

## Possibilities for Implementing Reproductive Function in Endometrial Cancer, Atypical Endometrial Hyperplasia in PCOS and Infertility

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### Abstract

**Introduction:** The common and key in the pathogenesis of PCOS and chronic endometritis (CE) is the chronic course of inflammation [2-4]. Persistent damage to the endometrium leads to impaired endometrial receptivity and creates conditions for the development of infertility [5,8].

**The Purpose of the Study:** Was to identify the most common endometrial pathology in women with PCOS and infertility and to analyze the effectiveness of infertility treatment in women with this pathology, to evaluate reproductive outcomes.

**Materials and Methods:** Analyzed 240 case histories of patients of LLC "Clinic of Professor Pasman", Novosibirsk Clinical Oncological Dispensary for the period 2012-2022, diagnosed with PCOS, Infertility. Patients were included in the study group by random sequential selection.

The frequency of occurrence of each of the PCOS phenotypes was analyzed, as well as the prevalence of endometrial pathology. The most common pathology is chronic endometritis, therefore, in addition to the standard methods of treating infertility in PCOS, CE was additionally treated by the following methods: photodynamic therapy (PDT) and the introduction of a macrophage medium into the uterine cavity.

**Results and Discussion:** In 61% of cases, hysteroscopy was performed and endometrial pathology was detected, which indicates the need to diagnose the endometrium in women with PCOS, especially before using ART. The most common endometrial pathology is chronic endometritis (61.6%). PDT and the introduction of macrophage medium increase the effectiveness of the treatment of CE and infertility in PCOS. The results obtained indicate a high incidence of PCOS without hyperandrogenism and obesity.

**Keywords:** PCOS; Infertility; Chronic Endometritis

### Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women, reaching 8 - 13% in women of reproductive age [2,3] often recorded in patients with signs of hirsutism - the incidence of PCOS among this group reaches 72.6%. PCOS is also a familial disease: studies of twins show that it is hereditary in about 70% [4].

The main clinical manifestations of PCOS are oligomenorrhea, irregular menstruation, and infertility. Frequent morphological mi of the endometrium in this pathology are chronic endometritis with impaired endometrial receptivity, endometrial hyperplasia [4], which develops against the background of hyperandrogenemia, insulin resistance (IR), hyperinsulinemia, obesity and metabolic syndrome (MS).

For the diagnosis of PCOS, the Rotterdam criteria [8] are used: 1) anovulation or infrequent ovulation; 2) polycystic ovarian changes detected by ultrasound, in which one or both ovaries have  $\geq 12$  follicles with a diameter of 2 - 9 mm and/or an ovarian volume  $\geq 10$  ml; 3) clinical hyperandrogenemia and/or biochemical manifestations of hyperandrogenemia. PCOS can be diagnosed if two of the three criteria are met, but other conditions that cause hyperandrogenism, hyperprolactinemia, and thyroid dysfunction should be ruled out. Based on the Rotterdam criteria, the following classification of PCOS phenotypes is distinguished. Phenotype A (classic) is considered the most severe: it is characterized by all three Rotterdam criteria. Obesity and insulin resistance, high AMH levels, although not included in the diagnostic criteria, are closely associated with this phenotype. Phenotype B (also the classic (NIH) phenotype) is characterized by severe menstrual dysfunction and is characterized by a higher incidence of insulin resistance and metabolic disorders compared to non-hyperandrogenic forms of PCOS. In the C (ovulatory) phenotype, patients have elevated serum androgen and lipid levels, as well as mild hyperinsulinemia with a lower incidence of metabolic syndrome and hirsutism than in other PCOS phenotypes. In patients with the D (non-androgenic) phenotype, several studies have shown the maximum number of regular menstrual cycles, the lowest degree of metabolic disorders [9].

The main etiological factor of PCOS has not been established; however, an association of PCOS with genetic and environmental factors has been described. In women of childbearing age, ovulation disorders are mainly observed - chronic oligoanovulation. The following drugs are used to induce ovulation - clomiphene, letrozole, tamoxifen, gonadotropins. The frequency of ovulation after their use is approximately 60 - 80%, although the incidence of clinical pregnancy is only 35 - 40% [7]. Thus, the proportion of failed embryo implantations and spontaneous abortions in women with PCOS is still relatively high. During assisted reproductive technologies (ART), when using oocytes from women with PCOS, the pregnancy rate does not decrease compared to oocytes from healthy women [8], which strongly suggests that the decrease in fertility of women with PCOS is associated with the influence of environmental factors, a decrease in oocyte quality and decreased endometrial receptivity.

