Original Article

Perinatal Outcomes of Pregnancy with Anogenital Warts at the Time of Delivery

Rekhawasin T, MD[1], Chayachinda C, MD, MSc[1], Thamkhantho M, MD, FRCOG, MSc[1], Thuwasee T, BNS[2], Munn A, MD[3]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2] Department of Nursing, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[3] Department of Psychiatry, Oregon Health and Science University, Portland, Oregon, USA

Background: Anogenital wart (AGW) is normally more pronounced during pregnancy. However, its impact on perinatal outcomes remains limited.

Objective: To demonstrate perinatal outcomes in pregnant women with AGWs at the time of delivery.

Materials and Methods: All medical charts of pregnant women with AGWs at the time of delivery at Siriraj Hospital, Mahidol University between January 2007 and December 2016 were reviewed. The characteristics and perinatal outcomes were compared with all deliveries during the same period using inferential statistics.

Results: From the 90,262 deliveries, 490 women (0.54%) with AGWs were included in the present study. The participants' mean age was 24.5±6.8 years with the GA at 38.0±2.3 weeks. Of them, 70.0% was primigravida and 3.5% had history of AGWs before the current pregnancy. Two thirds were educated to at least high school. Screening for sexually transmitted infections (STIs) showed human immunodeficiency virus (HIV) infection at 5.3%, hepatitis B at 1.6%, and syphilis at 1.2%. The cesarean section rate was 41.6%. Compared with all deliveries during the same period at Siriraj Hospital, Mahidol University, the participants had higher prevalence of LBW (RR 1.39; 95% CI 1.16 to 1.67), VLBW (RR 1.82; 95% CI 1.09 to 3.06), overt DM (RR 2.94; 95% CI 1.32 to 6.55), teenage pregnancy (RR 3.13; 95% CI 2.72 to 3.61), syphilis (RR 6.79; 95% CI 3.02 to 15.27), HIV infection (RR 9.47; 95% CI 6.44 to 13.91), and hepatitis B infection (RR 20.73; 95% CI 10.03 to 42.85).

Conclusion: Pregnant women with AGWs at the time of delivery had a higher risk of having overt DM, concurrent sexually-transmitted infections, and low birth weight newborn.

Keywords: anogenital warts, perinatal outcomes, pregnancy

Received 23 Jan 2020 | Revised 11 Feb 2020 | Accepted 12 Feb 2020

J Med Assoc Thai 2020;103(3):270-5
Website: http://www.jmatonline.com

Anogenital wart (AGW) is the most common sexually transmitted disease (STD) worldwide with a prevalence of 2% to 43% in the female population[1]. The prevalence may decline in countries that have high accessibility to the vaccine against its etiologic organism, human papillomavirus (HPV) type 6 and 11[2]. However, AGW remains problematic in many regions, including Thailand. AGW is a disease involving mucocutaneous junction or cutaneous area rather than mucous membrane[3]. During pregnancy, there is a high tendency for excessive proliferation and recurrence, which may lead to obstructed birth canal. This has been explained by the increased moisture in vaginal milieu and the down-regulated cell-mediated immunity[4-7].

Previous studies have shown the adverse association between AGW and pregnancy, including premature rupture of membranes (PROM)[8-10], preterm birth (PB)[9,11-15], and pre-eclampsia[14,15]. The presence of HPV increases the expression of

Correspondence to:

Thamkhantho M.

Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4194775, **Fax**: +66-2-4194997

Email: manopchai.tha@mahidol.ac.th

How to cite this article: Rekhawasin T, Chayachinda C, Thamkhantho M, Thuwasee T, Munn A. Perinatal Outcomes of Pregnancy with Anogenital Warts at the Time of Delivery. J Med Assoc Thai 2020;103:270-5.

metalloprotease (MMP), a cytokine that weakens fetal membranes, resulting in PROM[8]. PB and pre-eclampsia may partly be explained by the damaged extravillous trophoblastic cells caused by HPV, leading to placental dysfunction[11-14].

