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Human Papilloma Virus infection & spontaneous preterm delivery among pregnant women attending OBG clinic at SMS medical college Jaipur: A case control study

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Abstract

Objective(s): To assess and compare the proportion of Human Papilloma Virus infection in preterm and term delivery.

Method(s): This study was a hospital based case control analytical type of observational study conducted in Dept. of Obs. & Gynae, SMS Medical College, Jaipur from August 2014 to august 2015. All patients coming with labour pains and delivering before 37 weeks gestational age were taken as preterm deliveries (cases)-Group A. All patients coming with labour pains and delivering at or after 37 weeks gestational age were taken as full term deliveries (controls)-Group B. They were selected according to inclusion criteria. Patients were evaluated after informed consent and detailed history was taken and examination done. After the patient delivered, placental tissue was taken with forceps and saved in normal saline. This sample was sent for HPV PCR-DNA test to microbiology advanced department to detect infection.

Result(s): Both groups were matched according to age, religion, literacy, rural/urban and socioeconomic status characteristics. 2 samples out of 36 samples of group A tested HPV DNA positive with p value <0.001 which is highly significant.

Conclusion(s): HPV is able to infect and replicate in invasive trophoblast cells and that infection by HPV induces pathological sequelae that are associated with placental dysfunction and spontaneous preterm delivery. Perinatal transmission of human papilloma virus may occur directly, during the passage of the fetus through the birth canal and on coming into contact with infected maternal secretions or indirectly, during vaginal delivery from contaminated objects and intrauterine transmission at the time of fertilization from sperm carrying latent virus. HPV PCR technology identifies maternal HPV DNA, thus considerably increasing the sensitivity and specificity to identify HPV.

Keywords: HPV, preterm

Introduction

Preterm birth is defined as birth before 37 weeks of gestation. Late preterm birth (between 34 completed weeks and 36 weeks and 6 days) accounts for about 74 % of all preterm births whereas the very preterm birth (less than 32 weeks) rate has remained relatively constant during the last two

decades.[1]The incidence of preterm birth ranges from 10 to 15 %. Lower genital tract infections, such as bacterial vaginosis and trichomoniasis, are widely recognized as the main causes of preterm birth. However, Placental infection with the Human Papilloma Virus (HPV) may also be a risk factor for spontaneous preterm birth.[2]

Human Papilloma viruses are composed of an icosahedral viral particle (virion) containing an 8000 base pair double stranded circular DNA molecule surrounded by a protein capsid and belongs to papilloma virus family. It is an epitheliotropic virus typically infecting keratinocytes and epithelial trophoblastic placental cells[3] therefore affecting human skin and the moist membranes that line the body.The Pathophysiological cause of such outcomes is because viral infection of the placenta may sensitize the pregnant mother to bacterial products and promote preterm labor.The immunological role of the placenta and the fetus affect the global response of the mother to microbial infections.[4]Decrease in natural killer cells or reduction in the helper T cell Type 1 cell-mediated response could account for the increase in HPV replication permitting increased HPV detection.[5]It involves bacterial invasion of the choriodecidual space, which triggers decidua and fetal membranes to produce a number of cytokines that stimulate prostaglandin synthesis and release, leading to uterine contractions and onset of preterm labour.[6]Failed invasion by extravilloustrophoblast cells leads to placental dysfunction and adverse obstetrical outcomes associated with placental dysfunction, including pre-eclampsia and spontaneous preterm delivery.[7] Infection has been cited as the major cause of membrane damage in PROM.[8] Organisms secrete cytokines, such as metalloproteases (MMP), that degrade collagen and weaken the fetal membranes, which can lead to rupture.[9] Cervical infection with high-risk HPV(HPV -16 and HPV -18) detected using HPV DNA testing is associated with the findings of thrombosis and villitis in placental examinations and is strongly associated with preterm birth. [10,11]The Apgar test is used to determine quickly whether a newborn needs immediate medical care; it was not designed to make long-term predictions on a child's health.[12]

Aims and objectives

To assess and compare the proportion of Human Papilloma Virus (HPV) infection in preterm and term delivery and to determine association of spontaneous preterm delivery with infection.

