Survey of Human Papillomavirus Types and Maternal-fetal Transmission in Pregnant Women

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Abstract: Background, In this study, we sought to determine the prevalence, types, and maternal-fetal transmission of HPV in pregnant women in Nanjing, Jiangsu Province. Results, The overall cervical HPV-DNA positivity rate among pregnant women was 13.44% (422/3139). The most frequently detected HPV types in mothers were HPV-16 (29.62%, 125/422), HPV-18 (14.69%, 62/422), and HPV-58 (14.22%, 60/422). The HPV-DNA concordance rate in maternal-neonatal pairs was 23.60% (55/233). HPV type-specific concordance occurred in 26 cases. Female neonates had a higher HPV-DNA positivity rate than males (17.69% vs. 11.65%). Conclusion: The cervical HPV-DNA positivity rate among pregnant women was 13.44% during pregnancy in Nanjing, China. The HPV-DNA transmission rate in maternal-neonatal pairs was 23.60%. The most frequently detected HPV genotype in pregnant women and newborns was HPV-16 in 46.38%.

List of abbreviations:

human papillomavirus (HPV)

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Contribution to authorship
Ying Hong: conceived and designed the project. She performed specific operations, analyzed data, and provided materials and the final thesis. She is responsible for this project.
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Running title: HPV genotype in pregnant women and newborns

Disclosure: The authors report no conflict of interest.

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Condensation
The cervical HPV-DNA positivity rate among pregnant women was 13.44% during pregnancy in Nanjing, China. The HPV-DNA transmission rate in maternal-neonatal pairs was 23.60%.
Abstract

Objective: We sought to determine the prevalence, types, and maternal-fetal transmission of human papillomavirus (HPV) among pregnant women in Nanjing, Jiangsu Province, China.

Setting and Population or Sample: We screened for cervical HPV in 3139 healthy pregnant women in the Outpatient Department of Drum Tower Hospital.

Methods: Cervical cells were collected (gestational age: 24.65 ± 2.07 weeks) for cytological evaluation and determination of HPV infection status. Oral and genital exfoliated cells were collected from the neonates (<24 h old) of 233 HPV-positive mothers for HPV-DNA detection. Assays were performed using HPV Gene Chip technology with 23 HPV genotype probes.

Main Outcome Measures: Statistical analyses were performed using the SPSS software package. The influence of delivery type and neonate gender on neonatal HPV infection was analyzed using the $\chi^2$ or Fisher’s exact test. Probability values of <0.05 were regarded as significant.

Results: The overall cervical HPV-DNA positivity rate among pregnant women was 13.44% (422/3139). The most frequently detected HPV types in mothers were HPV-16 (29.62%, 125/422), HPV-18 (14.69%, 62/422), and HPV-58 (14.22%, 60/422). The HPV-DNA concordance rate in maternal-neonatal pairs was 23.60% (55/233). HPV type-specific concordance occurred in 26 cases. Female neonates had a higher HPV-DNA positivity rate than males (17.69% vs. 11.65%).

Conclusion: The cervical HPV-DNA positivity rate among pregnant women was 13.44% during pregnancy in Nanjing, China. The HPV-DNA transmission rate in maternal-neonatal
pairs was 23.60%. The most frequently detected HPV genotype in pregnant women and newborns was HPV-16 in 46.38%.

**Key words:** Human Papillomavirus; Maternal-fetal Transmission; Pregnancy

**Introduction**

Cervical cancer is the second-most commonly occurring cancer among women worldwide. Human papillomavirus (HPV), one of the most commonly transmitted infections, has been recognized as the primary cause of cervical cancer, papillomatosis, and anogenital warts [1, 2]. Low-risk, nononcogenic forms of HPV are associated with anogenital warts and laryngeal papillomatosis, and high-risk, oncogenic types are associated with cancers of the cervix, anogenital areas, and head and neck [3].

The five most prevalent HPV types associated with genital and oral cancers in the global female population are HPV-16, -18, -31, -58, and -52, ranked in varying orders of regional prevalence [4]. Previous surveys in China have found HPV-52 and -58, to be more prevalent than HPV-16 in some areas [5, 6]; this distribution is consistent with those in Japan and eastern Africa [4]. Most studies have found a higher HPV-DNA detection rate among pregnant women than among those who are not pregnant [7, 8].