Literature data show that another possible mechanism of infertility in PCOS is impaired endometrial receptivity, one of the causes of which is chronic inflammation [9,10]. Chronic inflammation is associated, on the one hand, with persistence in the tissues of the infection, and on the other hand, with immune disorders in the body. It is the persistent damage to the endometrium, leading to disruption of the normal cyclic transformation and receptivity of the endometrium, that creates the conditions for the development of infertility [14]. It was these factors that predetermined the need to study and evaluate the effectiveness of the treatment of endometrial pathologies in women with PCOS and infertility [15].

### Aim of the Study

The aim of the study was to identify the most common endometrial pathology in women with PCOS and infertility and to analyze the effectiveness of infertility treatment in women with this pathology, to assess reproductive outcomes depending on the pathology of the endometrium.

## Materials and Methods

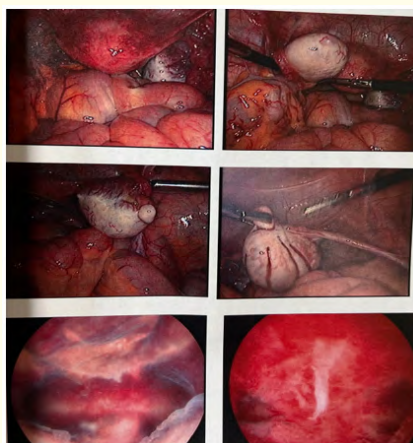
We analyzed 240 case histories of patients of LLC "Clinic of Professor Pasman", GBUZ NSO "NOKOD" for the period 2012 - 2022. diagnosed with infertility, PCOS. Patients were included in the study group by random sequential selection. The mean age of the patients was  $29.4 \pm 5.13$  years. The duration of infertility varied from 1 to 18 years. The following research methods were used: anthropometric study (height, body weight), general clinical examination (general blood test, general urinalysis, biochemical blood test: CRP, glucose, total cholesterol), ultrasound of the pelvic organs, endometrial aspiration biopsy was used to assess the state of the endometrium, hysteroscopy with pathomorphological examination. Statistical analysis: quantitative data of the study are presented using descriptive statistics: means and standard deviation, median and 1<sup>st</sup> and 3<sup>rd</sup> quartiles of distribution, qualitative data - in the form of frequencies and percentages. To compare the values of quantitative and qualitative indicators by groups, the nonparametric Mann-Whitney test was used, because small groups were compared.

Comparison of the shares of qualitative indicators was carried out using the z-test for equality of shares.

At the 1<sup>st</sup> stage, the diagnosis and treatment of endometrial pathology was carried out. In 61% (n = 146), hysteroscopy was performed followed by a morphological study of the endometrium, the indications for hysteroscopy were as follows: infertility; suspicion of endometrial disease (hyperplasia / polyps) detected during ultrasound; suspicion of submucosal myomatous node; suspicion of internal endometriosis, synechia in the uterine cavity. The diagnosis was verified pathomorphologically and immunohistochemically.

In the general group (n = 240), the prevalence of each endometrial pathology was assessed. The most common in women with PCOS and infertility was chronic endometritis (61.6%). The existing method of treatment - antibiotic therapy has a number of limitations for women with PCOS and infertility. The constant use of antibiotic therapy is highly effective against the infectious process, but reduces the effectiveness of infertility treatment, which, according to the literature, is associated with a violation of the microbiome in the uterine cavity, and as a result, a violation of endometrial receptivity. Therefore, more effective methods for the treatment of endometrial pathologies are needed. Such methods are photodynamic therapy of the uterine cavity (PDT) and the introduction of a macrophage conditioned medium into the uterine cavity [6,7].

The use of these methods is pathogenetically justified, since they affect one of the links in pathogenesis - chronic inflammation. Depending on the method of treatment in the CE group, patients were divided into two groups: group 1 - 34 patients aged 15 to 35 years who were treated with PDT and the introduction of macrophage medium, group 2 - the control group, 28 patients aged from 19 to 32 years old, in whom these methods of treating CE were not used. The effectiveness of the treatment of chronic endometritis was assessed by increasing the thickness of the M-echo by ultrasound, as well as by the frequency of pregnancy (Figure 1).

