Clinical Presentation Of Persistent Viral Infection In Women Of Reproductive Age

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ABSTRACT

Persistent virus infection among pregnant women and women with reproductive disorders is characterized by specific clinical picture, which has clinical and diagnostic significance. The analysis of the clinical material has found abnormal genital discharge to be the leading symptom of the persistent viral infection with the prevalence from 59.4 ± 2.7 to 76.9 ± 2.3 % women. It’s often accompanied by a putrid odor, irritation, itching and burning of genitals. Four clinical forms of the disease can be clearly distinguished: asymptomatic (an average incidence is 14.5 ± 2.0%), mild (34.8 ± 2.1%), medium (32.6 ± 2.6%) and severe (18.2 ± 2.1%). An incidence of medium and severe clinical forms of persistent viral infections, which varies from 4.1 to 23.6 ± 6.1% increases in the presence of pathogenic organisms, chlamydia and trichomonas in urogenital tract. This shows the necessity for selection and use of therapeutic measures both effective against all these pathogens.

INTRODUCTION

Reducing the incidence of the disease in pregnant women and newborns and stimulating reproductive function in women is one of the leading public health problems in many countries [1, 2]. In this aspect, a priority aim of public health is an identification of factors aggravating course of the pregnancy and reducing the reproductive function in women as well as the elimination of these factors according to WHO experts [3]. Viral infections are among the most common diseases among pregnant women and women of childbearing age. Being sexually transmitted infections, they have a pronounced impact on complicating of pregnancy and reproductive pathology [4, 5, 6]. High frequency of persistent viral infections with various representatives of the microflora, uncertain clinical symptoms and asymptomatic course for a long time were the main reasons for inadequate attitude to these diseases [7, 8, 9, 10]. Therefore, early detection and effective treatment of infected women is an issue of extreme importance nowadays.

Objective: to study the clinical symptoms of patients with the reliable presence of persistent viral infection, to reveal their identity.

MATERIAL AND METHODS

The work involved 325 women with persistent viral infections (PVI) revealed in the survey of 1,119 women (29.0 ± 1.4%).

Inclusion criteria:

• identification of DNA from biological substrates: peripheral blood, urine, discharge from the vulva, cervix;

• age – from 17 years to menopause.

Exclusion criteria:

• decompensation of extragenital diseases;

• infectious diseases in the acute stage.

From the total number of 325 women with confirmed diagnosis of PVI, 151 women were pregnant, 64 with miscarriage, 81 with premature birth and 29 with infertility. Respectively, 635, 74, 33 and 52 women were not diagnosed with PVI. Etiological structure of PVI was determined in 325 positive cases of which 143 cases were monoinfection and 182 cases were polyinfection (148 cases with 2 species of viruses, 15 cases - 3 species of viruses, 19 cases - 3 species of viruses).
The necessary clinical history was collected in all the women. Various PVI clinical symptoms were observed among the selected groups of women: abnormal discharge from the genital tract, putrid odor of the discharge, irritation, itching, burning of genitals, painful sexual intercourse, menstrual dysfunction, dizuria phenomenon, pulling pains in the abdomen. Based on the synthesis of the obtained results by their incidence and severity, clinical symptoms are grouped under the following gradations: asymptomatic (a total of 47 women with PVI and 578 women without these infections), mild (respectively 113 and 169 women), medium (106 and 37 women) and severe (59 and 10 women). In addition, frequency and severity of the above-noted forms of clinical symptoms were compared with the results of the general microbiological examination of the urogenital tract in 325 women with PVI, which resulted in 158 cases of the presence of normal microflora, opportunistic microflora in 144 cases, pathogenic microflora in 158, chlamydia in 35 cases and trichomonas in 44 cases.

Diagnosis was based on the comprehensive medical examination, which included medical history, detection of complaints, gynecological examination, ultrasound examination of the pelvic organs, simple and extended colposcopy, cytology from exo- and endocervix, bacteriascopical, biological, molecular biological and immunological study of the material.

Diagnostic criteria of persistent infection were the following:
- Clinical manifestations are absent, however viruses were detected in laboratory studies.
- Molecules of the viral agent were detected in various biological environments by accurate laboratory methods (DNA hybridization, PCR, immunomorphological investigations).
- Serum specific IgG were detected in medium or high titers; no specific IgM were detected.