Although there is overwhelming evidence for the sexual transmission of high-risk HPV genotypes, several studies have examined other routes, such as maternal-fetal transmission before or during childbirth, direct contact during labor, or horizontal transmission among children through contact with infected skin lesions [9, 10]. However, similar studies of transmission modes in different regions have obtained disparate results. Studies of maternal-fetal HPV transmission have found a wide range of neonatal infection rates; these
conflicting findings are primarily due to differences in populations and experimental techniques, and may also have been influenced by risk factors such as gender, type of delivery, and maternal status before delivery.

It is important to study the distribution of HPV genotype in pregnant women, as it will be helpful to use same HPV genotype vaccine for the prevention of cancer due to HPV infection. The prevalence of maternal-fetal HPV transmission may have an important impact on clinical handling and vaccination strategies for infected women during pregnancy.

In this study, we sought to determine the prevalence, types, and maternal-fetal transmission of HPV in pregnant women in Nanjing, Jiangsu Province.

**Materials and methods**

**Participants**

For this survey, we recruited 3139 consecutive healthy pregnant women out of 11696 who had their first obstetric examinations in the Department of Obstetrics and Gynecology, Affiliated Drum Tower Hospital, Nanjing University Medical School between January 2006 and April 2010. The pregnant women had a follow-up study after the delivery. The exclusion criteria for this study were: (1) threatened abortion or abnormal vaginal bleeding, (2) cervical lesions apparent upon simple visual inspection during gynecological examination, (3) sexual intercourse and/or vaginal medication in the previous 3 days, (4) HPV detected by cervical cytological examination within 1 year, (5) mental or physical incompetence, (6) in vitro fertilization (IVF) or precious fetus, and (7) refusal of gynecological examination. Consequently, 5204 pregnant women received this examination within one year while 2265
pregnant women refused gynecological examination. 1088 pregnant women were ruled out due to the exclusion criteria. The final study sample included 3139 pregnant women with a mean age of 29.89 years (range: 20–44 years). Most (81.49%, 2558/3139) women were in the 22\textsuperscript{nd}–26\textsuperscript{th} week of gestation upon enrollment in the study. All participating women provided written informed consent.

Data collection

We recorded the mothers’ socio-demographic characteristics, the gestational age when samples were collected, and parity data between January 2006 and April 2010. The pregnant women had a follow-up study after the delivery.

Samples were collected from all pregnant women and from 233 infants of the 422 HPV-positive women. The sample collection was carefully executed to prevent cross-contamination between subjects and anatomical sites by using disposable equipment and changing the bed lining and collector’s gloves between each subject.

During gynecological examination, two cervical smears were collected from each participant for cervical cytological analysis and HPV detection. A cervix brush was used to obtain exfoliated cells from the squamocolumnar junction of the cervix. The collection instrument was then rinsed in transport medium [12, 13]. A collection device (Decipher Bioscience, Shenzhen, China) was used to obtain cervical exfoliated cells for HPV-DNA detection. In accordance with the manufacturer's instructions, the samples were collected by scraping the uterine cervical canal with a cervical brush and were sent to the laboratory within 24 h.
Less than 24 h after birth, oral and genital exfoliated cells were collected from the subset of clean neonates using the same collection device for HPV-DNA detection. The child avoided close contact with mother to prevent the contamination of the mother’s exfoliated cells. Oral samples were obtained by allowing the neonate to suck on the sampler for about 10 sec. Genital samples were collected from males by gently rubbing the penis glans and the inner mucosal part of the prepuce. Specimens were obtained from females by gently rubbing the vulvar mucosa. Tips containing cellular material were then placed into transport medium tubes and immediately stored at -20°C.

**Laboratory methods**

The cytological specimens were sent to the pathology laboratory for examination. They were prepared using the ThinPrep 2000 Processor (AutoCyte Inc., Burlington, NC, USA), according to the manufacturer's instructions. The suspensions were used to make liquid-based cytology slides that were examined by trained cytologists using the ThinPrep imager. This computer-based imaging technology is a recent introduction that facilitates primary cervical screening for epithelial cell abnormalities, as defined by the 2001 Bethesda System for Reporting Cervical Cytology [14]. This system uses the following classifications: (1) negative for intraepithelial lesion or malignancy (encompassing the previous category of “within normal limits”), (2) atypical squamous or glandular cells of undetermined significance (ASCUS, AGUS), (3) atypical squamous cells, not excluding high-grade squamous intraepithelial lesion (ASC-H), (4) low-grade squamous intraepithelial lesion (LSIL), (5) high-grade squamous intraepithelial lesion (HSIL), and (6) squamous-cell or
adenomatous carcinoma (SC, AC). Many studies have confirmed that ThinPrep liquid-based cytology has improved accuracy and reading times, enhancing laboratory productivity and clinical outcomes. This technology also allows HPV testing of the same sample [15, 16].

