

Evaluation of the Microbial Flora of the Genital Tract and the Morphofunctional State of the Endometrium in Antiphospholipid Syndrome

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Abstract Currently, the available literature data indicate that the formation of obstetric and perinatal pathology largely depends on the presence of an infectious process in the mother. Since the main trigger mechanism in the development of inflammation is microbial invasion, we conducted a study of the bacteriological contamination of the genital tract and endometrium in women with antiphospholipid syndrome (AFS).

Keywords Antiphospholipid syndrome, Obstetric and perinatal pathology

According to the World Health Organization (WHO), an increased rate of loss of desired pregnancies determines not only the medical but also the social significance of the problem of miscarriage. One of the main problems of obstetrics is miscarriage, the frequency of which is 10-25%, remaining high to this day. According to a number of authors, among the multiple causes of miscarriage, about 55-62% is defects in coagulation proteins or platelets, one of the manifestations of which is antiphospholipid syndrome (APS).

To improve the effectiveness of measures for the early diagnosis, treatment and prevention of APS complications, a wide range of scientific research is being carried out in the world, therefore, in our country, the optimal schemes for screening activities are being improved, the optimal tactics of the screening approach are being selected, and a system is being developed to prevent the risk of reproductive complications among women. reproductive age in women with APS.

There are no definite data on the frequency of APS in women in our region in the general population. This is due to difficulties in diagnosis and inconsistency between clinical and laboratory data. But, despite this alignment, most studies have shown that APA circulation is observed in 2-4% of healthy pregnant women, as well as in healthy non-pregnant women [1,6]. The fact that habitual miscarriage, a characteristic sign of APS, occurs exclusively in women, suggests that APA are found 2-5 times more often than in men [2,5].

Currently, the available literature data indicate that the formation of obstetric and perinatal pathology largely depends on the presence of an infectious process in the mother [1-3]. Since the main trigger in the development of inflammation is microbial invasion, we conducted a study of bacteriological contamination of the genital tract and endometrium in women with antiphospholipid syndrome (APS) [4,5] in order to study the interaction between the pathogenesis of APS and the inflammatory process.

1. Purpose of the Study

Assessment of the microbial flora of the genital tract and the morphological and functional state of the endometrium in women with antiphospholipid syndrome (APS) in order to study the interaction between the pathogenesis of APS and the inflammatory process.

2. Material and Methods of Research

To assess the condition of women, we studied the somatic and reproductive anamnesis, heredity, the nature of the diseases suffered, the formation of menstrual and generative functions of women, including the outcomes of pregnancies (childbirth, spontaneous abortions, ectopic pregnancy). The complex of laboratory tests included: detailed general analysis of blood, urine, determination of blood type and Rh factor, HIV, RW, carrier of the Australian antigen, biochemical blood analysis with determination of urea, bilirubin and blood content, blood coagulation system, blood test for STIs. In addition, infection screening was performed for all patients: bacteriological and bacterioscopic examination of smears from 3 points.

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Bacterioscopic examination of the vaginal discharge, cervical canal and scraping of the uterine mucosa. Evaluation of the microbial flora of the vagina, cervical canal and uterine cavity was carried out by bacterioscopic, bacteriological methods and polymerase chain reaction (PCR). In the bacteriological laboratory of the clinic, a survey was conducted on the microbial landscape from the cervical canal in all women, pregnant women and maternity patients with the determination of sensitivity to antibacterial and antifungal drugs. The diagnosis of vaginal candidiasis was made based on the results of microscopic and cultural examination of pathological material taken from the cervical canal. The etiological factor was considered to be the material isolated only in the III and IV degrees of massiveness. Preparations for microscopy were stained using the Gram method. Sowing was carried out on elective media, including Sabur medium to identify fungi of the genus *Candida*. The test material was incubated in a thermostat for 48 hours at a temperature of 22°C.

Morphological and morphometric examination of the placenta. Pathomorphological examination of the placenta and histological examination of endometrial scraping were performed in the Department of Pathological anatomy of the ASMI clinic.

