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Influence of Human Papilloma Virus (HPV) infection on early pregnancy

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ABSTRACT

Objectives: HPV infection in early pregnancy may be a cause of miscarriage. Pregnancy significantly increases the risk of HPV infection. While ascending intrauterine infection with colonization of the trophoblast is commonly observed, descending hematogenous infection should also be considered.

The aim of the study is to assess the prevalence of HPV infection and its influence on pregnancy.

Material and methods: The study was conducted in the years 2010–2015 on a group of 143 pregnant women. The study group consisted of 84 women with abnormal course of the first trimester of pregnancy. The control group consisted of 59 women with normal pregnancy who delivered healthy neonates. Samples of cervix tissue along with samples of trophoblast or placenta were taken for the study. The presence and genotype of the HPV virus were detected using a BIOTOOL B&M Labs set. Statistical analysis was conducted using R software.

Results: The rate of HPV infection in the entire studied population was 13% (19/143): the virus was confirmed in 18% (15/84) of patients in the study group and in 7% (4/59) of the control group. HR HPV was detected in 13 patients in the study group and three patients in the control group. HR HPV infection was more frequent in patients with an abnormal course of the first trimester of pregnancy ($p = 0.03$). HR HPV trophoblast infection was found only in patients in the study group ($p = 0.02$). In two members of the study group, the HPV virus was found in the trophoblast only.

Conclusions:

1. The obtained results may confirm the presence of adverse effects of HPV infection on early pregnancy.
2. HR HPV trophoblast infection was observed only in women with 1st trimester complications.
3. The presence of HPV only in trophoblast samples in some patients may suggest a descending — hematogenous route of primary infection.

Key words: HPV; infection; early pregnancy; miscarriage

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INTRODUCTION

Human Papilloma Virus (HPV) infection is one of the most common sexually transmitted diseases. It is estimated that the probability of infection is twice as high during pregnancy [1–3]. This applies to both activations of viruses that previously remained in a latent phase and new primary infections. Of known HPV types, HR types 16, 18, 31, 33 and 35 are activated most often [4, 5–7].

HPV infection in early pregnancy may be a cause of miscarriage [8, 9]. It has been proved that HPV effectively attacks syncytiotrophoblast cells [10–13]. The route of infection could be vertical ascending; however, the possibility of a descending — hematogenous infection should also be considered.

The influence of HPV infection on early pregnancy is not fully understood. Epidemiological data suggests that the HPV infection rate in European population is 8.1% [14].

Objectives

The aim of the study is to assess the prevalence of HPV infection and its influence on pregnancy.

MATERIAL AND METHODS

The study was conducted on a population of 143 pregnant women in the years 2010–2015. The study group consisted of 84 women with an abnormal course of the first trimester of pregnancy (miscarriages and missed miscarriages), who were referred to the Department of Fetal Medi-

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Table 1. Distribution of positive results in both groups (studied and control group)

	Studied group (84 patients)		Control group (59 patients)	
	Sample	(+) Result	Sample	(+) Result
High-risk HPV type (HR HPV)	trophoblast + cervix	6	placenta + cervix	0
	trophoblast only	2	placenta only	0
	cervix only	5	cervix only	3
Low-risk HPV type (LR HPV)	trophoblast + cervix	2	placenta + cervix	1
	trophoblast only	0	placenta only	0
	cervix only	0	cervix only	0
HPV — total	15 (18%)		4 (7%)	

cine and Gynaecology of the Medical University of Lodz. The control group consisted of 59 pregnant women with a normal course of pregnancy, who gave birth to healthy neonates.

A medical history focused on HPV infection risk factors was taken, and an ultrasound scan performed with pregnancy evaluation.

Samples of the cervix and trophoblast were taken from the patients in the study group, while samples of the cervix and placenta were taken after delivery from patients in the control group. The study was approved by the Bioethics Committee of the Medical University of Lodz.

