than in healthy women (p <0.001). Doppler-based ovarian artery parameters in the primary group patients were expressed in the increase of PI by 3.3-fold (2.50±0.75 (95% CI [2.3; 2.7]) vs. 0.75±0.22 (95% CI [0.64; 0.85]); p <0.001; and IR increased by 1.8 times (0.84±0.10 (95% CI [0.81; 0.87]) vs. 0.48±0.10 (95% CI [0.43; 0.53]); p <0.001. The results characterize a highly resistant blood flow in the ovarian vessels in the background of CSO. In comparison to healthy women, the indices of ED markers in the blood serum of patients in the main group were substantially elevated by 2.5 times (p <0.001; Table 2). The analysis revealed that the level of thrombogenic substances (WF) in women with CSO was two times higher than in healthy women, while the level of atrombogenic thrombomodulin was 1.4 times lower than in the healthy women group (p 0.001).

The mean BA diameter at rest did not differ between the primary group and the control group, as indicated by the ultrasound evaluation of endothelial vasomotor function (p=0.52). However, after 5 minutes of occlusion, the endothelium-dependent vasodilation of the BA in CSO patients was negative in most cases, averaging –0.82±10.60% (95% CI [–2.4; 4.0]), with values in the control group of 19.30±4.70% (95% CI [17.1; 21.5]), p <0.001.

DISCUSSION

The study of the hormonal status of patients with reduced ovarian reserve and CSO revealed a 2.7-fold reduction in

Table 1. Hormonal profile of the women being studied

Studied hormones	Main group	Control group	*p*
Follicle-stimulating hormone (mIU/ml)	8.62±3.70 95% CI [7.60; 9.70]	5.39±1.40 95% CI [4.70; 6.00]	<0.001
Anti-Mullerian hormone (ng/ml)	2.36±1.54 95% CI [1.89; 2.82]	7.12±1.87 95% CI [6.20; 8.00]	<0.001
Estradiol (pmol/l)	52.30 [33.60; 102.80]	197.00 [171.00; 279.00]	<0.001

Table 2. Endothelial dysfunction markers

Markers of endothelial function	Main group	Control group	*p*
Nitric oxide (μmol/l)	11.70±0.30 95% ДИ [11.60; 11.80]	4.87±1.30 95% ДИ [4.30; 5.50]	<0.001
Endothelin-1 (pg/ml)	1.13±0.12 95% ДИ [1.10; 1.17]	0.40±0.03 95% ДИ [0.39; 0.40]	<0.001
Von Willebrand factor (U/ml)	2.20±0.40 95% ДИ [2.10; 2.30]	0.92±0.20 95% ДИ [0.83; 1.00]	<0.001
Thrombomodulin (pg/ml)	54.60±4.30 95% ДИ [53.30; 55.90]	86.40±5.70 95% ДИ [83.70; 89.10]	<0.001