Clinical cases of carrier states or diseased women were determined by the above-noted signs, as well as by the absence of infectious diseases in the acute stage.

This is the polymerase chain reaction (PCR) method that was used for the laboratory diagnosis of viral infections. The following biosubstrates were used: peripheral blood, urine, discharge from the vulva. Statistical processing of the results was carried out on a personal computer using the software StatSoft Statistika 8.0.

RESULTS AND DISCUSSION

When examining the patients, both cases of the viral monoinfection (44.0%) and combination of infections (56.0%) were identified. The most commonly detected infection were herpesviruses - 126 cases (38.7%), cytomegalovirus - 111 cases (34.3%) and less common enteroviruses - 88 cases (27%).

![Fig. 1: Etiological structure of PVI in the studied patients](image_url)

Legend: 1 - the number of patients (abs); 2 - the number of patients, %.

The most common gynecological diseases and pathologies were chronic salpingo (22.4%), vaginitis (12.4%), cervicitis (11.4%), bacterial vaginosis (9.4%). Also, there was a high incidence of ovarian dysfunction (14.0%).

The list of identified clinical symptoms and its frequency is analyzed separately for similar groups of women with and without PVI (Table 1 and Table 2).
Indicators of clinical symptoms are expressed considerably more on the background of PVI than those indicators without the disease. The persuasiveness of this difference is confirmed by a valid van der Waerden criterion, when comparing the series of clinical symptoms indicators for all groups of women with and without PVI ($X^2 = 4.08-6.13$, $p < 0.001$).

In particular on the background of PVI only 6.9 ± 4.8% to 8.6 ± 3.1% ($x^2 = 0.09$, $p > 0.05$) women with miscarriage, premature birth and infertility didn’t have any complaints. The incidence of such cases among pregnant women was somewhat longer – 21.8 ± 3.4% ($x^2 = 6.45, p < 0.02$). Whereas, in the absence of PVI the incidence of cases without any complaints on clinical symptoms increases dramatically among women with reproductive disorders ($x^2 = 35.63, p < 0.01$) and varies from 55.8 ± 7.0 to 60.8 ± 5.7% ($x^2 = 0.32, p > 0.05$).

The most common symptoms among women with reproductive pathology on the background of PVI was an abnormal discharge from the genital tract - from 80.2 ± 4.5 to 90.6 ± 3.7% ($x^2 = 2.93, p > 0.05$). With the some lower-frequency ($x^2 = 0.94, p > 0.05$) vaginal discharge was accompanied by a putrid odor with an incidence from 70.4 ± 5.1 to 73.4 ± 4.4% ($x^2 = 0.10, p > 0.05$), irritation, itching and burning of genitals with an incidence from 6.9 ± 4.4 to 72.4 ± 8.4% ($x^2 = 0.21, p > 0.05$). Although the incidence of such clinical symptoms as painful sexual intercourse, menstrual disorders, dizuria and pulling pains in the lower abdomen was lower than the incidence of abnormal discharge from the genitals ($x^2 = 11.33, p < 0.01$), but it is also quite high and varies from 44.4 ± 5.6 to 55.6 ± 5.6% ($x^2 = 2.02, p > 0.05$).

The above-noted clinical symptoms are also highly expressed among pregnant women on the background of PVI, but to a lesser extent among women with reproductive disorders. So, an abnormal discharge from the genitals was noted in 67.5 ± 3.8% of pregnant women, putrid odor of the discharge – 51.0 ± 4.1% ($x^2 = 8.57, p < 0.01$), irritation, itching, burning of genitals – 47.7 ± 4.1% ($x^2 = 0.33, p > 0.05$), while such complaints as painful sexual intercourse, dizuria and pulling pains in the abdomen were decreased ($x^2 = 10.17; p < 0.01$) and ranged from 20.5 ± 3.3 to 29.8 ± 3.7% ($x^2 = 3.45, p > 0.05$). As it can be seen, clinical symptoms among all groups of women with PVI were highly expressed and had a similar incidence. So for a clearer distinction we found it useful to analyze its frequency for the entire group of the surveyed women (Table 3).

