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Research Article

Prenatal Transmission of High- Risk HPV 16 And HPV 18 Among Antenatal Mothers In Western Nigeria

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Abstract

Several reported evidences do exist that the transmission of human papilloma (HP) viral infection may occur via non-sexual routes while others show the possibility of detecting HP-viral-DNA in reproductive cells, cord blood, and placental cells. However, there is paucity of background information on HP-viral infection transmission among mothers and newborns which necessitates study. The study aims at determining prenatal transmission of high-risk human papillomavirus genotypes HPV 16 and HPV 18 among antenatal mothers and maternal cervical cells in Western Nigeria. We investigated 113 pregnant women from whom cervical samples were collected during the antenatal clinic and their newborns at the University of Ilorin Teaching Hospital. HP-viral screening, DNA extraction and molecular detection was carried out using MY09/MY11 and GP5+/GP6+ consensus primers while HP-viral high risk genotypes were detected using type-specific primers. HP-viral DNA was detected among 54 (47.8%) cord blood samples and 11 (9.7%) cervical specimens with nine specimens from mothers while newborns samples showed a corresponding HP-viral-DNA results. The genotypic characterization/identification of HP-virus type 16 and 18 from both specimens showed an overall prevalence of 15.0% (7/113) for HPV-16 and 8.0% (9/113) for HPV-18, while only three specimens from corresponding mothers and newborns had HPV-16. Such observation indicates/suggests that mothers are the most probable transmission source of HP-viral-DNA to newborns. Furthermore, the presence of HPV-16 (a high-risk genotype) could portend HP-viral diseases in newborns. In order to avoid transmission during pregnancy, routine monitoring and surveillance are advised for mothers-to-be and those who have recently given birth. HPV vaccinations are required during family planning prior to pregnancy.

1. Introduction

The human papillomavirus, or HPV, is a tiny, non-enveloped virus with an icosahedral structure and a diameter of about 50–60 nm. It is a member of the Papillomaviridae family, which is distinguished by a double-stranded, closed circular DNA genome that is shielded by a capsid made of two late proteins (L1 and L2). HPV is the most common sexually transmitted infection of viral origin among humans which drives a well-established course for the development of cervical, anogenital, head, and neck cancers [1]. Evidence exists that the transmission of HPV infection may occur via non-sexual routes [2], as its DNA detection in reproductive cells, cord blood, and placental

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cells supports this claim. Also, this virus has been detected in infants, children, and individuals who have never had sexual intercourse [2–4]. The transmission of HPV via saliva has been used to explain cases of oral infection in infants whose mothers are HPV negative [2]. The evidence of hematogeneous and vertical spread of HPV yet requires further investigation to understand infection and adoptable preventive measures [5].

Infants have been observed to show signs of HPV-induced lesions, such as laryngeal and anogenital lesions at birth which has led to the assumption that intrauterine HPV transmission may occur [5]. Futhermore, HPV DNA has been detected in amniotic fluid [3], placenta, and the umbilical cord [6]. It is also known that both chorionic and placental tissue may be infected through the hematogenous route hence, HPV may spread to amniotic cells that are then ingested by developing fetus [2, 3]. The study of Tsend and his colleagues [7]. have demonstrated an increased rate of HPV detection among newborns due to the type of delivery either vaginal delivery and/or cesarean section. It is recorded that HPV has been detected in more than 50% of those who had vaginal delivery when compared to approximately 30% among those delivered by cesarean section [8]. Another study showed an increased incidence of juvenile respiratory papillomatosis after prolonged delivery of more than 10 hours [7, 8]. has also observed a low potential for viral transmission to the oropharyngeal mucosa of newborns from mothers without changes in cervical cytology or a history of genital warts. A study on HPV infection by [9] reported a relatively high prevalence of high - risk HPV among women infected with cervical cancer. Also, [10] reported a high prevalence of HPV in women without abnormal lesions in their cervix.

However there is dearth of information describing the detection of HPV among intra-uterine specimens Hence, this study investigates prenatal transmission of high-risk human papilloma virus genotypes among antenatal mothers in Western Nigeria.

2. Materials and Methods

A prospective hospital-based cross-sectional study was carried out among pregnant women and their newborns at the Obstetrics and Gynaecology unit of the University of Ilorin Teaching Hospital (UITH), Ilorin, Nigeria between August 2017 and June 2018. A Consecutive non-probability sampling technique was applied to select consenting participants that participated in the study. One hundred and thirteen pregnant women with gestational age above 37 weeks who had vaginal delivery at UITH participated in this study after understanding the protocol and giving of a written informed consent. Cervical exfoliated cells were collected from mothers with a sterile swab into a tube containing an alcohol-based preservativeOn the day of delivery, matching cord blood samples were taken into EDTA anticoagulant tubes. Both specimens were then sent to the Central Research Laboratories, University of Ilorin, Virology laboratory, where they were kept at -20°C until analysis. The specimens were sent in cooler ice boxes.