Placenta examination was carried out according to a standardized scheme modified by A. P. Milovanov [11]. The study of the placenta began immediately from the moment of birth of the placenta, when the weight and size of the placenta, the length of the umbilical cord were determined. Attention was paid to the features of the maternal and fetal surface, the nature of the tissue on the incision, the severity of the vascular network, the location of the veins and arteries of the umbilical cord, the presence or absence of various inclusions. The mass of the placenta was determined after preliminary removal of the fruit shells and umbilical cord with scissors.

For histological examination of the placenta, immediately after the birth of the placenta, pieces of placental tissue measuring 1x1x1 cm were taken from three zones: central, paracentral and marginal. After fixation of placental tissue in 4% neutral formalin on a phosphate buffer (pH 7.2-7.4), the material was poured into paraffin according to the Lloyd 3 method. et al. (1982). Then serial sections were made, which were stained with hematoxylin and eosin, picrofuxin according to Van Gieson.

Ultrasound, Doppler examination of the examined women, cardiotocography of uterine activity and fetal cardiac activity were performed in the Department of pathology of pregnant women of the 2nd maternity complex of Andijan. Determination of hormones of the fetoplacental complex, as well as immunological studies were carried out at the Central Research Institute of ASMI (head of the laboratory of Prof. Aleynik V. A.). Polymerase chain reaction to determine the presence of STIs was carried out at the GEN-MED Medical Center in Andijan (Head of the laboratory of Ph.D. Parpieva D. A.). The morphological part of the work was carried out in the Department of Pathological anatomy of the ASMI clinic (head of the department of Assoc. Ablazimova T. B.)

3. Discussion of the Results

A bacteriological study of the microbial flora of the vagina was conducted in 92 women with AFS and 25 practically healthy women. Evaluation of the microbial flora of the vagina, cervical canal and uterine cavity was carried out by bacterioscopic, bacteriological methods and polymerase chain reaction (PCR).

In the control group, vaginal normocenosis was detected in 19 (76.0%) women, in the remaining 6 (24.0%), signs of candidal vaginitis without clinical manifestations of this disease were detected with bacteriological smear cultures. This can be regarded as candidiasis, which, apparently, was associated with the previously performed antimycotic treatment in 4 women and self-medication (clotrimazole) in 2 patients from this group. In the main group, during bacteriological culture of smears of the II st. vaginal purity was found in only 9 (9.8%) patients.

Among inflammatory diseases of the lower genitals, the highest frequency belonged to nonspecific vaginitis, which occurred in every third woman of the main group (37.0%).

Vulvovaginal candidiasis was detected in almost every fourth woman (21.7%) of the same group. Bacterial vaginosis was diagnosed somewhat less frequently (13.0%), trichomonas colpitis in 5.4% of cases in patients of the main group. Mixed infection was detected in the genital tract in women of the main group in 13.0% of cases.

To determine the degree of endometrial contamination, a PCR study of scraping from the uterine cavity was performed, which was taken from 43 maternity patients of the main group (Table 2).

Table 1. Results of bacteriological examination of smears from the genital tract in the examined women

The state of vaginal biocenosis	Control group (n=25)		Main group (n=92)		P
	abs	%	abs	%	
Nonspecific colpitis	19	76,0±8,5	9	9,8±3,1	<0,001
Bacterial vaginosis	0	0	34	37,0±5,0	<0,001
Vaginal candidiasis	0	0	12	13,0±3,5	<0,001
Trichomonas colpitis	6	24,0±8,5	20	21,7±4,3	>0,05
Mixed infection	0	0	5	5,4±2,4	<0,05
The state of vaginal biocenosis	0	0	12	13,0±3,5	<0,001

Table 2. Results of a PCR study of endometrial scraping in women with premature birth

Infectious agent	Abs	%
HSV	5	11,6
CMV	2	4,7
HSV+CMV	6	14,0
No infection detected	14	32,6

Out of 43 PCR studies of the endometrium, no infection in the endometrium was detected in 14 (32.6%) cases. Of the monoviruses, HSV 5 was more common (11.6%), CMV was much less common (4.7%). The combination of HSV and CMV infection was observed in 13.9% of cases.

To objectify the state of the endometrium, we conducted a histological examination of the scraping of the mucosa of the endometrium in 63 women with prematurity. Generalization of the results of histological examination of the endometrium revealed 3 variants of pathomorphological changes of the endometrium.