### Table 1: Clinical symptoms among different groups of women with PVI

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Pregnant women (n = 151)</th>
<th>Miscarriage (n = 64)</th>
<th>Preterm birth (n = 81)</th>
<th>Infertility (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abs %</td>
<td>%</td>
<td>abs %</td>
<td>%</td>
</tr>
<tr>
<td>Abnormal discharge from the genital tract</td>
<td>102</td>
<td>67.5 ± 3.8</td>
<td>58</td>
<td>90.6 ± 3.7</td>
</tr>
<tr>
<td>Putrid odor of the discharge</td>
<td>77</td>
<td>51.0 ± 4.1</td>
<td>47</td>
<td>73.4 ± 4.4</td>
</tr>
<tr>
<td>Irritation, itching, burning of genitals</td>
<td>83</td>
<td>47.7 ± 4.1</td>
<td>45</td>
<td>70.3 ± 5.8</td>
</tr>
<tr>
<td>Painful sexual intercourse</td>
<td>45</td>
<td>29.8 ± 3.7</td>
<td>33</td>
<td>61.6 ± 6.3</td>
</tr>
<tr>
<td>Menstrual disorders</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>46.9 ± 6.3</td>
</tr>
<tr>
<td>Dysuric phenomena</td>
<td>4</td>
<td>27.8 ± 3.1</td>
<td>35</td>
<td>54.7 ± 6.3</td>
</tr>
<tr>
<td>Pulling abdominal pain</td>
<td>31</td>
<td>20.5 ± 3.3</td>
<td>29</td>
<td>45.3 ± 6.3</td>
</tr>
<tr>
<td>No complaints</td>
<td>33</td>
<td>21.8 ± 3.4</td>
<td>5</td>
<td>7.8 ± 3.4</td>
</tr>
</tbody>
</table>

### Table 2: Clinical symptoms among different groups of women without PVI

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Pregnant women n = 635</th>
<th>Miscarriage n = 74</th>
<th>Prematurity n = 33</th>
<th>Infertility n = 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abs. %</td>
<td>%</td>
<td>abs. %</td>
<td>%</td>
</tr>
<tr>
<td>Abnormal discharge from the genital tract</td>
<td>76</td>
<td>12.0±1.3</td>
<td>18</td>
<td>24.3±5.0</td>
</tr>
<tr>
<td>Putrid odor of the discharge</td>
<td>47</td>
<td>7.4±1.0</td>
<td>15</td>
<td>20.3±4.7</td>
</tr>
<tr>
<td>Irritation, itching, burning of genitals</td>
<td>66</td>
<td>10.4±1.2</td>
<td>16</td>
<td>21.6±4.8</td>
</tr>
<tr>
<td>Painful sexual intercourse</td>
<td>45</td>
<td>7.1±1.0</td>
<td>10</td>
<td>13.5±4.0</td>
</tr>
<tr>
<td>Menstrual disorders</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>13.5±4.0</td>
</tr>
<tr>
<td>Dysuric phenomena</td>
<td>69</td>
<td>10.9±1.2</td>
<td>8</td>
<td>10.8±3.6</td>
</tr>
<tr>
<td>Pulling abdominal pain</td>
<td>50</td>
<td>7.9±1.1</td>
<td>9</td>
<td>12.2±3.8</td>
</tr>
<tr>
<td>No complaints</td>
<td>485</td>
<td>76.4±1.7</td>
<td>45</td>
<td>60.8±5.7</td>
</tr>
</tbody>
</table>
These series of indicators of clinical symptoms are obviously predominate among women with PVI than without it, as evidenced by a significant value of van der Waerden criterion \(X = 4.62, p < 0.01\). Pathogenetic role of viruses is especially manifested by the fact that only 14.5 ± 2.0% of women with PVI did not show any complaints. Whereas, in the absence of this disease there were overwhelming majority of women, i.e. those without any complaints of various ailments from the urogenital tract – 72.8 ± 1.6% \((p < 0.001)\). The analysis of the carried clinical material allows to consider abnormal genital discharge accompanied by a putrid odor, irritation, itching and burning of genitals to be a leading symptom of PVI as it occurs in 59.4 ± 2.7 to 76.9 ± 2.3% women \((t = 4.93; p < 0.001)\). At least each woman with PVI has 2 of 3 these clinical symptoms, which may be considered as a differential marker of this disease.