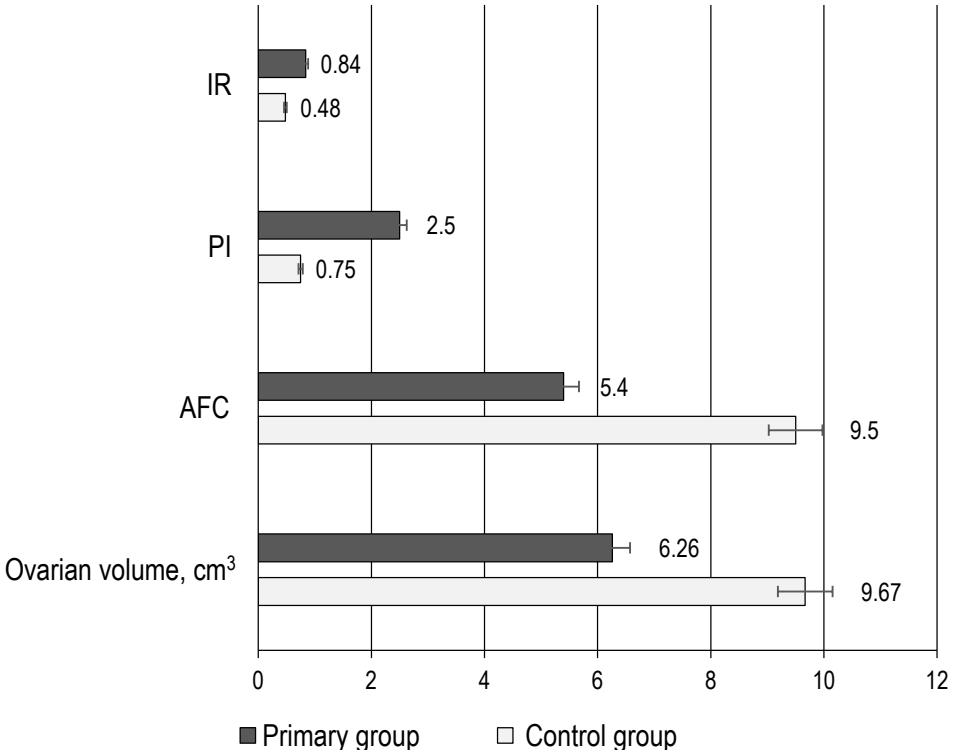

Fig. 1. Ultrasound of ovaries and Dopplerometry of ovarian arteries: IR, resistance index; PI, pulsatility index; AFC, number of antral follicles.

estradiol levels, a 3-fold decrease in AMH levels, and a 1.6-fold decrease in the FSH levels. The data collected indicate a disturbance of ovarian endocrine function and folliculogenesis in CSO patients. A decrease in ovarian volume and AFC in the main group that is more than 1.5 times greater than that in the control group suggests a reduction in ovarian reserve in patients with CSO. Recently, AMH and AFC have been regarded as more promising indicators in the evaluation of ovarian reserve due to their high sensitivity and specificity in predicting ovarian response, as well as their satisfactory inter-cycle reliability [28]. The doppler-based parameters in the primary group patients were found to be higher than those of the control group. Since high PI and IR values suggest a decline in ovarian perfusion [29], the data obtained indicate a deterioration of intra-ovarian blood flow in CSO patients.

In the primary group patients, the level of thrombogenic substances increased 2-fold, and the level of non-thrombogenic substances was lower compared to the control group. The degree of vascular endothelial injury is also reflected in the increase in serum levels of WF [30]. Thus, the study of ED markers revealed the thrombogenic state of the endothelium in CSO patients and its dysfunction. The endothelial function study, which employed the cuff test, revealed a paradoxical vasomotor response of the vessel, as evidenced by negative values of BA vasodilation following occlusion. These findings confirm the presence of ED in CSO patients.

CONCLUSIONS

The study demonstrated that the hormone-producing function of the ovaries and folliculogenesis were impaired in CSO patients. Ultrasound and dopplerometry data have verified that the ovaries' volume decreased, and their blood flow deteriorated in conjunction with the chronic inflammatory process in the uterine appendages. The serum markers of vascular dysfunction were revealed to be elevated, and the test with POVD demonstrated a significant impairment of endothelial vasomotor function, indicating the presence of ED in CSO patients. Ovarian function is adversely affected by persistent changes in hemodynamics and vascular endothelial function in the pathologic focus, leading to a decrease in ovarian reserve. This confirms the importance of influencing all components of the pathologic process to achieve childbearing objectives.

ADDITIONAL INFO

Authors' contribution. T.S. Klimentova — examination of patients, review of literature, collection and analysis of literary sources, preparation and writing of the text of the article; N.A. Burova — concept development, writing of the text and editing of the article; O.A. Yarygin — collection and analysis of literary sources, preparation and writing of the text of the article; L.G. Burdenko — literature review, examination of patients, writing the text of the article. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

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