Besides, AGWs appears to be a risk factor for maternal episiotomy wound infection[16]. Likewise, there is an increased rates of neonatal respiratory papillomatosis, which is a rare event with the incidence of 1.7 to 4.3 per 100,000 infants, in infants born to women with active lesions during delivery with long exposure to vaginal secretion of more than 10 hours[17-21]. In contrast, some studies have shown such sequelae among women with AGWs. For example, an epidemiological study in 227,267 Israeli women demonstrated no adverse perinatal outcomes except the higher rate of cesarean delivery[18]. Due to the high prevalence of HPV-related disease in Thailand, the present study aimed to demonstrate perinatal outcomes in Thai pregnant women, who had never received HPV vaccine, with active AGW at the time of delivery.

Materials and Methods

The present study was a retrospective chart-review conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University between January and June 2018. It was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 310/2561). Of the 90,262 medical charts of pregnant women, 490 cases with active AGWs delivered at Siriraj Hospital, Mahidol University between January 2007 and December 2016. AGW was clinically diagnosed using inspection of flat or cauliflower-like masses along the genital tract, including external genitalia and perianal area.

Outcome measures

In Thailand, all pregnant women were tested for human immunodeficiency virus (HIV) infection, syphilis, and hepatitis B infection by checking serum anti-HIV, venereal disease research laboratory (VDRL), and hepatitis B surface antigen (HBsAg), respectively, at the first antenatal care (ANC) visit and during gestational age (GA) 28 to 32 weeks. Maternal outcomes of interest included presence of gestational diabetes mellitus (GDM), gestational hypertension (GHT) or preeclampsia, PB, postpartum hemorrhage, requested for cesarean delivery, poor ANC, and maternal anemia.

GA was based on either crown-rump length in the first trimester or last menstrual period correlating with biparietal diameter in the second trimester. GDM was screened with 50-g oral glucose challenge test (OGCT) in pregnant women with risk factors. Women with an abnormal OGCT of 140 mg per dl or more underwent a 100-g oral glucose tolerance test. Following the Carpenter-Coustan criteria, GDM was diagnosed if there was more than one abnormal value. Overt diabetes mellitus (DM) was defined as being diagnosed with DM prior to the current pregnancy. GHT and pre-eclampsia were defined according to the American College of Obstetricians and Gynecologists (ACOG)[22]. PB was defined as delivery before GA 37 weeks. Poor ANC was defined as having less than four ANC visits. Maternal anemia were those who had hematocrit of less than 33%.

The neonatal outcomes of interest included meconium-stained amniotic fluid, birth asphyxia (BA), low birth weight (LBW), very low birth weight (VLBW), and fetal growth restriction (FGR). FGR was defined as estimated fetal weight below the tenth percentile. BA was defined as having an Apgar score of less than 7 at 5 minutes after birth. LBW was defined as a birth weight of less than 2,500 grams and VLBW was defined as a birth weight of less than 1,500 grams.

Statistical analysis

Stata, version 12.0 (StataCorp LP, College Station, TX, USA) was used for data analysis. Descriptive statistics were used as appropriate, including n (%), mean ± standard deviation (SD), and median with interquartile range (IQR). The chi-square test was used for the comparison of categorical variables. Inferential statistics, which was presented by risk ratio (RR) and 95% confidence interval (CI), was used to compare the outcome measures between deliveries with active AGW and overall deliveries during the same period. A p-value of less than 0.05 was considered statistically significant.

Results

Among all 90,262 deliveries, there were 490 pregnant women having active AGW at the time of delivery at Siriraj Hospital between 2007 and 2016. The incidence of active AGW at the time of delivery was 0.54% and was mostly found among pregnant women aged between 20 and 29 years old (Figure 1).

The demographic and clinical characteristics of all participants are shown in Table 1. The participants' mean age was 24.5±6.8 years with the mean GA at 38.0±2.3 weeks. Of those, 70.0% was primigravida and 3.5% had history of AGW before the current

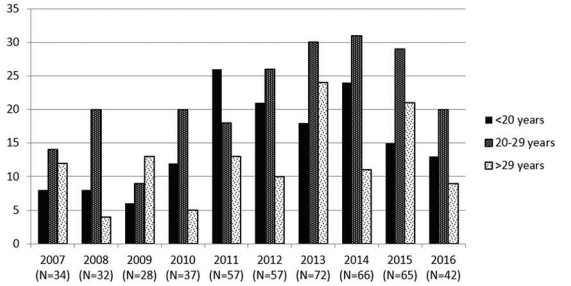

Figure 1. Number of pregnant women with active AGW at the time of delivery at Siriraj Hospital from January 2007 to December 2016.

pregnancy. Two thirds were educated to at least high school or vocational school, and around half were unemployed. Screening for sexually transmitted infections (STIs) showed HIV infection at 5.3%, hepatitis B at 1.6%, and syphilis at 1.2%. The cesarean section rate was 41.6%.