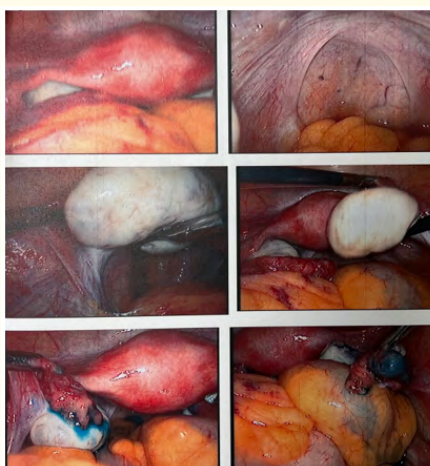


**Figure 1:** Laparoscopy, ovarian drilling. Hysteroscopy, chronic endometritis.

In the group with hyperplastic processes of the endometrium (endometrial hyperplasia, endometrial polyp), the presence of clinical manifestations, the nature of complaints, the presence of ultrasound changes in the endometrium, obstetric and gynecological history, the methods of treatment used and their effectiveness were additionally assessed. To prevent the recurrence of hyperplastic processes after hysteroscopy, photodynamic therapy was carried out and dydrogesterone 10 mg was prescribed 2 times from the day of surgery for 2 - 3 months, then from 16 to 25 days of the cycle in terms of pregravid preparation. For the treatment of recurrent hyperplastic processes in combination with PCOS, the following scheme was used: gonadotropin-releasing hormone agonists from the day of hysteroscopy, three times after 28 days, followed by the use of COCs with antiandrogens for up to 6 months to reduce the size of the ovaries, photodynamic therapy. For patients with a combination of PCOS, endometrial hyperplasia and in the presence of fibroids and/or endometriosis, the scheme was used: gonadotropin-releasing hormone agonists from the day of hysteroscopy, three times after 28 days, at the second stage, dienogest 9-12 months, continuously, 2 mg, for 3 stage - dydrogesterone 10 mg 2 times from 16 to 25 days in terms of pregravid preparation.

For the treatment of atypical hyperplasia, an organ-preserving method of treatment was used - local administration of levonorgestrel in the form of an intrauterine therapeutic system with mandatory pathological and anatomical examination of the biopsy (surgical) material of the endometrium every 3 months (according to the clinical recommendations of the Ministry of Health of the Russian Federation).

For the treatment of endometrial cancer in the initial stages and in patients of reproductive age (n = 4), an organ-preserving method was used - Mirena IUD for 6 months + RGHL agonists once every 4 weeks - 6 months. Dynamic control: after 3 months - ultrasound, pipel biopsy, after 6 months - cervicohysteroscopy + WFD, morphological examination following (Figure 2). In 2 patients, a radical operation was performed - extirpation of the uterus without appendages.



**Figure 2:** Endometrial cancer, condition after hormone therapy. Laparoscopy, ovarian drilling.

After the treatment of endometrial pathology, infertility treatment was carried out at the 2<sup>nd</sup> stage. Treatment of infertility in PCOS was carried out by the following methods: controlled ovulation induction, artificial insemination with husband's sperm, ovarian drilling, *in vitro* fertilization. An analysis of the effectiveness of infertility treatment methods for PCOS was carried out, the percentage of pregnancy was considered as the criterion for effectiveness. For all cases of pregnancy, reproductive outcomes (frequency of spontaneous and missed miscarriages, ectopic pregnancies, term births) and the frequency of pregnancy complications were analyzed.

## Results and Discussion

In the total sample among PCOS phenotypes, the following phenotypes were the most common: phenotype D (70.0%), C (17.1%), A (12.9%), phenotype B was not found, which is comparable with the literature data [5,16]. In the structure of endometrial diseases, the most common endometrial pathologies in the sample were: chronic endometritis diagnosed in 90 patients (61.6%), endometrial hyperplasia - in 24 women (16.4%), endometrial polyp - in 18 (12.3%), endometrial hypoplasia - in 8 (5.5%), endometrial cancer - in 6 (4.1%). The data are presented in table 1. The data obtained by us are comparable with the literature data [4].

Pathological conclusion	N = 146	%
Chronic endometritis	90	61,6%
Glandular fibrous endometrial polyp	15	10,3%
Glandular endometrial polyp	3	2%
Simple non-atypical glandular hyperplasia	19	13%
Atypical endometrial hyperplasia	5	3,4%
Hypoplasia of the endometrium	8	5,6%
Endometrial cancer	6	4,1%

**Table 1:** Pathology of the endometrium, confirmed by pathological examination.

In the group with hyperplastic processes, 38.7% of patients had no complaints. In 32.3% of cases, there were complaints of intermenstrual spotting. In 19.4% there were complaints of delayed menstruation, and in 9.6% - pain in the lower abdomen. Concomitant pathology was identified in 100% of cases, and the most common concomitant diagnosis - internal endometriosis 1 - 2 stage - occurred in 42.3% of cases. In 77%, a combination of endometrial hyperplasia with chronic endometritis was noted. As for the effectiveness of the applied methods of treatment, relapses of hyperplastic processes occurred in 3 patients (7.1%), the progression of the disease to endometrial cancer was not observed.

