The occurrence of genital types of human papillomavirus in normal pregnancy and in pregnant renal transplant recipients

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Abstract

OBJECTIVE: The aim of this study was to evaluate:
1. The prevalence of human papillomavirus (types 6 and 11 carrying a low risk of neoplasia, and type 16 implicated as cause of cervical neoplasia and cancer) in normal pregnant women and pregnant renal transplant recipients.
2. The correlation between maternal HPV infection and HPV presence in the cord blood and the oral cavity of the neonate. Evaluation of a likely, additional route of HPV transmission to the fetus, apart from the infected birth canal during vaginal delivery. The correlation between the mode of delivery in HPV-infected patients and the presence of HPV in their offspring.
DESIGN: Thirty-nine pregnant patients were included in the study. The study group consisted of nine pregnant renal transplant recipients. The control group consisted of 30 patients with normal pregnancy. The DNA of HPV types 6, 11 and 16 was studied in the discharge from the cervical canal, the maternal venous blood, the cord blood and the buccal smear obtained from the neonates.
SETTING: A university teaching hospital delivering approximately 2000 women annually.
RESULTS: Human papillomavirus (HPV) was found in 10 (26%) of 39 subjects. HPV types 6 and 11 was found in 7 (18%) of 39 subjects while HPV type 16 was present in 5 (13%) of the subjects. The co-occurrence of HPV types 6, 11 and 16 was detected in 2 patients from the control group. Transmission of HPV was established in 70% of study patients and their offspring.
CONCLUSIONS: (1) The HPV was found with 26% pregnant women. (2) The occurrence of HPV infections with pregnant renal transplant recipients in comparison with normal pregnancy was on similar level. High percentage of HPV transmission from mother to neonate was obtained. (3) The cesarean section probably doesn't protect from HPV infection. (4) There's a suggestion, the HPV infection of fetus may occur in utero.

ORIGINAL ARTICLE

Introduction

Nowadays, cervical cancer is considered essentially a sexually transmitted disease (28) and human papillomavirus (HPV) infection and the development of cervical neoplasia are strongly associated (1, 11, 13, 26, 32). At present, HPV is one of the most thouroughly investigated ethiologic factors responsible for neoplasms in humans. Walboomers *et al.* (32) confirmed the presence of HPV in 99.7% cases of cervical squamous cell neoplasia. According to Evander *et al.* (5) HPV is found in 80–100% of high-grade cervical dysplasia. The incidence of HPV infection has dramatically increased in recent years. It may involve the cervix, the vagina, the vulva, the perineum and the anus. HPV infection is linked to intraepithelial neaoplasia of the vulva, the vagina, the cervix and the penis (7). Genital types of HPV are transimitted mainly sexually, but HPV may be also transmitted by oral contact, by fingers and during the fetus's passage through the infected birth canal (9). According to the available data 76% of cases of juvenile papillomas of the larynx, linked mainly to HPV types 6 and 11, appear before age of 5 years (23, 33). The link of these tumours to HPV presence in the maternal birth canal has been documented (23). However, it is a matter of debate whether HPV is transmmited from mother to fetus during its passage through the infected birth canal or the infection develops *in utero*.

In pregnancy, the immune system is physiologically suppressed (1,34), which protects the developing fertilized ovum against rejection by the mother's body. Generally, this suppression is thought to be brought about by the humoural mechanism rather than weakening of the cell-mediated response (15). The serum of a pregnant woman contains many immunomudulating agents capable of blocking the function and proliferation of T lymphocytes which predominate in the normal cervical epithelium.

In pregnant transplant recipients the immunosuppression is even greater. The reduction of resistance is achieved with immunosuppressive therapy, which suppresses mostly the cell-mediated response and controls the acute rejection reactions (15). Immunosuppressants also interfere with humoural immune responses. These drugs suppress all immunologic reactions and as a result are linked to more frequent occurrence of neoplasms and irreversible damage to the internal organs as well

Table 1. Characteristic of study groups.