The characteristics of the participants by age groups are shown in Table 2. Adolescent participants tended to have less than four ANC visits, maternal anemia, extended AGW lesions, and LBW infants ($p<0.05$ for all). GDM, overt DM as well as GHT and pre-eclampsia were more prevalent in older participants ($p<0.05$ for all). The following characteristics were not significantly different among all age groups, no ANC, PB, FGR, meconium-stained amniotic fluid, VLBW, and BA.

Comparison of demographic data and pregnancy outcomes between patients with and without coincident anogenital warts is shown in Table 3. Compared with all deliveries during the same period of time at Siriraj Hospital (n=90,262), the participants with anogenital warts had higher prevalence of LBW (RR 1.39; 95% CI 1.16 to 1.67), VLBW (RR 1.82; 95% CI 1.09 to 3.06), overt DM (RR 2.94; 95% CI 1.32 to 6.55), teenage pregnancy (RR 3.13; 95% CI 2.72 to 3.61), syphilis (RR 6.79; 95% CI 3.02 to 15.27), HIV infection (RR 9.47; 95% CI 6.44 to 13.91), and hepatitis B infection (RR 20.73; 95% CI 10.03 to 42.85) ($p<0.05$ for all).

Table 1. Baseline demographic and clinical characteristics of the participants (n=490)

Characteristics	n (%)
Age (years); mean±SD	24.5±6.8
Gestational age (weeks); mean±SD	38.0±2.3
Education	
Primary school or less	141 (28.8)
High school/vocational school	266 (54.3)
Bachelor degree or higher	83 (16.9)
Occupation	
Temporary job	133 (27.1)
Unemployed/ housewife	215 (43.9)
Office job	28 (5.7)
Student	28 (5.7)
Business owner	86 (17.6)
Primigravida	344 (70.2)
History of prior abortion	48 (9.8)
History of AGWs before pregnancy	17 (3.5)
Human immunodeficiency virus infection	26 (5.3)
Hepatitis B	8 (1.6)
Syphilis	6 (1.2)
Delivery	
Normal delivery	280 (57.2)
Vacuum extraction	6 (1.2)
Cesarean section	204 (41.6)

AGWs=anogenital warts; SD=standard deviation

Discussion

Coincident AGWs at the time of delivery appeared more common in pregnant women aged 20 to 29 years. The present study is consistent with the previous studies in that AGW is more prevalent in young people regardless of pregnancy status[14,23]. Compared with all women who delivered during the same period of time (2007 to 2016), the coincidence of AGWs occurs more commonly among teenage pregnant women, those with STDs such as HIV infection, syphilis, and hepatitis B, and those with DM prior to the current pregnancy. In addition, it increases the incidence of LBW and VLBW. With the largest collection of pregnant women with AGWs, the present study findings are compatible with those in previous studies[8-16].

Abnormal function of placenta in pregnant women with AGWs has been proposed as a cause of PB[11-14]. Despite that, in line with the studies by Ambühl et al and Cohen et al in Danish women and Israeli women, the present study showed that pregnant women with active AGW at the time of delivery did not have a greater chance to have PB[18,24]. The finding may be explained by the study setting that Siriraj Hospital is a quaternary hospital. The baseline prevalence of PB is quite high (15.4%) while that in the Israeli women[18], it is only 7.9%.

According to the present study, HIV infection was about 9.5 times more commonly found in

Table 2. Characteristics of the participants by age groups (n=490)