In the group of patients with chronic endometritis, analysis of menstrual function showed that women's age, duration of infertility, insulin resistance (blood glucose, total cholesterol), BMI, duration of the menstrual cycle, its duration within the two groups were comparable. In group 1 with the additional use of CE treatment methods, pregnancy occurred in 22 (64.7%) patients, in group 2 (control group) - in 12 (42.9%) women ( $p < 0.05$ ). The thickness of the endometrium in group 1 increased by an average of  $1.42 \pm 1.06$  mm, in group 2 - by  $1.01 \pm 0.73$  mm. The analysis data are presented in table 2 and 3.

	Group 1 (PDT + macrophage conditioned medium)n = 34		Group 2 (Without PDT + macrophage conditioned medium) n = 28		P-values Mann-Whitney U-test
	Mean ± SD	Me [Q1;Q3]	Mean ± SD	Me [Q1;Q3]	
Woman's age, y.o.	27,47 ± 5,57	29 [23;32]	28,86 ± 5,83	28,5 [25;34]	0,739
Duration of infertility, y	2,88 ± 2,0	2 [1;4]	3,0 ± 2,63	2 [1;4]	0,830
Blood glucose, mmol/l	4,94 ± 0,51	4,9 [4,8;5,16]	5,05 ± 0,43	5,02 [4,7;5,3]	0,544
Total cholesterol, mmol/l	4,71 ± 0,52	4,75 [4,6;5,04]	5,10 ± 0,90	4,7 [4,5;5,98]	0,597
BMI, kg/m <sup>2</sup>	22,52 ± 5,30	21 [19;23,6]	22,82 ± 7,20	20,45 [19;21,7]	0,710
The duration of the menstrual cycle, number of days	30,65 ± 2,71	30 [29;32]	30,23 ± 2,05	30 [29;31]	0,891
Duration of menstruation, number of days	4,82 ± 1,01	5 [4;5]	4,79 ± 1,12	4,5 [4;6]	0,860

**Table 2:** Comparison of indicators of groups with chronic endometritis.

	<b>Group 1(PDT + macrophageconditioned medium) n=34 PC (%)</b>	<b>Group 2 (Without PDT + macrophageconditioned medium) n = 28 PC (%)</b>	<b>P-value Z-test</b>
Multifollicular structure of the ovaries on ultrasound	34 (100%)	28 (100%)	-
Irregular menstrual cycle	30 (88,2%)	24 (82,4%)	0,417
Normal BMI (under 25)	28 (82,4%)	22 (78,6%)	0,395
The onset of pregnancy	22 (64,7%)	12 (42,9%)	0,026

**Table 3:** Comparison of indicators of groups with chronic endometritis.

Among the methods used to treat infertility, IVF/ICSI showed the highest efficiency - pregnancy occurred in 29.4% of cases, artificial insemination with the husband's sperm - in 20.8%, laparoscopy, ovarian drilling - in 15.4%.

The reproductive outcome in 68.4% was an urgent delivery, in 15.8% - a missed miscarriage, in 10.5% - an ectopic pregnancy, in 5.3% - a spontaneous miscarriage in the first trimester.

Preeclampsia developed during pregnancy in 12%, which confirms the need for prevention and early diagnosis of this complication in PCOS.

## Conclusion

1. The results obtained indicate a high incidence of chronic endometritis in PCOS, which is 61.6%, which may indicate a relationship between PCOS and chronic inflammation.
2. The high incidence of endometrial pathology (61.6%) with the absence of clinical manifestations in 38.7% in patients with endometrial hyperplasia indicates the need to diagnose the state of the endometrium in women with PCOS, and especially before using ART.
3. The prevailing combination of endometrial hyperplastic processes with chronic endometritis (77%) is a pathogenetic rationale for the use of PDT of the uterine cavity in combination with a macrophage conditioned medium, which significantly increases the effectiveness of infertility treatment in PCOS: in patients with PCOS and chronic endometritis, pregnancy occurred at 64,7% with PDT, in the control group - 42.9%
4. For the group of atypical hyperplasia and the initial stages of endometrial cancer in PCOS, it is also possible to use organ-preserving methods of treatment.

## Conflict of Interest

The authors declare no conflict of interest.

## Funding Support

The work was performed without external funding.

## Compliance with Patient Rights

The study protocol was approved by the Biomedical Ethics Committee of Novosibirsk National Research State University. The patients signed an informed consent to participate in the study.

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