2.1. Genomic DNA extraction of Viral Nucleic acid from Blood and Tissue

DNA was extracted from cervical cells and blood using a DNA extraction kit (Favorgen, South Korea). With a few minor modifications, the previously described methods of [11] were followed for HPV detection in a nested PCR using the MY09/11 and GP5+/6+ consensus primers. An initial denaturation of 95ºC for 9 min was followed by 40 amplification cycles at 95ºC for 30 s. The annealing step was for 2 min each at 50ºC and 45ºC for the first and nested round of amplifications, with extension at 72ºC for 1 min 30 s, and a final extension at 72ºC for 4 min. A 450 bp and 150 bp fragments, respectively, were seen on a 1.5% agarose gel dyed with Sybr safe dye Using the InGenius 3 TM +System (Syngene, USA). As previously reported by [12], genotyping was carried out using HPV 16 and 18 type-specific primers, with anticipated amplicon band sizes of 457 bp and 322 bp fragment, respectively. 40 amplification cycles were applied to DNA that tested positive for HPV. Nine minutes of initial denaturation, thirty seconds of denaturation at 95 degrees Celsius, two minutes of annealing at 45 degrees Celsius, one minute of extension at 72 degrees Celsius, and four minutes of final extension at 72 degrees Celsius were all conducted. A Veriti Thermal Cycler (Applied Biosystem, USA) was used for every PCR. The InGenius 3 ^{TM} +System (Syngene, USA) and the Edvotek electrophoresis system (Edvotek USA) were used for the electrophoresis and detection processes.

2.2. Statistical analysis

Data generated in this study were systematically analysed to generate mean, proportion and chi-square test using Graph Pad Prism 8.02 (San Diego, USA). The chi-square test was used to determine the differences between groups and a two-sided probability of < 0.05 was considered statistically significant.

3. Results

This study included 113 pregnant women with a mean age of 27.0 years who were between the ages of 19 and 42. The majority of participants fell into the 25–34 age range Table 1. Out of the participants, only one was single, and 5.4% (6/112) of the pregnant women were in polygamous marriages. Compared to women who have been pregnant four times (6/113), a higher percentage of women—50.4%(57/113)—have been pregnant twice.

HPV DNA was detected in 54 (47.8%) cord blood of newborn while 11 (9.7%) cervical specimens from their mothers were positive Figure 1. Comparison of HPV prevalence in mother's cervical specimen and cord blood of newborn showed a statistically significant difference (x^2=39.93, 1; P value <0.0001). It was observed that only nine specimens from mother and their newborn had corresponding HPV DNA results Figure 2. Concordance of positive HPV DNA in mothers and their newborn showed statistically significant difference (x^2 = 5.656, 1; P value= 0.0174)

Genotypic Identification of HPV-16 and HPV-18 from both specimens showed a prevalence rate of 15.0% (7/113) for HPV-16 and 8.0% (9/113) for HPV-18 as shown in Figure 3. The comparison of prevalence rate of both HPV-16 and HPV-18 showed no significant difference

among mothers and newborn (HPV 16: x^2 = 0.8771, 1; P= 0.3490; HPV 18: x^2 = 0.01492, 1; P= 0.9028).
It was observed that only three specimens from corresponding mother and newborn had HPV-16. Concordance of positive HPV-16 and HPV-18 DNA in mothers and their newborn showed there was no statistically significant difference among them as shown in Figure 4 (HPV-16: x^2 = 0.002753, 1; P= 0.9582; HPV-18: x^2 = 0.2490, 1 P= 0.6178).

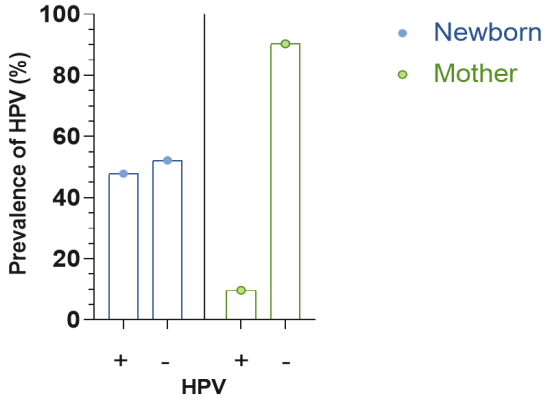

Figure 1: Prevalence of HPV among mothers and newborns. x^2= 39.93, 1; P value ¡0.0001

Figure 1 shows the prevalence of HPV among mothers and newborn. HPV prevalence was higher among newborn 47.8% (54/113) when compared to their mothers 9.7% (11/113). 90% of moms (102/113) were found to have no detectable HPV DNA in their cervix. There was a statistically significant difference when prevalence of HPV DNA was compared among newborn and their mothers (2= 39.93, 1; P value ¡0.0001).