	Study group	Control group
age		
< 25 age	0	9(30%)
25–30 age	6(67%)	13(43%)
31–35 age	2(22%)	6(20%)
>35 age	1(11%)	2(6.7%)
Medium hight	161.6±4.71	164.9±5.96
Medium weight before pregnancy	57.6±9.56	56.7±8.66
Medium increase of body mass in pregnancy	10±3.22	15.8±8.66
Medium period of pregnancy	35±1.41	39.4±1.27
Education		
• elementary	5 (55%)	5 (16.7%)
• secondary	4 (45%)	12 (40%)
• university		13 (43.3%)
Smoking	0	4(13%)
Oral conception before pregnancy	0	9 (30%)

Table 2. The presence of HPV 6/11 i 16 in pregnant renal transplant recipients.

	Pregnant women	The discharge from the cervical canal		Venous blod		Cord blod		Buccal smear from the neonates	
1	JK	6/11	16	6/11	16	6/11	16	6/11	16
2	RB	+	---	---	---	---	---	+	---
3	MS	---	---	---	---	---	---	---	---
4	DZ	---	---	---	---	---	---	---	---
5	KM	---	---	---	---	---	---	---	---
6	SE	---	+	---	+	---	+	---	+
7	MG	---	---	---	---	---	---	---	---
8	AO	---	---	---	---	---	---	---	---
9	MM	---	---	---	---	---	---	---	---

Table 3. The presence of HPV 6/11 and 16 in normal pregnancy.

	Pregnant women	The discharge from the cervical canal		Venous blod		Cord blod		Buccal smear from the neonates	
1	WL	+	---	---	---	---	---	+	---
2	AW	---	---	---	---	---	---	---	---
3	IG	---	---	---	---	---	---	---	---
4	A R-C	---	---	---	---	---	---	---	---
5	SB	---	---	---	---	---	---	---	---
6	E P-Z	---	---	---	---	---	---	---	---
7	EC	---	---	---	---	---	---	---	---
8	J B-R	---	---	---	---	---	---	---	---
9	EP	---	---	---	---	---	---	---	---
10	RJ	---	---	---	---	---	---	---	---
11	EW	+	---	+	---	---	---	---	---
12	RF	---	---	---	---	---	---	---	---
13	KL	---	---	---	---	---	---	---	---
14	MG	---	---	---	---	---	---	---	---
15	MM	---	---	---	---	---	---	---	---
16	AB	---	---	---	---	---	---	---	---
17	GN	---	---	---	---	---	---	---	---
18	MP	---	+	---	---	---	---	---	+
19	BŚ	---	---	---	---	---	---	---	---
20	AZ	+	+	---	+	---	+	---	+
21	KC	---	---	---	---	---	---	---	---
22	DK	---	---	---	---	---	---	---	---
23	MD	---	---	---	---	---	---	---	---
24	AZ	---	---	---	---	---	---	---	---
25	BO	---	---	---	---	---	---	---	---
26	BO	+	---	---	---	---	---	---	---
27	MD	---	---	---	---	---	---	---	---
28	MI	+	---	+	---	+	---	+	---
29	RJ	---	+	---	---	---	+	---	+
30	KN	+	+	---	---	---	---	---	---

as increased susceptibility to fungal, bacterial and viral infections.

The aim of this study was to evaluate:

1. The prevalence of human papillomavirus (types 6 and 11 carrying a low risk of neoplasia, and type 16 implicated as cause of cervical neoplasia and cancer) in the genital tract of the pregnant patients, the venous blood, the cord blood and the oral cavity of the neonates. Normal pregnant women and pregnant renal transplant recipients were included in the study.
2. The correlation between maternal HPV infection and HPV presence in the cord blood and the oral cavity of the neonate. Evaluation of a likely, additional route of HPV transmission to the fetus, apart from the infected birth canal during vaginal delivery.
3. The correlation between the mode of delivery in HPV-infected patients and the presence of HPV in their offspring.

Material and methods

Thirty-nine pregnant patients were included in the study. Initially, 50 patients were to be enrolled, but three pregnant renal transplant recipients and seven normal pregnant patients did not give their consent to participate in the study. In one case of normal pregnacy, the patient did not consent to obtaining a buccal smear from the neonate.

The study group consisted of nine pregnant renal transplant recipients aged 27 to 40 years. All patients had received immunosuppressive therapy since the time of transplantation and throughout pregnancy (cyclosporine A 125–175 mg twice a day, azathioprine 50–75 mg/day and prednisone 10 mg/day). The women were patients of the Department of General and Transplantation Medicine, Transplantation Institute, Medical University of Warsaw. During pregnacy they received perinatal care and gave birth at the 1st Department of Obsterics and Gynaecology, Medical University of Warsaw, in the years 1999–2002.