Diagnosis of HPV infection was based on the detection of viral DNA in cervix and trophoblast/placenta samples by PCR. Immediately after sampling, the tissues were incubated for 12 hours at a temperature of 37°C in a reaction mixture for DNA isolation and purification. DNA concentration was measured using a fluorometer with a sensitivity of 2–1000 ng. PCR reaction was conducted using a BIOTOOLS B&M Labs set, which allows qualitative assessment of the presence of HPV DNA in the sampled material. The test detects 32 genotypes of HPV (6, 11, 13, 16, 18, 30, 31, 32, 33, 34,35, 39, 40, 42, 43, 44, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68 and 69).

Statistical analysis was conducted using R software. Results were analysed using Barnard's test and Fisher's exact test.

RESULTS

The prevalence of HPV infection in the entire studied population was 13% (19/143): 18% (15/84) of patients in the study group and 7% (4/59) in the control group (Tab. 1).

HR HPV was identified in 13 patients in the study group and in three patients in the control group (Tab. 2), and was more commonly observed in trophoblastic tissue in the study group than the control group (Tab. 3).

Table 2. Comparison of infection rate with HR HPV in patients in both groups (Barnard's test; p = 0.03)

	Studied group	Control group
HPV HR +	13	3
HPV HR –	71	56
	p = 0.03	

Table 3. Comparison of infection rate with HR HPV in trophoblast and placenta in patients in both groups (Fisher's exact test; p = 0 .02)

	Studied group	Control group
HPV HR + in trophoblast/placenta	8	0
HPV HR – in trophoblast/placenta	76	59
	p = 0.02	

HR HPV infection was found to be significantly more common in patients with an abnormal course of the first trimester of pregnancy (p = 0.03). This finding confirms previous observations that HPV infection has a negative influence on early pregnancy.

The most important finding is that HR HPV trophoblast infection was observed only in patients in the study group (p = 0.02). Coexisting infection of the cervix and the trophoblast was observed in 8/15 patients, while infection in the trophoblast alone was found in 2/15 patients (Fig. 1).

DISCUSSION

Pregnancy is characterized by an increased risk of infections, including HPV. Elevated progesterone serum concentration is used by the virus to regulate its life cycle and activity as the non-coding LCR segment of the viral genome shows high degree of structural similarity to steroid hormone receptors thus enabling a cross-reaction between the

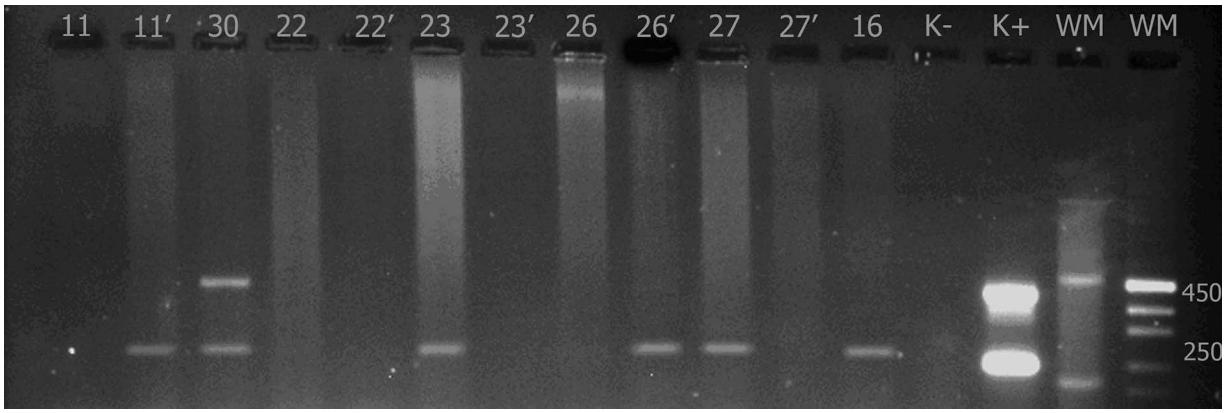

Figure 1. The results of one of the PCR analyses

ligand (i.e. steroid hormone) and glucocorticoid receptor, as well as the analogous LCR sequence. The role of the LCR is to influence the transcription and replication processes by producing signals controlling other viral genes. Furthermore, the immunological response is impaired during pregnancy, which also promotes the development of infections.