Although to a lesser extent \(t = 4.61; p < 0.001\) the role of differential clinical marker can be also played by symptoms such as painful sexual intercourse, dizuria and pulling pains in the abdomen observed among 34.8 ± 2.6 to 41.8 ± 2.7% of women \((t = 1.87; p > 0.05)\), as well as menstrual dysfunction among women with reproductive pathology – 24.9 ± 2.4% \((t = 2.80; p < 0.01)\). In our opinion these symptoms have a large clinical and differential importance relative to PVI, as this condition is quite rare on the background of other inflammatory and infectious diseases of the urogenital tract. Whereas abnormal discharge from the genital tract is accompanied by putrid odor and irritation, itching, burning of genitals - typical symptoms of many infectious inflammatory diseases of the urogenital tract. Perhaps when speaking about these symptoms we face the diseases caused by association of viruses with various representatives of pathogenic microflora of the urogenital tract.

The point of view regarding differential significance of the listed clinical symptoms is supported by the fact that among women without PVI it was not fully presented - from 7.6 ± 0.9 to 15.1 ± 1.3% \((t = 4.75, p < 0.001)\) - and there were not any considerable confinement. The clinical picture of PVI is so multifaceted and ambiguous that it’s almost impossible to take into account and organize all its manifestations. Therefore, the literature data on PVI clinic is unspecific and contradictory. In our cases there was also a very wide range of clinical symptoms, in particular disorders of the gastrointestinal tract as dyspepsia, colds and many other conditions. However they were rare and were most likely caused by women’s general state. With all probability we can assume that PVI favors the development of different morbidity which clinical manifestations are superimposed on the above analyzed differential clinical symptomatology. In addition still there’s no clear distinction of the severity of PVI clinical symptoms.

In order to bring some clarity to this issue, we decided to group clinical symptoms of PVI by the severity and analyze its affinity to different groups of women according to their childbearing age. Careful analysis of the clinical history obtained by the questionnaire of 325 pregnant women with miscarriage, premature birth and infertility suffering from PVI made it possible to distinguish the following groups of clinical symptoms: asymptomatic, mild, moderate and severe one (Fig.2).

\(n = 325\)

**Fig. 2:** Severity of clinical symptoms among women of childbearing age with PVI. Legend: Clinical symptoms:

- 1: asymptomatic
- 2: mild
- 3: medium
- 4: severe
The data shown on the figure strongly indicate clinical severity of PVI, the proportion of asymptomatic course being 14.5 ± 2.0%. In particular, among the surveyed women suffering from this form of the disease no any clinical manifestations of the disease can be identified. The proportion of a mild form of PVI was equal to 34.8 ± 2.1%. This form is characterized by the observed discharge from the genital tract often accompanied by a putrid odor and irritation, itching, burning of genitals. All these symptoms begin to disturb women, making them to be more concerned with the hygiene of the genital tract. However serious therapeutic measures are carried out rarely, patients are tried to avoid admission to hospital. The proportion of medium form of PVI is considerably higher – 32.6 ± 2.6% of cases. It’s characterized by copious, putrid odor and irritation, itching, burning of genitals. Often, women have one or two of the following symptoms: painful sexual intercourse, menstrual disorders (excluding pregnant women), dizuria or pulling pain in the abdomen. Almost all women with this form of PVI take antibiotics but most common without doctor’s prescription. Admission to medical institutions is increased among these women. Apparently, qualification of health care for women is low, as in many cases we can see relapses, which cause the beginning of repeated courses of antibiotics. Finally, the proportion of severe PVI has been also very high – 18.2 ± 2.1% of women with this form have all the listed symptoms. General condition of women is also unsatisfactory, they are depressed, nervousness, completely refuse sexual relations, often hospitalized. However even inpatient treatment doesn’t always lead to the desired results. Therefore, the repeated courses of antibiotics therapy are very high among this group of women.