The control group consisted of 30 patients aged 18 to 38 years, with normal pregnancy. The women received perinatal care and gave birth at the 1st Department of Obsterics and Gynaecology, Medical University of Warsaw, in the years 2000–2002.

The characteristics of the two groups are summarized in Table 1.

The DNA of HPV types 6, 11 and 16 was studied in the discharge from the cervical canal, the maternal venous blood, the cord blood and the buccal smear obtained from the neonates. Pap smears were obtained from the cervix in the 3rd trimester of pregnancy during routine check-up examinations in the Antenatal Clinic. Two sterile swabs were used to obtain the smears. The obtained material was placed in 10 ml of physiological saline. At delivery, c. 10 ml of maternal venous blood and c. 10 ml of cord blood were collected into heparinized test tubes. A buccal smear was obtained using two sterile swabs from each neonate in the 2nd day of life. The obtained material was placed in 10 ml of physiological saline.

Each patient enrolled in the study gave her informed consent.

The statistic analise was performed on the base of Fisher test.

Results

Presence of human papillomavirus

Human papillomavirus (HPV) was found in 10 (26%) of 39 subjects.

HPV types 6 and 11 was found in 7 (18%) of 39 subjects while HPV type 16 was present in 5 (13%) of the subjects. The co-occurrence of HPV types 6, 11 and 16 was detected in 2 patients from the control group.

HPV was found in 2 (22%) of the 9 pregnant renal transplant recipients.

Types 6 and 11 were seen in one (11%) patient (Table 2): a 30-year-old primipara, 3 years post renal transplant, with condylomata acuminata of the vulva and vagina, an HCV-carrier. Delivery by caesarean section was performed at 37 weeks gestation because condylomata acuminata were present in the vaginal vestibulum.

The DNA of HPV type 16 was detected in one (11%) pregnant patient (Table 2): a 40-year-old multipara, 8 years post renal transplant, an HBV-carrier. Delivery by caesarean section was performed at 37 weeks gestation because of a positive obsteric history.

Of the 30 control patients, HPV DNA was detected in eight (26%). In two (6.6%), infection with oncogenic and non-oncogenic types of HPV was diagnosed.

The DNA of HPV types 6 and 11 was found in six (20%) subjects (Table 3). These were women aged 21 – 33 years with deliveries between 37 and 41 weeks of gestation – vaginal delivery in four cases and delivery by caesarean section because of obsteric indications in two cases.

Of the 30 control patients, the DNA of HPV type 16 was detected in four (13.3%), see Table 3. The patients aged 24 – 30 years, gave birth between 37 and 40 weeks gestation (vaginal delivery in two cases and delivery by caesarean section due to obsteric indications also in two cases).

Discussion

The presence of HPV DNA was established in ten (26%) of the 39 pregnant patients participating in the study, including two (22%) renal transplant recipients and eight (26.7%) control subjects.

In spite of iatrogenic immunosuppression, human papillomavirus was found to occur slightly less frequently in our group of renal transplant recipients compared with the control group (22% vs. 26.7, $p>0.05$). On the other hand, Schneider *et al.* (22) and Sillman *et al.* (25) observed an increased incidence of HPV infections in immunosuppressed females. Dyall-Smith *et al.* (4) who invesitigated the presence of HPV in renal transplant recipients 5 years after transplantation found skin warts (HPV types 1, 2, 3, 4, 5, 7, 8, 10, 14 and 17) in 92% of the subjects.

The estimated presence of HPV DNA in pregnant women reported by different authors varies considerably. The percentage of positive findings depends on the method of assay and the number of particular primers used. Our group of 39 patients was tested for the presence of HPV types 6, 11 and 16. Fife *et al.* (6), who investigated HPV type 18 in addition to HPV types 6, 11 and 16, reported a lower incidence (11.1%). Chang-Claude *et al.* (3) found HVP types 6, 11, 16, 18, 31, 33 and 35 in 13.9% of the study subjects. Tseng *et al.* (31) who studied the occurrence of HPV type 16 alone in the cervical canals of women with uncomplicated pregnancy, found the virus in 11.5% of the subjects. In our control group, HVP type 16 was isolated from the cervical smears of four (13.3%) women, the finding similar to that reported by Tseng *et al.* (31).