In variant I - 19 (30.2%) cases - minor areas of epithelial cell dystrophy alternated with areas of normal epithelium of the parietal endometrium. There were no signs of vasculitis with uniform development of spiral artery walls in the uteroplacental region. Areas of cytotrophoblast were detected in anchor villi, indicating its full-fledged invasion. This variant was designated by us as "endometrium without pathological changes".

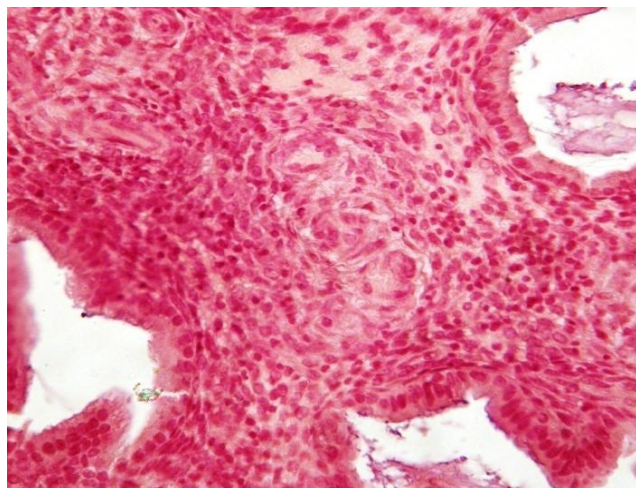


Figure 1. Concentration of lymphocytes around the uterine glands with severe dystrophy of epithelial cells, with their nodular proliferation, as well as necrosis of individual scattered highly differentiated decidual cells. The wall of the spiral arteries is unevenly developed. Staining with hematoxylin and eosin (40×15)

Variant II - 29 (46.0%) cases - was characterized by the presence of inflammatory infiltrates in the parietal endometrium with maximum leukocyte infiltration under the uterine epithelium, which indicated an ascending path of infection (Fig. 1). At the same time, there was a concentration of lymphocytes around the uterine glands with severe dystrophy of epithelial cells, as well as necrosis of individual decidual cells. In the uteroplacental region, small foci of hemorrhages were noted, along the periphery of

which necrosis of the surrounding layers of decidual cells was observed. This variant is characterized by us as "inflammatory changes of the endometrium" due to dysfunction of small vessels.

In the 3rd variant - 15 (23.8%) cases - against the background of an inflammatory reaction of the parietal endometrium, necrosis of many decidual cells, focal fibrosis of the stroma, occupying in some cases significant areas, was detected. In the uteroplacental region, sclerosis of the walls of many spiral arteries, signs of arteritis were noted, superficial trophoblastic invasion was observed, leading to incomplete gestational restructuring of the spiral arteries. This variant of endometrial changes, given the presence of destructive changes, is designated as "endometrial sclerotic changes".

The study of the anamnesis of women from various subgroups of endometrial changes showed that the group with "unchanged" endometrium consisted of 8 primiparous (42.1%), 11 (57.9%) repeat births had uncomplicated postpartum period in the past. Of the 19 women in this subgroup, only 3 (15.8%) had a medical history of abortions.

The second subgroup of the histological picture of the endometrium consisted of 29 women who had relapses of inflammatory diseases of the genital and urinary tract. The majority (65.5%) of these women had a history of spontaneous miscarriages (31.1%), medical abortions (41.4%). 16 (55.2%) patients from this subgroup were protected from pregnancy by inserting an IUD.

Sclerotic changes of the endometrium on the background of inflammation in the third subgroup were associated with repeated medical abortions in 7 (46.6%), spontaneous miscarriages in 5 (33.3%), undeveloped pregnancy in 5 (33.3%), with early premature birth and perinatal losses in 3 (20.0%) patients, and in the same A combination of several aggravating factors was noted in women. 9 (60.0%) women from this subgroup noted long-term wearing of the IUD (more than 5 years).

Having studied the characteristics of individual links of the fetoplacental system in preterm labor, we tried to find the dependence of the detected changes in the mother-placenta-fetus system on the state of the endometrium (Fig. 2).