HPV genotyping was performed using a polymerase chain reaction (PCR) amplifier provided by the laboratory of the Affiliated Drumtower Hospital, Nanjing University Medical School (Bio-Rad Laboratories, Shanghai, China), a hybridization incubator (Decipher Bioscience), and an HPV genotyping DNA chip (Decipher Bioscience). DNA was extracted from the samples and centrifuged at 13,000 rpm for 10 min. Primer-mediated PCR assays were performed in reaction tubes containing 5 μL DNA and 20 μL reaction buffer. The buffer contained specific primers designed and synthesized with biotin. The PCR conditions were: preheating at 50°C for 15 min and at 95°C for 10 min, followed by 40 cycles of 30 sec at 94°C, 90 sec at 42°C, and 30 sec at 72°C, and a final extension of 5 min at 72°C. Reverse hybridization was performed using a line-probe assay to enable the PCR products hybridized with specific probes to become fixed on the membrane. Chemical colorization [0.1 M sodium citrate, tetramethylbenzidine (TMB) substrate, 30% H2O2, 30 min] was then performed to determine the results.

Statistical analyses

Statistical analyses were performed using the SPSS software package (ver. 17.0 for Windows; SPSS Inc., Chicago, IL, USA). Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) to determine the factors associated with HPV infection. The influence of delivery type and neonate gender on neonatal HPV infection
was analyzed using the χ² or Fisher’s exact test. *P*-values of <0.005 were regarded as significant.

**Results**

Table 1 shows the risk factors for HPV infection and the cervical detection rates of one or more HPV genotypes in this sample of 3139 pregnant women. The overall HPV-DNA positivity rate was 13.44% (422/3139). The mean age of HPV-positive mothers was 27.88 ± 3.48 years. The risk factors listed in the table have been verified by previous studies [17, 18]. The mean age of all mothers at delivery was 29.89 years (range: 20–44 years), while that of HPV-positive mothers was 27.88 ± 3.48 years. Pregnant women younger than 24 years of age had a significantly higher HPV positivity rate ($\chi^2 = 12.07, P = 0.001$). The HPV positivity rate for women in their first gestation was 13.83% (234/1692; $\chi^2 = 0.67, P = 0.41$). Parity was not associated with HPV positivity (OR for $\geq 3$ vs. 1–2 gestations = 1.20, 95% CI: 0.91–1.58). Also, most (72.44%) women in this study had a greater than high-school education. A significant difference was found in HPV positivity rates among women with different education levels (OR for $\leq 11$ and 12–17 years vs. $\geq 18$ years = 4.44, 95% CI: 1.78–11.09; and 2.99, 95% CI: 1.21–7.39, respectively, *P* for trend < 0.01). Abnormal cervical cytological results were found in 42 (1.34%) mothers, consistent with data from Shanghai, the largest city in southern China [17]. Among these, the HPV positivity rate was 76.19% (32/42). This rate is much higher than that among mothers with normal cytology results, verifying the strong association between cervical lesions and HPV infection.

Figure 1 shows the HPV genotypes and frequencies of detection in mothers and neonates.
Most (95.49%, 403/422) of the HPV-positive mothers (13.44%) were infected with high-risk HPV genotypes. The most frequently detected HPV genotypes in mothers were HPV-16 (29.62%, 125/422), HPV-18 (14.69%, 62/422), and HPV-58 (14.22%, 60/422). The HPV-16 and HPV-18 genotypes, which are prevented by current HPV vaccines, thus accounted for 44.3% (187/422) of HPV infection. Of the 422 HPV-positive samples, 353 (83.65%) were single infections and 69 (16.35%) were positive for two or more HPV types. HPV-16 infection was present in 46.38% (32/69) of these multiple infections.

The oral and/or genital mucosa of 55/233 (23.61%) neonates showed HPV-DNA positivity. No significant difference was found between male and female infants ($\chi^2 = 1.64, P = 0.268$) and between different delivery types ($\chi^2 = 0.283, P = 0.71$). The HPV-16 genotype accounted for the majority (56.36%, 31/55) of infants. In 233 mother-neonate pairs, the HPV DNA concordance rate between mothers and newborns was 23.60% (55/233). HPV type-specific concordance occurred in 26 cases and HPV-16 was the most detected genotype (18/26), followed by HPV-11 (2/26) and HPV-31 (2/26) (Table 2).

