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## ABSTRACT

**Background:** Viral infections, such as HIV, are associated with an increased risk of preterm birth. The exact mechanism between viral infection and preterm birth is unclear but the phase of infection may be an important determinant of pregnancy outcome. Longer duration of human papilloma virus (HPV) infection is associated with higher grade cervical lesions.

**Objective:** We sought to determine the association between duration of HPV infection and the risk of spontaneous preterm birth (SPTB) using cervical cytology and colposcopy as surrogates for duration of infection

**Design/Methods:** Retrospective cohort study of women referred to colposcopy for evaluation of abnormal cervical cytology during pregnancy from 2004-2008 at a university clinic. Shorter duration of infection was defined as atypical squamous cells of undetermined significance high risk HPV+ (ASCUS-HR+) or low grade squamous intraepithelial lesions (LSIL) on a pap smear or a colposcopic impression of cervical intraepithelial neoplasia grade1 (CIN1). Longer duration of infection was defined as high grade (HSIL) or atypical squamous cells favors high grade (ASC-H) on a pap smear or colposcopic impression of CIN grade 2 or 3. The primary outcome was the incidence of SPTB <37 weeks. The incidence of SPTB was also compared between women with and without a history of abnormal pap smears.

**Results:** We identified 176 pregnant women referred for colposcopy. Mean age was 24 years (14-41), 77% were African American, 13% had prior PTB, and 18% used tobacco. Pap smear results were ASCUS-HR+/LSIL 91% (n=161) and HSIL/ASC-H 9% (n=15). Colposcopic impression was Normal, CIN1, and CIN2/3 in 11% (n=19), 76% (n=132), and 13% (n=22) respectively. Overall, 27 (15%) of 176 women delivered prematurely including 7 indicated PTB and 20 SPTB. There was no significant difference in the incidence of SPTB based on pap smear results (ASCUS-HR+/LSIL 20 (100%) vs HSIL/ASC-H 0 (0%); p=0.30) or colposcopic impression (CIN1 18 (100%) vs CIN2/3 0 (0%); p=0.10). History of abnormal pap smears 36% (n=59) was not predictive of SPTB (14% vs. 10%; p=0.54).

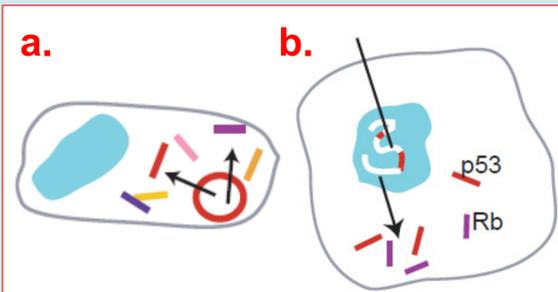
**Conclusions:** Duration of HPV infection was not a significant risk factor for SPTB, however a larger sample size may be necessary to show a difference.

## BACKGROUND

- Viral infections, such as HIV, are associated with an increased risk of preterm birth (PTB).
  - Like bacterial infections, viral infections can cause cell death and release of inflammatory cytokines
  - However, the exact mechanism of viral infection leading to PTB is unclear
- The prevalence of human papillomavirus (HPV) is 39% among reproductive age women
  - HPV infection of extravillous trophoblast cells induces cell death and may reduce placental invasion into the uterine wall
  - HPV infection of cervical epithelium can remain in the cytoplasm (low grade lesions) or become integrated into the genome (high grade lesions)

## OBJECTIVE

• To determine the association between duration of HPV infection and the risk of spontaneous PTB using cervical cytology and colposcopy.



**Figure:** a. Viral replication in the cytoplasm of cervical squamous epithelial cells. b. Integration of HPV into the genome (adapted from Man S. Expert Reviews in Molecular Medicine. 1998)

## MATERIALS & METHODS

- Retrospective cohort study of pregnant women referred for colposcopy at an academic center between 2004-08
- Exclusion criteria: atypical glandular cells; cytology, colposcopy, or delivery information not available
- Primary outcome was the incidence of spontaneous PTB <37 weeks
  - Secondary outcomes: mean gestational age at birth and birthweight
- Duration of infection defined as:
  - Shorter
    - Atypical squamous cells of undetermined significance, high risk HPV positive (ASCUS, HPV +)
    - Low grade squamous cell intraepithelial lesion (LSIL)
    - Cervical intraepithelial neoplasia grade 1 (CIN 1) by colposcopic diagnosis
  - Longer
    - High grade squamous cell intraepithelial lesion (HSIL)
    - Atypical squamous cells, cannot rule out high grade (ASC-H)
    - CIN 2 or CIN 3 by colposcopic diagnosis

## RESULTS

- We analyzed 186 pregnant women referred for colposcopy due to abnormal cervical cytology
  - 7 women were excluded (no cytology result n=2; no colposcopy diagnosis n=1; missing delivery information n=3)
  - 28 women delivered prematurely <37 weeks (15.6%)
    - 7 indicated PTB <37 weeks
    - 21 spontaneous PTB <37 weeks
- Demographic variables for the remaining 172 women are shown in Table 1

**Table 1:** Demographics

Variable*	Shorter ASCUS-HPV+/LSIL	Longer HSIL/ASC-H	P
Age	24 ±5.0	26 ±5.0	.15
African American	120 (76.4)	14 (93.3)	.13
Tobacco	37 (23.7)	4 (30.8)	.56
STI	90 (58.1)	7 (53.9)	.77
Prior PTB	24 (15.2)	2 (14.3)	>.99
Prior Abnl Cervical Cytology	50 (32.2)	6 (46.2)	.31
LEEP/CKC	5 (3.4)	2 (15.4)	.04

Data presented as n (%) or mean±SD. STI, sexually transmitted infection; PTB, preterm birth; LEEP, Loop electrosurgical excisional procedure; CKC, cold knife conization. \*Data not available for all women.

- There were no demographic differences when comparing women with a colposcopic impression of CIN1 versus CIN 2/3

## RESULTS cont.

**Table 2:** Pregnancy Outcomes

	Groups	n	SPTB	GA (wk)	Birthweight (g)
Shorter	ASCUS, HPV+/LSIL	21/158	13.3%	38.2	3066
Longer	HSIL/ASC-H	0/14	0%	38.9	3155
	<i>p-value</i>		.30	.047	.60
Shorter	CIN 1	18/130	13.8%	38.2	3086
Longer	CIN 2/3	1/21	4.8%	38.7	2943
	<i>p-value</i>		.20	.42	.31

Data presented as n (%) or mean±SD.

## Additional Analyses

- **History of abnormal versus first abnormal**
  - Cervical cytology history was available for 168 women.
  - There was no difference in the incidence SPTB <37 weeks between women with NO history of prior abnormal cervical cytology (ACC; 11.1%) compared to women with prior ACC (13.6%; p=.64)
- **Intrauterine Fetal Demise**
  - The incidence of fetal death ≥ 23 weeks was 4/185 (2.2%) versus United States rate of fetal death ≥ 20 weeks = 6.2/1000 (0.62%).

## CONCLUSIONS

- Duration of HPV infection was not a significant risk factor for spontaneous PTB <37 weeks
  - Cervical HPV DNA and HPV serology may further delineate the relationship between HPV infection and SPTB <37 weeks
  - A larger sample size may be necessary to show a difference
- The 3.5x higher rate of fetal death ≥ 23 weeks in our study (compared to fetal death ≥ 20weeks in the U.S.) needs further investigation