Materials and methods

This study was a hospital based case control analytical type of observational study conducted in Dept. of Obs. & Gynae, SMS Medical College, Jaipur from August 2014 to august 2015. All patients coming with labour pains and delivering before 37 weeks gestational age were taken as preterm deliveries (cases)-Group A and all patients coming with labour pains and delivering at or after 37 weeks gestational age were taken as full term deliveries (controls)-Group B. Cases and controls were selected according inclusion(singleton pregnancy with known LMP and regular menstrual cycles and women presenting after 28wk of gestation) and exclusion criteria (congenital anomalies of uterus and cervix, incompetent cervix, sexually transmitted diseases, urinary tract infection, multiple pregnancy, abnormal placentation) as per sample size. Patients of both groups were evaluated after informed consent and detailed history (including menstrual history, obstetrical history, past and family history) was taken. General and systemic examination was done. Routine blood investigations and ultrasound were done. After the patient delivered, placental tissue was taken with forceps and saved in normal saline. This sample was sent for

HPV PCR-DNA test to microbiology advanced department to detect infection.
The hc2 High-Risk HPV DNA Test using hybrid capture and PCR technology is a nucleic acid hybridization assay with signal amplification using microplate chemiluminescence for the qualitative detection of high risk types of HPV (16 and 18) DNA in placental samples. Specimens containing the target DNA hybridize with a specific HPV RNA probe. The resultant RNA:DNA hybrids are captured onto the surface of a microplate well coated with antibodies specific for hybrids. Immobilized hybrids are then reacted with alkaline phosphatase conjugated antibodies specific for the RNA: DNA hybrids, and detected with a chemiluminescent substrate. It results in substantial signal amplification. As the substrate is cleaved by the bound alkaline phosphatase, light is emitted which is measured as relative light units (RLUs) on a luminometer. The intensity of the light emitted denotes the presence or absence of target DNA in the specimen.
Statistical analysis was done using computer software (SPSS version 20 and primer).Qualitative data was expressed in the form of proportion. Quantitative data was expressed in mean +- SD (complications).Qualitative data was compared by Chi square test.Unpaired t test was used to infer the difference in means. The significance level for all statistical analysis was kept at 95%.

Observation and results

The data thus obtained were analyzed and the observations made are summarized in the ensuing tables.

Table no. 1 enlists intergroup comparison of different demographic variables as age, residence, religion, literacy, socioeconomic status, birthweight of newborn and gravida of mother.

The data of table no. 2 shows that out of 36 patients of group A, 2 were HPV DNA PCR positive out of which one had gestational age between 29-32 weeks and one belonged to 33-36 weeks gestational age group.

The table no. 3 observed distribution according to HPV DNA status and birth weight of newborn baby in preterm delivery. Out of 7 patients who had VERY LOW birth weight infants, 1 (14.28%) patient came to be HPV DNA PCR positive. Out of 29 patients who had LOW birth weight infants, 1 (3.45%) patient came to be HPV DNA PCR positive.

Table no. 4 demonstrated distribution according to HPV DNA status and NICU admission in preterm delivery. Out of 36 mothers, 2 (5.56%) had HPV DNA PCR positive. Out of these 2 mothers, 2(100%) newborn babies were admitted in NICU.

Discussion

The two groups were compared using the standard tests of significance and conclusions were drawn after matching according to age, religion, literacy, rural/urban and socioeconomic status characteristics. It was observed that religion has no effect on spontaneous preterm delivery in HPV infected and non-infected patients and patients belonging to lower socioeconomic classes had more chances of infection. Literacy had no causal relationship with preterm delivery. On analysis of data it was found that 2 patients belonging to lower socioeconomic class were HPV DNA PCR positive while none belonging to upper class was HPV DNA positive, with the p value <0.001 which was highly significant. 2 samples out of 36 came to be HPV DNA positive with p value <0.001 which was highly significant.

Table 1: Intergroup comparision of demographic parameters.