In the present study, the mean HPV infection rate among all patients was 13%: 18% in the study group and 7% in the control group. The presence of HR HPV in the trophoblast and placenta was observed significantly more frequently in the group of patients than in the control group. This finding confirms previous reports that HPV infection has a negative influence on early pregnancy [8, 9, 15–17]. An important observation in our study is that HR HPV trophoblast infection was only found in patients in the miscarriage group.

In addition, it is interesting to note that the combined presence of HPV DNA in both trophoblast and cervix was relatively rare, with only nine of 19 women that tested positive (confirmed HPV infection) presenting HPV DNA in both of these tissues. It should be emphasized that HPV was detected in the trophoblast but not the cervix in two cases. This may be accounted for by a descending hematogenous route of primary infection: the virus may choose readily-available, rapidly-dividing trophoblastic cells for infection.

There is clearly a need for further research regarding the relationship between HPV infection and abnormal course of early pregnancy leading to miscarriage or fetal defects.

In 2001, it was discovered that the entire life cycle of HPV virus can occur in trophoblastic cells, not only in keratinocytes [10]. This discovery broadened the perspective on HPV and its biology, and added further support to the proposed association between HPV infection and miscarriage. Later studies have since confirmed this relationship between HPV trophoblast infection and spontaneous miscarriage [13]. It has been established that HPV infection rate is three times

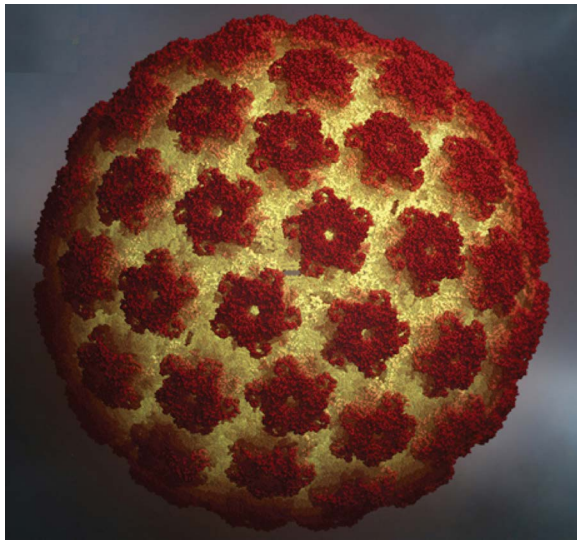

Figure 2. Human Papilloma Virus

higher in tissues from patients after miscarriage compared to those who had undergone induced or surgical abortion [8]. In other studies, the presence of HPV DNA was confirmed in 30% of tissue samples taken from patients after spontaneous miscarriage, while only 17% tested positive on cervical smear [15]. It has since been revealed that asymptomatic HR HPV infection can result in transmission of the virus to the fetus, FGR and preterm labor [1, 3] (Fig. 2).

The HPV infection rate in pregnant women in Poland varies according due to the studied patient group. While Szepietowska reports an infection the rate of 8% in women with third trimester complications [5], a 2007 study found a relatively low rate of 5%; however, this difference may be accounted for by the selection procedure, as only patients with normal cytology were enrolled in the latter study [4]. A study based on global epidemiological data reports HPV

infection rate in Europe in women with normal cytology to be 8% [14].

CONCLUSIONS

1. The obtained results may confirm the presence of adverse effects of HPV infection on early pregnancy.
2. HR HPV trophoblast infection was observed only in women with 1st trimester complications.
3. The presence of HPV only in trophoblast samples detected in some patients may suggest descending — hematogenous route of primary infection.

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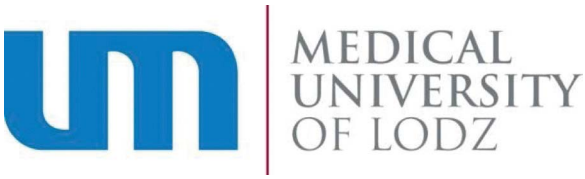

Figure 3. Medical University of Lodz — logo

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