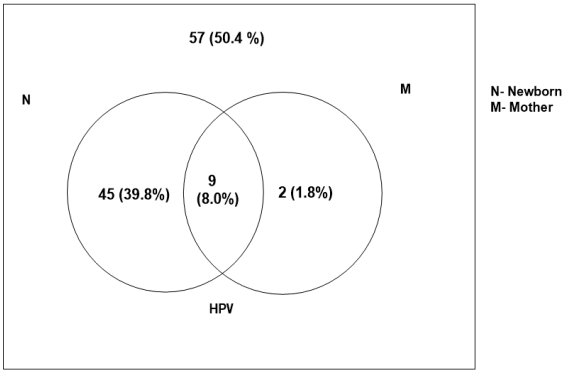

Figure 2: Venn diagram showing concordance of HPV among mothers and newborns. x^2 = 5.656, 1; P value= 0.0174

Figure 2 shows that only nine mothers and their newborn had HPV DNA while 57 (50.4%) did not have HPV at all. HPV DNA was present in 45 cord-blood samples (39.8%) without being present in their mothers while only 2 mothers (1.8%) had HPV DNA with no HPV detected in the cord-blood of their newborn.

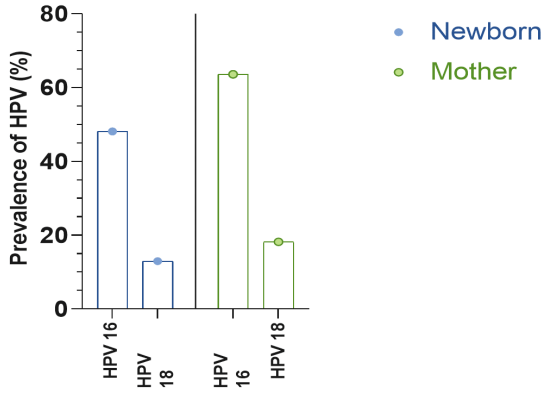

Figure 3: Prevalence of HPV 16 and 18 among mothers and newborn. HPV 16: x^2 = 0.8771, 1; P= 0.3490; HPV 18: x^2 = 0.01492, 1; P= 0.9028

Figure 3 shows the prevalence of HPV 16 and HPV 18 among mothers and newborn. It was observed that 48.1% (26/54) of newborn had HPV 16 DNA in their cord-blood while about 13% (7/54) had HPV 18 DNA in their cord-blood samples. HPV 16 DNA was detected frequently among HPV positive mothers (63.6%, 7/11) when compared to HPV 18 (18.2%, 2/11). There was no statistically significant difference when HPV 16 and 18 were compared among mothers and their newborn in this study.

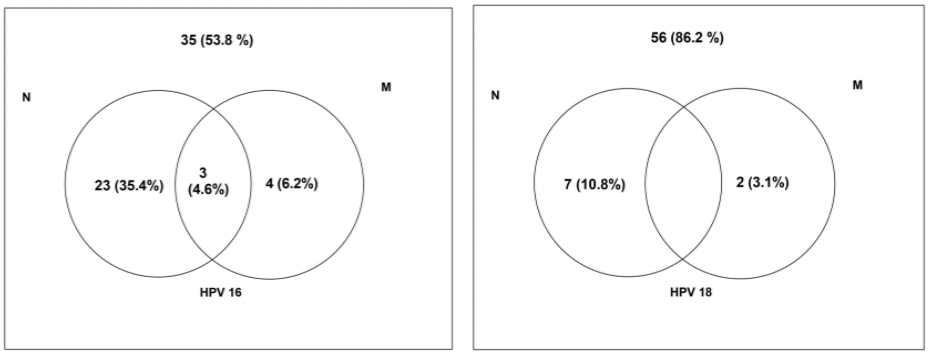

Figure 4: Venn diagram showing concordance of HPV 16 and 18 among mothers and newborns

HPV 16: x^2 = 0.002753, 1; P= 0.9582; HPV 18: x^2 = 0.2490, 1 P= 0.6178. Figure 4 shows concordance of HPV 16 among three mothers and their newborns in this study when compared to HPV 18 that was found among seven newborns (10.8x^2) and two mothers (3.1x^2) without concordance. HPV 16 was also found alone among 23 (35.4x^2) newborn and four (6.2x^2) mothers without concordance. There was no statistically significant difference when HPV 16 and HPV 18 concordance were considered among mothers and their newborn in this study.