As can be seen from the figure, with all variants of endometrial changes, the presence of a vaginal infection was detected. Normocenosis corresponded to the first variant of endometrial changes in 4 (21.1%) cases, the cumulative frequency of vaginal infections among women of this subgroup was 78.9%. In both the second and third variants of endometrial changes, normocenosis did not occur, the cumulative frequency of vaginal infections was 100%. Contamination of the endometrium with infectious agents in all three variants of the histological picture of the endometrium occurred in 21.1%, 48.3% and 73.3% of cases, respectively. But it should be noted that the third option corresponded to a higher percentage of viral and chlamydial contamination of the endometrium.

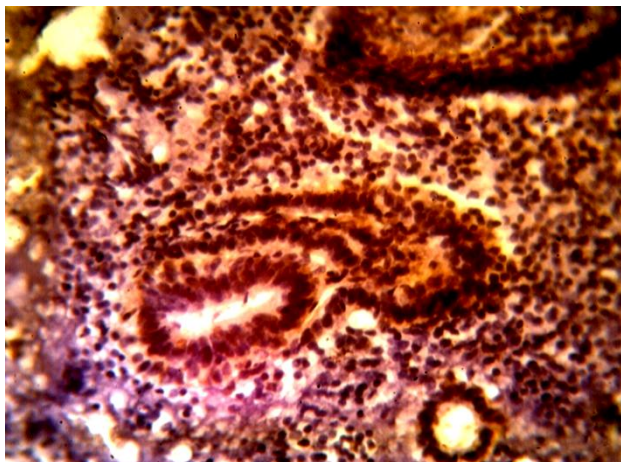


Figure 2. Sclerotic changes in the endometrium against the background of inflammation with severe degeneration of epithelial cells, with their nodular proliferation, as well as necrosis of individual scattered highly differentiated decidua cells. Stained with hematoxylin and eosin (40×15)

The Doppler study revealed a different degree of blood flow disorders: the 1st variant corresponded to cases without blood flow disorders (31.6%) and initial changes in blood flow in the uterine pool (68.4%), the 2nd variant – blood flow disorders in both the uteroplacental (20.7%) and the fetoplacental link (44.8%), as well as combined disorders of blood flow in the utero-placental-fruit complex (MPPC) (34.5%). The most severe blood flow disorders in the uteroplacental link without critical values (46.7%) and with the presence of critical values (53.3%) corresponded to the 3rd variant of endometrial changes.

Morphological examination of placentas also revealed certain patterns: in the 1st variant, in 9 cases (24.3%) with morphometry, the mass of placentas corresponded to the gestational norm, in 2 (5.4%) uterine hypoplasia was noted. Histological examination revealed inflammatory and circulatory changes in 11 placentas (29.7%) in the placentas of women with prematurity, but compensatory reactions (the presence of syntial kidneys, expansion of the interstitial space, the formation of specialized terminal villi) persisted. In the 2nd variant – with morphometry in 4 cases (10.8%), the placental mass also corresponded to the gestational norm, an increased placental mass relative to the norm at this stage of pregnancy was found in 8 cases (21.6%). Histological examination of 12 placentas (32.4%) revealed significant inflammatory and circulatory changes without the preservation of compensatory mechanisms. With the 3rd variant in the placentas, hypoplasia of the mass in relation to the gestational norm was detected in all 14 placentas studied (37.8%), and with morphological examination, along with inflammatory and circulatory changes, dystrophic changes in the form of sclerosis of the villi, gluing of the villi with extensive fibrinoid, immaturity of the villi tree.

So, in itself, the fact of carrying an infection during pregnancy is not a necessary condition for the manifestation of pathogenetic properties of infectious agents. This is evidenced by the data that women in the control group also had episodes of exacerbation of infections during pregnancy,

infection in the genital tract was detected, infectious lesions in the placentas were observed. Infectious agents only lead to reproduction disorders when their pathogenic effect is realized in the endometrium in the form of its various pathological changes, in particular, morphofunctional inferiority, in connection with the emerging areas of necrosis and infarction of endometrial vessels, which is a consequence of APS [6-10].

4. Conclusions

Studies have shown that despite the presence of infection in women with APS, infectious agents are not pathogenetic in the complicated course of APS, which could lead to increased production of antiphospholipid antibodies. But APS itself may well be the cause of increased viral contamination, which could subsequently cause impairments in the ability of trophoblast initiation into the endometrium during pregnancy.

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