

Clinical Manifestations of Papillomavirus Infection in Women with Secondary Infertility

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Abstract This article analyzes the main factors of female infertility, including tubal-peritoneal, endocrine, immunological, infertility caused by genital diseases, and idiopathic infertility. The etiological aspects are considered, including the influence of infectious agents on female fertility. Particular attention is paid to the role of sexually transmitted infections - the human papillomavirus, in the development of infertility. Data from numerous studies on the prevalence of HPV and its impact on women's reproductive health are presented. The article emphasizes the importance of a comprehensive approach to the diagnosis and treatment of female infertility to improve treatment outcomes and increase the chances of successful conception.

Keywords Secondary infertility, Papillomavirus infection, Condyloma acuminata, Diagnosis of "thin" endometrium

1. Introduction

In the field of reproductive health today, infertility occupies a special place. According to modern sources, 8 to 12% of married couples have infertile marriages, in which the woman's share is about 50-80% [3,6,10,29,38].

There are five main groups of factors of female infertility:

Tubal-peritoneal

Endocrine

Infertility caused by genital diseases and anatomical abnormalities

Immunological

Idiopathic (infertility of unknown origin)

Analyzing these factors, it should be recognized that infectious agents can become a predictor of female infertility in all five groups. Undoubtedly, infection affects the condition of the fallopian tubes and endometrium, but the inflammatory autoimmune process contributes to the disruption of the structure and function of the ovaries. And finally, the disruption of the vaginal microbiota in connection with the presence of microorganisms with impaired immunoreactivity contributes to the development of antisperm antibodies and impaired sperm motility [7,9,8,11,12,23,14,31,24,34]. In this regard, the problem of sexually transmitted infections (chlamydia, ureaplasmosis, mycoplasmosis, gonorrhoea), as predictors of infertility, has already been sufficiently studied. However, the etiological role of viral sexually transmitted infections (STIs) in fertility impairment, including human papillomavirus infection, has not yet been studied. The frequency of human

papillomavirus infections (HPV) in the world, according to various researchers, has increased more than 10 times over the past decade [5,4,2,20,21,16,22,35,36,27]. Almost all of the reports cited are based on the detection and treatment of oncogenic HPV strains. However, in practice, clinical manifestations of the human papillomavirus in the form of condyloma acuminata are increasingly encountered, which is the main reason for women to seek medical attention, in whom, upon closer examination, other infections are also detected [19,17,37,40]. This state of affairs even led to the need to publish clinical guidelines for the management of women with condyloma acuminata [32]. Although most researchers agree that human papillomavirus infection itself does not lead to infertility in women, but can be the cause of male infertility in her partner [5,25,26,30,18,39]. the frequent referral of infertile patients with manifestations of condyloma acuminata served as the reason for conducting this study.

Objective of the study: To study the condition of the endometrium in infertile patients with condyloma acuminata.

2. Materials and Methods

Using ultrasound, the condition of the endometrium was studied in 78 patients with secondary infertility who applied to the private medical clinic MCHJ "Mama i Ya" in 2022-2023 (main group). The control group consisted of 50 patients with secondary infertility without condyloma acuminata.

The inclusion criteria for the study were: age not older than 35 years; absence of developmental anomalies of the pelvic organs; history of pregnancy; absence of pregnancy for 12 months without the use of contraceptives; signed

informed consent to participate in the study; condyloma acuminata detected during genital examination.

Exclusion criteria: age over 35 years; absence of condyloma; congenital malformations of the pelvic organs; somatic diseases that are contraindications for pregnancy and childbirth; patient's refusal to participate in the study; alcohol abuse, drug or drug addiction; male infertility.

Standard clinical and gynecological research methods were used. In the middle of the menstrual cycle, an ultrasound examination of the pelvic organs with Dopplerography was performed on a Sonoscape 3D/4D device.

The obtained results were subjected to statistical processing using methods presented in the Statistica 6.0 program. To assess the differences between groups according to quantitatively measured indicators, the parametric Student's t-test was used. To compare the control and main groups according to qualitative characteristics, the Fisher's multifunction criterion was used. Using the χ^2 criterion, the frequency of Dopplerometry changes in the groups was compared. Statistically significant differences were considered at $p < 0.05$ (95% confidence level).

3. Results

The patients included in the study were aged 25 to 35 years. We did not find statistically significant differences in age between the study groups: the average age of patients in the main group was 30.5 ± 1.2 years, patients in the control group – 30.2 ± 1.29 . When comparing the main characteristics of the menstrual cycle according to anamnestic data (menarche, duration of the menstrual cycle, duration and nature of menstruation), it was shown that the groups are comparable in all these parameters. There were no significant differences in marital status and education level between the patients in both groups.

Of the somatic diseases, anemia, which was found with the same frequency in both groups of women – 50% and 52% respectively, is noteworthy. Mostly it was chronic iron deficiency anemia of moderate severity.

Particular attention was paid to the obstetric history and gynecological morbidity in the examined women, as well as to the types of surgical interventions performed on the pelvic organs (Tables 1, 2, 3).