Summing-up, the finding of 26% pregnant women who tested positive for HPV types 6, 11 and 16 is much higher than most reported results. The application of polymerase chain reaction (PCR) which is a very sensitive assay most likely accounted for this high proportion of HVP-positive patients in our study.

HPV was detected in ten of the 39 women enrolled in the study and in the buccal smears of seven infants born to HPV-positive mothers, which means that the virus transmission from HPV-positive mother to fetus was confirmed in 70% of cases. The findings were compared with those reported by other authors. The incidence of reported vertical transmission varied widely from 5.29% (33), 27% (2), 30% (29), 31.6% (17), 33.3% (19), 37% (18) to 39.7% (30), but was considerably lower than the one established in the present study, i.e. 70%. Puranen *et al.* (18) and Cason *et al.* (2) reported vertical HPV transmission from mother to fetus in 70 – 80% of the investigated cases. In their study group,

however, 18% of pregnant women demonstrated clinical manifestations of HPV infection. In our study only one pregnant woman (1.9%), a renal transplant recipient, was found to have clinical features of HPV infection.

Transmission of HPV was established in 70% of study patients and their offspring. Two infants (29%) were born by vaginal delivery. In one case, HPV was detected in the patient's cervical canal and in the oral cavity of the neonate. In the other case, HVP was found in all four samples. In five patients (71%), the delivery was by caesarean section. In two of these cases, HVP was detected in the patient's cervical canal and in the oral cavity of the neonate, in two other patients in all four samples and in one case, in the cervical canal, the cord blood and the oral cavity of the neonate.

Of the ten HPV-positive patients, vaginal delivery was empolyed in four cases. In two of them (50%), HPV transmission from mother to infant was detected. In six (60%) of infected patients, delivery was by caesarean section. HPV was detected in five (83%) of thus delivered infants. Sedlacek *et al.* (23) detected HPV DNA in 11 (47.8%) of infants born by vaginal delivery to mothers with diagnosed HPV infection of the cervical canal of the uterus. Similarly, Tenti *et al.* (29) confirmed the presence of HPV DNA in 30% of infants born by vaginal delivery to HPV-positive mothers. A statistically significant proportion of HPV types 16 and 18 infection was detected in infants born by vaginal delivery compared to those delivered by caesarean section – 51.4% vs. 27.3% (30). The same was observed in a study by Puramen *et al.* (18) – 69% vs. 45%. HPV detected in the oral cavities of infants delivered by caesarean section, in the maternal venous blood and in the cord blood confirms fetal HPV infection before birth and thus suggests vertical transmission.

There are reports of the oocyte or zygote infection prior to or shortly after implantation or of infection spread with the semen (14). This observations may account for the presence of HPV in the cervical canal of the uterus of one HPV-positive patient and the cord blood and the oral cavity of the infant and in the cervical canal of another HPV-positive patient and the cord blood of the infant.

The likelihood of HPV infection of the fetus prior to delivery remains debatable. However, juvenile papilloma of the larynx, congenital condylomata acuminata, and HPV detected in the prepuce, the oral cavity and the amniotic fluid of infants delivered by caesarean section present arguments for the possibility of prenatal foetal infection with human papilloma virus.

There are very few papers in the world literature concerned with human papilloma virus in pregnant renal transplant recipients which makes the comparison and interpretation of the present findings difficult. A similar incidence of HPV infection was found in the two groups studied. It should be noted that the commonest route of infection with the genital types of HPV is through sexual contacts with an infected partner. The risk of infection increases with the number of partners (1, 3, 9, 30). It may be assumed that women after renal transplantation remain in more stable relationships that healthy women. This may explain the less frequent presence of HPV in spite of immunosuppressive therapy. However, to confirm this hypothesis prospective studies are required involving a much larger group of pregnant renal transplant recipients.

Conclusions

1. The HPV was found with 26% pregnant women. In comparison with other studies, when three or more types of HPV were inspected, this percentage is higher (26 vs 5.4, 11.1, 13.9)
2. The occurrence of HPV infections with pregnant renal transplant recipients in comparison with normal pregnancy was on similar level. High percentage of HPV transmission from mother to neonate was obtained (70 vs 5.29, 30, 37).
3. The cesarean section probably doesn't protect from HPV infection.
4. There's a suggestion, the HPV infection of fetus may occur in utero.

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