Table 1: Demographic Characteristics of Participants in relation to HPV Infection.

Characteristics	HPV + (x^2)	HPV – (x^2)	x^2	DF	P-value
Age of Mother (Years)					15-24
3 (2.7)	41 (36.3)	1.64	2	0.441	
25-34	5 (4.4)	47 (41.6)			
35-44	3 (2.7)	14 (12.4)			
Marital Status					
Married	11	101	0.11	1	0.742
Type of Marriage					
Monogamy	10	96	0.34	1	0.563
Polygamy	1	5			
Parity					
1	3 (2.7)	26 (23.0)	1.44	3	0.697
2	4 (3.5)	53 (47.8)			
3	3 (2.7)	17 (15.0)			
4	1 (0.9)	5 (4.4)			
Gender of Newborn					
Male	29 (25.7)	37 (32.0)	0.94	1	0.332
Female	25 (22.1)	22 (19.5)			

4. Discussion

Transplacental infection is one possible means through which HPV intrauterine transmission may occur from the ascending route of the maternal genital tract as previously reported by related investigators [13]. The current study focused specifically on the prevalence and transmission dynamics of HPV among cord-blood specimen of newborns and their mothers in Ilorin, Nigeria. The results of this study may be used as a model for future research on HPV infection in mothers and their newborn offspring. We carried out our investigation during the third trimester of pregnancy, which is when HPV clearance was clearly visible, as reported by [14] and [15] who tracked pregnant subjects from the first to the third trimester.

There was evidence of potential vertical transmission of HPV from mother to newborn occurence in this study which is similar to other reports [5, 16]. However, the high prevalence of HPV in the cord-blood of newborns (47.8%) in this study calls for attention in the public health system especially when a high-risk genotype with carcinogenic potential is involved. There was also observable potential for perinatal transmission in this study arising from the higher prevalence rate in spite of the low concordance of HPV DNA which is also similar to the meta-analysis report of [17]. The association of HPV positivity in newborns to HPV negative mothers suggests that the mother might be the most probable source of HPV Figure 2. This may be associated with the fact that HPV may be transmitted vertically during pregnancy, as evidenced by the presence of HPV DNA in cord blood. Furthermore, the observation of far less HPV in mothers when compared to the

cord-blood of newborns could be due to HPV clearance which peaks at the third trimester [14, 15]. This may be due to the third trimester samples analysed, potential reducuction in sexual activity and fewer sexual partners at this stage of pregnancy which translates to a lower chance of detecting/contracting a new HPV infection. Although some other studies that did not follow-up pregnant women have reported that there is increased or no difference between HPV detected in the different stages of pregnancy [18, 19]. The study design and population sampled might have influenced the results obtained.

This study also shows that HPV negative mothers had HPV detected in the cord-blood of newborns. Although, this observation seems to be in line with the work of [16, 20], the possible explanations for this discordant finding include insufficient HPV copy number to detect infection (latent infection) and clearing of infection at the later stages of pregnancy. It is obvious that, contrary to popular belief, it remains a possibility that HPV can be present in children born to negative mothers. [21] explained that in vast majority of instances, neither placental nor cord blood HPV positive was associated with HPV recovery in maternal vaginal or oral scrapings carried out before delivery. Consequently, the hypothesis that HPV may have entered the placenta earlier in pregnancy lends credence to the idea that HPV DNA maintenance occurs in human trophoblasts, which have been demonstrated to both express and promote HPV receptors [22].

The previous study of [2] also detected the HPV in cord-blood and placenta which reveals an associated with history of genital HPV but not with maternal HPV detection before delivery. In their study it was posited that HPV infection in mothers at the time of pregnancy could have been cleared from the cervix before delivery. The work of [7]. reported that HPV DNA is present in maternal peripheral blood lymphocytes and cord-blood also corroborates the exposure of newborn to HPV DNA through maternal peripheral blood rather than cervicovaginal cells. In this study only 9.7% of mothers had genital HPV DNA infection which is grossly not proportional to the number of newborns with HPV DNA detected in their cord-blood samples. This differs to the work of [23] who reported HPV in about 5% of placenta samples obtained from mothers with 36.6% HPV prevalence. This follows the thought of newborn acquisition of viral DNA from their infected mothers.