Table 1. Obstetric history of observed patient

Indicator	Main Group (n=78)	Control Group (n=50)	P-value (Level of Significance)
Cesarean section	35(44,9%)	23(46%)	p = 1,0
Preterm birth	10(12,8%)	6(12%)	p = 1,0
Manual examination of the postpartum uterus	19(24,4%)	12(24%)	p = 1,0
Miscarriage (>2)	8(10,3%)	4(8%)	p = 0.764
Postpartum endometritis	11(14,1%)	4(8%)	p = 0.402
Postpartum endometritis	17(21,8%)	11(22%)	p = 1,0

Table 2. Gynecological morbidity of observed patients (anamnestic data)

Indicator	Main Group (n=78)	Control Group (n=50)	P-value (Level of Significance)
Pelvic Inflammatory Disease	37 (47.4%)	23 (46%)	p = 1.0
Ovarian Cysts and Cystomas	7 (9%)	5 (10%)	p = 1.0
Uterine Fibroids	13 (16.7%)	9 (18%)	p = 1.0
Endometriosis	9 (11.5%)	6 (12%)	p = 1.0
Endometrial Polyps	30 (38.5%)	15 (30%)	p = 0.350
Combined Diseases	18 (23%)	8 (16%)	p = 0.350

Table 3. Past surgical interventions on the pelvic organs of served patients

Indicator	Main Group (n=78)	Control Group (n=50)	P-value (Level of Significance)
Cesarean section	35 (44.9%)	23 (46%)	p = 1.0
Laparotomy (including Cesarean section)	38 (48.7%)	23 (46%)	p = 0.856
Laparoscopy	19 (24.4%)	11 (22%)	p = 0.833
Hysteroscopy	25 (32%)	15 (30%)	p = 0.847
Hysterosalpingography (HSG)	16 (20.5%)	9 (18%)	p = 0.821
Pipelle biopsy	18 (23%)	12 (24%)	p = 1.0

The presented data demonstrate that both in terms of frequency and structure of the incidence of gynecological pathology, the groups are comparable ($p \geq 0.05$). It is obvious that the high frequency of endometrial polyps in the structure of past gynecological diseases (38.5% and 30% respectively), as well as information from the obstetric history about complications of childbirth and a high frequency of cesarean section (44.9% and 46% respectively) are quite understandable, since almost all patients included in the study had a "thin" endometrium, which can be considered as a predictor of complications that led to infertility. Laparotomy and laparoscopy on the pelvic organs in the history were performed in 71% ($n=128$) of patients in both groups. As can be seen from Table 3, in general, statistically significant differences in the frequency of past surgical interventions between the groups were not revealed ($p \geq 0.05$).

The vaginal microflora was disrupted (according to anamnestic data) in 36 patients in both groups, which amounted to 28.1%. Bacterial vaginosis occurred in 20 (25.7%) patients in the main group and in 5 (10%) patients in the control group ($p \geq 0.05$). Vulvovaginal candidiasis was diagnosed in

8 (10.3%) women in the main group and in three (6%) in the control group. The presence of a sexually transmitted infection (STI) in the history was diagnosed in both groups of observed patients: chlamydial infection in the history was more than 3 times more common in patients in the main group – 7.7% ($n=6$) compared to patients in the control group – 2% ($n=1$).

CINI-II was diagnosed 5 times more often in the group of women with condyloma acuminata compared to the control group (20.5% and 4% respectively). It should be noted that all patients with condyloma acuminata and CIN were not vaccinated against HPV.

All patients in this group were prescribed appropriate therapy. Due to the presence of an inflammatory process of the genital organs, invasive diagnostic procedures were postponed until the end of treatment.

In the structure of infertility in the main group of patients, the predominant factor was the violation of the morphological and functional ability of the endometrium - "thin" endometrium.

The condition of the pelvic organs was assessed according to ultrasound data (Fig. 1) and