Delivery type did not significantly affect the rate of vertical transmission from HPV-positive mothers; 36 (58.37%) of the 233 tested neonates were delivered vaginally and 97 (41.63%) were delivered by cesarean sections ($\chi^2 = 0.119, P > 0.005$). The HPV-DNA concordance rate between these 233 mother-neonate pairs was 23.60% (55/233). HPV type-specific concordance occurred in 26 cases (11.16%) and HPV-16 was the most frequently detected genotype (Table 3).

**Discussion**

This study is one of few that have examined the maternal-fetal transmission of HPV DNA
in a large patient population. Our results revealed that type-specific HPV concordance was high, suggesting other infection routes besides the maternal-neonate route. Although the HPV positivity rate of mothers with abnormal cervical cytology (76.19%) was much higher than that of mothers with normal cytology, none of the 19 neonates of mothers with abnormal cytology was HPV positive. We found no significant influence of delivery type on the vertical transmission of HPV; this result was consistent with reports of congenital condyloma after cesarean section without premature rupture of membranes [17]. Delivery via cesarean section did not eliminate the risk of vertical transmission, suggesting that such transmission of HPV DNA may occur before birth by the transplacental route. Several studies have found HPV in amniotic fluid, fetal membranes, and cord blood [20–22]. We found discordance in 52.73% of maternal and neonatal HPV genotypes, indicating transmission by fomites (e.g., contaminated instruments), contact with the child after birth, or experimental contamination of the samples.

Pregnant women in Jiangsu Province usually begin routine obstetric care around the 24th week of gestation; 81.49% of the women in this sample were in the 22–26th week of gestation. Given this small interval of gestational age, we did not examine the influence of this variable on HPV infection in pregnant women. We found that HPV infection in pregnant women was primarily associated with maternal age and education. The influence of education level on HPV infection is more likely to be explained by the early age of first sexual intercourse and first pregnancy [22].

We used the gene-chip technology (microarray) developed by Decipher Bioscience to detect 23 HPV genotypes in this study. As a diagnostic tool, the application of microarray technology has the advantage of discriminating HPV genotypes and detecting infection with
multiple HPV subtypes [23]. In a population-based cross-sectional screening study of 1137 women aged 15–59 years in Shenzhen, Li et al. [24] confirmed the clinical value of this technology for HPV detection in cervical cancer screening. Halfon [25] found 93% concordance (k = 0.82) between the HC-II assay and DNA-chip technology, indicating that the gene-chip technology had good sensitivity and specificity in the detection of HPV genotypes.

Immunological or hormonal changes may alter the rate of HPV positivity and clearance during pregnancy [27]. Some authors have reported decreased clearance of high-risk HPV types in the first two trimesters of pregnancy [27, 28], contributing to a high prevalence of HPV during pregnancy. We found an HPV-DNA positivity rate among pregnant women (13.44%) similar to that (13.80%) reported by a multicenter epidemiological survey for the general female population of China [30]. Similarly, Zhang et al. [29] found no significant difference in HPV-DNA positivity rates associated with the pregnancy status of 711 women in Beijing.

The prophylactic quadrivalent HPV 16/18 vaccine manufactured by GlaxoSmithKline is in phase-III clinical trials in Jiangsu Province. Few studies have evaluated the safety of this vaccine for pregnant women in China. Since the primary target population of the HPV vaccine is women of reproductive age, the risks associated with its administration during pregnancy are important factors affecting personal decisions and public health policy. In a study of 3599 pregnancies, Wacholder et al. [31] detected a small increase in the risk of miscarriage for pregnancies conceived within 3 months of vaccination.

The present study found a substantial prevalence of HPV positivity among pregnant
women in Nanjing, the urban center of a highly developed province in China. This prevalence did not differ significantly from that found among the general female population of China. Although some maternal-fetal transmission was documented, the high rate of discordance in the HPV genotypes of mothers and neonates indicates the need for efforts to prevent horizontal transmission. Subsequent investigations should examine the role of viral load (especially of infected maternal cervical cells) in maternal-fetal transmission [32].

This large-scale investigation evaluated the prevalence of HPV infection in pregnant women and the rate of maternal-fetal transmission. The most frequently detected HPV genotypes in mothers and neonates were HPV-16 and HPV-18, consistent with the target genotypes of HPV vaccines. Appropriate vaccination strategies for mothers and newborns, however, remain incompletely developed.

Conclusion

In conclusion, the most frequently detected HPV genotype in pregnant women and newborns was HPV-16.