From the forgoing, it is evident that even when a scenario of higher HPV DNA detection occurs in newborn (which is a deviation from the normal), the work of Wang and others who found HPV DNA in 35.6% of cervical cells and in 42.5% of fetal membranes shows some degree of similarity with this present study [24]. The possible reasons for high HPV DNA detection among cord-blood of newborn could be as a result of an ascending route of infection from maternal genital tract as a result of cervical HPV infection or infection that could not be accounted for as a result of sampling method which may be associated with medical procedure like transvaginal ultrasound as previously reorted by related researchers [3].

HPV transmission may also occur from the semen and ovaries which suggests the peri-conceptual acquisition, even though, this virus has been detected in ovarian malignancy, this argument has a theoretical basis [**? ?**]. This finding should not be ignored especially in an environment where practices like female genital mutilation, the use of herbal concoctions and indiscriminate use of drugs still exists. These may have a role to play in the unexplained reasons for increased HPV occurrence among newborns.

In neonatal and cervical samples, HPV 16 and 18 E6 genes were found Figure 3.4 This study found that mothers' cervical cells (63.6%) and newborns' cord blood specimens (48.1%) had higher frequencies of HPV 16 detection. This provides more evidence to support the findings that mothers and their newborns are more likely to contract HPV-16. Additionally, it was noted that mothers and newborns both have HPV 18. Nevertheless, this genotype did not show any concordance. Concordance of three mothers and their newborn pairs were observed among HPV 16 positive genotype.

The circulation of high-risk HPV genotypes 16 and 18 among mothers and newborn implies that there is a risk of HPV disease if the child does not clear the virus in early childhood. [25] has reported the persistence of high-risk HPV for at least 2 years after birth. [26] also reported HPV DNA among children between 3 months to 11 years who were born to HPV negative mothers. [27] found a high prevalence of HPV 16 (51.7%) among children aged 3 to 11 years. This suggests that infection with high-risk HPV 16 may become established in early life and persists thereafter.

It is important to note that this study did not follow up the newborn to examine viral persistence, however there is a possibility that high-risk HPV may persist among them. This study gives a clue to the increased circulation of HPV 16 among pregnant mothers when compared to HPV 18 in our environment.

Following the studies of various related investigators, It is known that the consequences of high-risk HPV transmission to humoral and cell mediated immunity are not yet fully defined. In a study by Koskimaa et al. (2017) who compared HPV 16 E2 and E6 reactivity among children and observed HPV DNA in placenta and or cord blood and concluded that HPV infection or exposure to viral antigens during the prenatal period might affect the activation and type of immune responses during later encounters with HPV as well as HPV prophylactic vaccines. This may also be the case I this study as positive detected high risk HPV genotype may also arouse activation of specific immune response.

As a suggestive strategy for control, some studies have proposed the introduction of HPV vaccine at birth. This may be a good idea. However, it is important to know and establish the effect of immune interactions as a result of the presence of HPV DNA in utero. Even though, it is known the efficacy of HPV 16/18 vaccine is not in doubt. The findings of this study give background information in the Nigerian population that could lead to a larger prospective cohort study that could elucidate the influence of HPV infection in utero on the immune system taking into consideration the influence of HPV prophylactic vaccines.

Limitations

This study enlists a number of limitations. We did not follow up the known HPV status of the newborn to determine persistence or clearance of infection as well as possible complications. An antibody test was not also conducted on negative specimen especially for blood related samples due to potential viral clearance that may be associated with the period of sample collection. Furthermore, the HPV genotypes detected were not sequenced for identification of genetic relatedness or differences.

5. Conclusions

The study's findings showed that women and their newborns had a preponderance or prevalence of HPV genotype 16. There is a larger chance of HPV discovery in gestation among Nigerians, as evidenced by the increased rate of HPV DNA detection in newborns when compared to

mothers. It is most likely that mothers are the source of HPV infection in-utero. Although, the reasons for this are still obscure, there is need for further research or study to substantiate this claim. We believe that the true clinical picture of HPV infection in this environment is still yet to be fully elucidated among women of child-bearing age. However, HPV vaccination during family planning prior to pregnancy can be recommended to prevent vertical transmission.

Article Information

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Consent to Publish (Ethics): The authors affirm that human research participants signed informed consent regarding publishing their data in a reputable Journal.
Conflicts of Interest: The author(s) declare(s) that there is no conflict of interest to declare

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