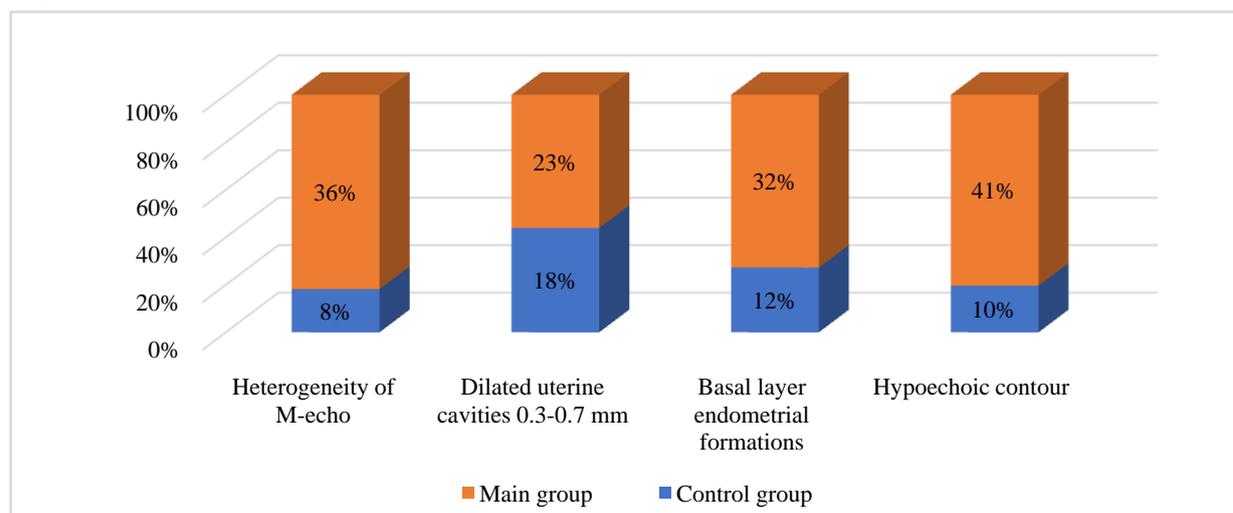


Figure 1. Dopplerometry

Table 4. Indicators of the median M-echo in the examined groups of patients.

In the conducted study, the echographic parameters of patients in the main and control groups were analyzed. The results showed the presence of significant differences in a number of indicators between the groups:

Heterogeneity of the M-echo was observed in 36% of patients in the main group and in 8% of patients in the control group, which indicates a significant difference between the groups ($p < 0.001$).

Expanded uterine cavities (0.3-0.7 mm) were noted in 23% of patients in the main group and in 18% in the control group. Statistical analysis showed no significant differences in this indicator ($p = 0.501$), which suggests that this symptom may be common in both groups, regardless of the presence of condyloma acuminata.

Formations of the basal layer of the endometrium were

detected in 32% of patients in the main group and in 12% of the control group, which also indicates a statistically significant difference between the groups ($p = 0.015$).

Hypoechoic contour was found in 41% of patients in the main group and in 10% of the control group, which also demonstrates significant differences ($p < 0.001$).

These data emphasize that patients in the main group have more pronounced pathological changes in the endometrium, which requires further in-depth study of their clinical significance and the development of appropriate treatment methods.

Table 4 shows the resistance index of uterine vessels in patients with "thin" endometrium in the second phase of the menstrual cycle.

In patients in the main group, the resistance index in the uterine arteries was 0.86 ± 0.03 , which is slightly higher than in the control group, where this indicator is 0.83 ± 0.01 . This

indicates a slight increase in resistance in the main group, although the differences are not significant ($p \geq 0.05$).

Table 4. Index of uterine vascular resistance in patients with "thin" endometrium

Examined arteries	Resistance index of uterine vessels in the II phase of the menstrual cycle (M+m)	
	Main group (n=78)	Control group (n=50)
Uterine	0,86±0,03	0,83±0,01
Arcuate	0,67±0,02	0,64±0,01
Radial	0,69±0,01	0,59±0,01
Basal	0,22±0,02	0,48±0,02
Spiral	0,18±0,02	0,38±0,03

In the main group, the resistance index in the arcuate arteries is 0.67 ± 0.02 , while in the control group it is 0.64 ± 0.01 ($p \geq 0.05$).

RI in the radial arteries in the main group is significantly higher (0.69 ± 0.01) compared to the control group (0.59 ± 0.01) ($p < 0.05$).

In the main group, the resistance index in the basal arteries was 0.22 ± 0.02 , which is significantly lower than the control group (0.48 ± 0.02) ($p < 0.05$). All this indicates a lower resistance of blood vessels in patients with "thin" endometrium in the main group.

RI in the spiral arteries in the main group (0.18 ± 0.02) is significantly lower compared to the control group (0.38 ± 0.03) ($p < 0.05$). These data indicate significant differences in vascular resistance between the groups.

Overall, the resistance index of uterine vessels in patients in the main group shows pronounced changes compared to the control group, especially in the radial, basal and spiral arteries. These data may indicate impaired blood supply to the uterus in patients with "thin" endometrium, which requires further study to understand the pathophysiological processes underlying these changes that led to secondary infertility.

4. Discussion

Analyzing the data we obtained, we can argue that HPV-positive patients have prerequisites for the development of infertility. This is also evidenced by studies conducted by Yu.N. Banashkaeva and co-authors (2022), which indicate that even in the treatment of infertility using assisted reproductive technologies, the lowest frequency of pregnancy after cryoprotocols of IVF was observed in the group of HPV-positive women (33.3%) compared to HPV-negative (73.9%) and previously vaccinated patients (60.7%); $p < 0.05$ [1]. The work of Italian researchers showed that in HPV-positive patients, unsuccessful IVF attempts were almost 3 times more common compared to HPV-negative (40 and 13.5%) [28]. According to the data of the US university clinic, when conducting ART programs in women with HPV persistence, the frequency of pregnancy was significantly lower than in women without the virus (57 and 23.5%) [15].

The negative impact of HPV on reproductive function is

also confirmed in a number of other works. Thus, a systematic review conducted in Germany demonstrates a reliable association between spontaneous abortion, spontaneous preterm birth and the presence of HPV both in the cervix and in the placenta [13].

5. Conclusions

The combination of condyloma acuminata with "thin" endometrium in patients with secondary infertility requires further research and determination of the tactics for managing these women.

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