Demographic Parameters		Cases	Controls	p value*	Statistical Significance
Mean Age (Mean±SD) (years)		22.44±2.67	24.44±3.66	>0.05	Non Significant
Residence	Rural	17 (47.22%)	16 (44.44%)	>0.05	Non Significant
	Urban	19 (52.78%)	20 (55.56%)		
Religion	Hindu	32 (88.89%)	27 (75%)	>0.05	Non Significant
	Muslim	4 (11.11%)	9 (25%)		
Literacy Status	Literate	21 (58.33%)	27 (75%)	>0.05	Non Significant
	Illiterate	15 (41.67%)	9 (25%)		
Socio-economic Status	Upper (I)	0	0	>0.05	Non Significant
	Upper Middle (II)	6 (16.67%)	7(19.44%)		
	Lower Middle(III)	14(38.89%)	14 (38.89%)		
	Upper Lower (IV)	2 (5.56%)	2 (5.56%)		
	Lower (V)	14 (38.89%)	13 (36.11%)		
Birth weight	LBW	36(100%)	1(2.78%)	<0.001	Highly Significant
	NBW	0 (0%)	35(97.22%)		
	Mean ±SD	1.60±0.24	2.91±0.35	<0.001	Highly Significant
Gravida	Primigravida	1.67	2.83	<0.001	Highly Significant
	Secundigravida	1.42	2.87	<0.001	
	Tertigravida	1.60	2.99	<0.001	

Table 2: Distribution according to HPV DNA Status & Gestational age in preterm delivery.

HPV DNA Status	GA (In weeks)		Total
	29-32	33-36	
Positive	1 (2.78)	1 (2.78)	2 (5.56)
Negative	15 (41.67)	19 (52.78)	34 (94.44)
Total	16 (44.44)	20 (55.56)	36 (100.00)
X 2=0.324	**df=1**	**p>0.05**	**NS**

Table 3: Distribution according to HPV DNA Status & Birth Weight of newborn in preterm delivery.

HPV DNA Status	Birth weight (In Kg)			Total
	1.000 - 1.499	1.500 - 1.999	2.000 - 2.499	
Positive	1 (2.78)	1 (2.78)	0 (0.00)	2 (5.56)
Negative	6 (16.67)	24 (66.67)	4 (11.11)	34 (94.44)
Total	**7 (19.44)**	**25 (69.44)**	**4 (11.11)**	**36 (100.00)**

Table 4: Distribution according to HPV DNA Status and NICU admission in preterm delivery.

HPV DNA Status	NICU Admission		Total
	Yes	No	
Positive	2 (5.56)	0 (0.00)	2 (5.56)
Negative	10 (27.78)	24 (66.67)	34 (94.44)
Total	**12 (33.33)**	**20 (55.56)**	**36 (100.00)**

Conclusion

Our work and effort have tried to provide a solid scientific basis for the continued critical investigation of the role of HPV in pregnancy complications related to placental dysfunction leading to spontaneous preterm delivery.[13] Perinatal transmission of human papilloma virus may occur directly, during the passage of the fetus through the birth canal and on coming into contact with infected maternal secretions or indirectly, during vaginal delivery from contaminated objects, ascending infection from secretions of maternal genital tract and transplacental. [14,15]HPV detection done by nested multiplex PCR methodology[16] is used to identify and type 9 types of HPV shown as the most prevalent. Our study has analyzed two strains of HPV i.e. HPV 16 and 18 in extravillous trophoblastic cells of placenta.

HPV PCR technology identifies maternal HPV DNA, thus considerably increasing the sensitivity and specificity to identify HPV. The use of this method is crucial to evaluate the concordance of type specific HPV DNA among the maternal/ placental/ newborn[17] samples, thus defining the vertical and transplacental transmission rates of the virus.[18]The mother and the newborn must be observed clinically and educational preventive measures must be established concerning the forms of HPV transmission, besides effective strategies for specific immunization.Human papilloma virus vaccine is available these days to prevent human papilloma virus related infections and cancers. A vaccine called Gardasil has been developed that protects against the two high-risk HPV types (types 16 and 18) and two low-risk HPV types (types 6 and 11). Gardasil is used in the school-based National HPV Vaccination Program. Another vaccine called Cervarix is available, which protects against the same two high-risk HPV types (types 16 and 18). It does not protect against low-risk HPV types.

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