Acknowledgements

Yan Yu: participated in part of the collection of data.

Jie Xu: participated in part of the collection of data.

Disclosure

The authors report no conflict of interest.

Contribution to authorship
Ying Hong: conceived and designed the project. She performed specific operations, analyzed data, and provided materials and the final thesis. She is responsible for this project.

Shu-Qin Li: participated in the recent part of the collection of data.

Ya-Li Hu: guided the project.

Zhi-Qun Wang: participated in part of the collection of data.

Details of Ethics approval

The study is approved by the Hospital Ethics Committee.

Cervical cancer screening is the conventional clinical examination, and does not have a question of ethics.
References


[8] Nobbenhuis MA, Helmerhorst TJ, Brule AJ van den, Rozendaal L, Bezemer PD, Voorhorst FJ, Meijer CJ: High-risk human papillomavirus clearance in pregnant women:


Figure legends

Figure 1. Prevalence of HPV genotypes (HPV-6, -11, -43, -16, -18, -33, -56, -58 and multiple infection) among 422 HPV-DNA positive mothers and 55 HPV-DNA positive newborns (oral and genital samples).
Table 1. Risk factors for HPV-DNA positivity among mothers.

Table 2. Neonatal HPV status among 233 infants with HPV-positive mothers.

Table 3. Neonatal HPV status by delivery type.

Table 1. Risk factors for HPV-DNA positivity among mothers.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number of cases (% , HPV+)</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤24</td>
<td>62/348 (17.82%)</td>
<td>1.19</td>
<td>0.85–1.67</td>
</tr>
<tr>
<td>25–29</td>
<td>243/2032 (11.96%)</td>
<td>0.75</td>
<td>0.58–0.95</td>
</tr>
<tr>
<td>≥30</td>
<td>117/759 (15.42%)</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1–2</td>
<td>348/2662 (13.11%)</td>
<td>Reference</td>
<td>-</td>
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<tr>
<td>≥3</td>
<td>73/477 (15.30%)</td>
<td>1.20</td>
<td>0.91–1.58</td>
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<td>Education (years)</td>
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<tr>
<td>≤11</td>
<td>150/865 (17.34%)</td>
<td>4.44</td>
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<td>12–17</td>
<td>267/2163 (12.34%)</td>
<td>2.99</td>
<td>1.21–7.39</td>
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<tr>
<td>≥18</td>
<td>5/111 (4.50%)</td>
<td>Reference</td>
<td>-</td>
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<tr>
<td>Cytological result</td>
<td></td>
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<td></td>
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<tr>
<td>Normal</td>
<td>390/3097 (12.59%)</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>ASCUS</td>
<td>22/32 (68.75%)</td>
<td>15.27</td>
<td>7.18–32.49</td>
</tr>
<tr>
<td>HPV status</td>
<td>Male (cases)</td>
<td>Female (cases)</td>
<td>Total (cases)</td>
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<tr>
<td>HPV+</td>
<td>12</td>
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</tr>
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<td>91</td>
<td>107</td>
<td>198</td>
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<tr>
<td>Total</td>
<td>103</td>
<td>130</td>
<td>233</td>
</tr>
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</table>

Table 2. Neonatal HPV status among 233 infants with HPV-positive mothers.
Table 3. Neonatal HPV status by delivery type.

<table>
<thead>
<tr>
<th></th>
<th>Cesarean section</th>
<th>Vaginal delivery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV+</td>
<td>16</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>HPV-</td>
<td>81</td>
<td>117</td>
<td>198</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>136</td>
<td>233</td>
</tr>
</tbody>
</table>

Note:

Among the 233 infants with HPV-positive mothers, 103 (44.2%) were males and 136 (58.4%) were born by vaginal delivery. No significant difference was found between male and female infants ($\chi^2 = 1.64, P = 0.268$) and between different delivery types ($\chi^2 = 0.283, P = 0.71$).
Figure 1

The bar chart illustrates the prevalence of different HPV genotypes in different groups:
- **Mother**
- **Newborn, Oral**
- **Newborn, Genital**

The x-axis represents the HPV genotypes (6, 11, 43, 16, 18, 33, 56, 58, Multi-infection), and the y-axis shows the prevalence in percent. The chart shows varying prevalence across different genotypes and groups.
<table>
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<td>HSIL</td>
<td>3/3</td>
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<td></td>
<td>422/3139 (14.44%)</td>
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Additional files provided with this submission:

Additional file 1: approval of ethics(c).pdf, 135K