According to the literature in many cases viruses reside in the urogenital tract together with various combinations of microflora. Finding out to what extent these associations affect clinical course of PVI was very important. In all 325 cases of identified PVI the condition of urogenital tract microflora was also determined. Microbiological growth was determined in all cases, of which 158 cases were presented by the normal microflora (48.6 ± 2.8%), opportunistic microflora was revealed in 144 cases (44.3 ± 2.8%), pathogenic microflora was revealed in 158 cases (48.6 ± 2.8%), chlamydia was identified in 35 cases (10.8 ± 1.7%), and trichomonas were found in 44 cases (13.5 ± 1.9%). Thus in all the cases more than 2 groups of the listed microorganisms were inoculated except virus. As it turned out to be, despite the presence of normal microflora in urogenital tract, 42.6 ± 7.3% of cases PVI are asymptomatic. The frequency of this form of the disease is relatively high in the presence of pathogenic microflora – 31.9 ± 6.9% (χ² = 1.14, p > 0.05). The frequency of asymptomatic form of PVI is significantly reduced (χ² = 6.35, p < 0.05) in the presence of urogenital tract of pathogenic organisms, chlamydia and trichomonas and varies from 6.4 ± 3.6% to 10.6 ± 4.5% (χ² = 0.55, p > 0.05).

Situation changes in the mild form of PVI, when the frequency of detection of all groups of microorganisms from the urogenital tract is virtually equalized and varies from 27.5 ± 3.0 to 59.6 ± 4.5% (χ² = 0.62, p > 0.05). Quite a different situation is with the medium form of PVI. In particular, the frequency of detection of normal and pathogenic microflora is considerably reduced to 11.3 ± 2.5 and 12.3 ± 2.7% (χ² = 0.20, p > 0.05) respectively, and as much increases (χ² = 4.61, p < 0.05). The frequency of detection of pathogenic organisms, chlamydia and trichomonas - from 23.6 ± 4.1 to 28.3 ± 4.4% (χ² = 0.6, p > 0.05). The difference in the above-noted indicators is even more striking in case of severe PVI. In particular, the frequency of detection of normal and pathogenic microflora (Esherihia, Klebsiella, Enterobacteria, group A and B streptococci) is reduced to a very minimum level, respectively to 3.4 ± 2.4 and 5.1 ± 2.9% (χ² = 0.21, p > 0.05), and the frequency of isolation of pathogenic organisms (pathogenic staphylococci, streptococci, stisrobakter), chlamydia and trichomonas has a maximum level (χ² = 11.80, p < 0.01), ranging from 28.8 ± 5.9 to 32.2 ± 6.1% (χ² = 0.16, p > 0.05).

At first glance, a little randomness of these indicators does not give a clear picture of the severity of the clinical picture of PVI flowing in association with different groups of microorganisms, which in turn are the causative agents of infectious inflammatory diseases of urogenital tract, but they allow us to make the following conclusion. Extreme forms of clinical symptoms of PVI (asymptomatic and severe) are identified for all groups of microorganisms, both in normal and pathogenic microflora, which are common inhabitants of the urogenital tract. These forms are also observed when there’s such pathogenic microflora, chlamydia and trichomonas, indicating independence of the clinical symptoms of PVI. More frequent detection of severe forms of PVI associated with pathogenic microorganisms, chlamydia and trichomonas are likely to be related to the clinical manifestations of overlaying of their symptoms on each other. Naturally, with such pathogenic associations a treatment strategy should provide an effective impact on all of its components.

**Conclusion:**

PVI among pregnant women and women with reproductive disorders is characterized by a specific clinical picture, which has clinical and diagnostic significance. Four clinical forms of the disease can be clearly distinguished: asymptomatic (mean 14.5 ± 2.0%), mild (34.8 ± 2.1%), medium (32.6 ± 2.6%) and severe (18.2 ± 2/1%). The asymptomatic form is the most common form among untreated patients who don’t use antibiotics (47.7 ± 6.2%). The proportion of severe disease is especially high among these patients (34.4 ± 6.1%). In the presence of pathogenic organisms, chlamydia and trichomonas in urogenital tract we can see an increased
incidence of medium and severe clinical forms of PVI, which vary from 23.6 ± 4.1 to 32.2 ± 6.1%, indicating the need for selection and use of therapeutic agents simultaneously effective against all these pathogens.

REFERENCES