Demographic data	Total (n=490) n (%)	Age (years); n (%)			p-value
		<20 (n=151)	20 to 29 (n=217)	≥30 (n=122)	
No antenatal care	26 (5.3)	12 (8.0)	11 (5.1)	3 (2.5)	0.129
Antenatal care <4 visits	90 (18.4)	42 (27.8)	37 (17.1)	11 (9.0)	<0.001
Maternal anemia	153 (31.2)	62 (41.1)	59 (27.2)	32 (26.2)	0.007
Diabetes mellitus					<0.001
Gestational DM	18 (3.7)	0 (0.0)	4 (1.8)	14 (11.5)	
Overt DM	6 (1.2)	0 (0.0)	3 (1.4)	3 (2.5)	
Pregnancy-induced hypertension					0.042
Gestational hypertension	14 (2.9)	1 (0.7)	5 (2.3)	8 (6.6)	
Pre-eclampsia	21 (4.3)	6 (4.0)	8 (3.7)	7 (5.7)	
Preterm birth					
Delivery at GA <34 weeks	26 (5.3)	10 (6.6)	8 (3.7)	8 (6.6)	0.362
Delivery at GA <37 weeks	91 (18.6)	34 (22.5)	33 (15.2)	27 (19.7)	0.197
Anogenital warts					
Intra-vaginal warts	98 (20.0)	38 (25.2)	34 (15.7)	26 (21.3)	0.074
External warts	432 (88.2)	135 (89.4)	195 (89.9)	102 (83.6)	0.197
Both	39 (8.2)	22 (14.6)	11 (5.6)	6 (4.9)	0.001
Fetal growth restriction	13 (2.7)	3 (2.0)	9 (4.2)	1 (0.8)	0.155
Meconium-stained amniotic fluid	15 (3.1)	2 (1.3)	10 (4.6)	3 (2.5)	0.180
Very low birth weight	14 (2.9)	6 (4.0)	5 (2.3)	3 (2.5)	0.611
Low birth weight	99 (20.2)	45 (29.8)	36 (16.6)	18 (14.8)	0.002
Birth asphyxia	43 (18.8)	13 (8.6)	21 (9.7)	9 (7.4)	0.770

DM=diabetes mellitus; GA=gestational age

Table 3. Comparison of demographic data, sexually transmitted infections and perinatal outcomes between women with AGWs and all women who delivered at Siriraj Hospital during 2007 to 2016

	Deliveries with active AGWs (n=490) n (%)	Total deliveries (n=90,262) n (%)	RR (95% CI)	p-value
Cesarean section	204 (41.6)	39,409 (43.7)	0.97 (0.86 to 1.09)	0.569
Teenage pregnancy	151 (30.8)	7,340 (8.1)	3.13 (2.72 to 3.61)	<0.001
Preterm birth	91 (18.6)	13,890 (15.4)	1.17 (0.97 to 1.42)	0.100
Low birth weight	99 (20.2)	12,369 (13.7)	1.39 (1.16 to 1.67)	<0.001
Very low birth weight	14 (2.9)	1,396 (1.6)	1.82 (1.09 to 3.06)	0.022
Fetal growth restriction	13 (2.7)	3,839 (4.3)	0.63 (0.37 to 1.08)	0.091
HIV infection	26 (5.3)	483 (0.5)	9.47 (6.44 to 13.91)	<0.001
Pre-eclampsia	22 (4.5)	3,639 (4.0)	1.11 (0.74 to 1.67)	0.622
Overt DM	6 (1.2)	373 (0.4)	2.94 (1.32 to 6.55)	0.006
Gestational DM	18 (3.7)	5,530 (6.1)	0.61 (0.39 to 0.97)	0.032
Hepatitis B infection	8 (1.6)	70 (0.1)	20.73 (10.03 to 42.85)	<0.001
Syphilis	6 (1.2)	161 (0.2)	6.79 (3.02 to 15.27)	<0.001

AGWs=anogenital warts; HIV=human immunodeficiency virus; DM=diabetes mellitus; RR=risk ratio; CI=confidence interval

women with active AGWs at the time of delivery than those without the lesions. The reason for HIV-infected women having proclivity to have AGWs is HIV-associated with immune suppressive state[25].

AGW tends to expand, multiply, and recur. Likewise, overt DM, a chronic disease that impairs cellular immunity[26], associated with the occurrence of AGWs at the time of delivery. Apart from HIV infection, the prevalence of HBV infection and syphilis appeared dramatically high in this population. The figures are much higher than those in overall deliveries at Siriraj Hospital, at 21 times and 7 times for HBV infection and syphilis respectively. This is paralleled to the authors previous report that 7.9% of women with AGWs had other STIs[23].

Unlike the study in Israeli women[18], the authors found no difference in cesarean section rate. The rate in the Israeli study was 35.4% while that in the present study was 41.6%. However, the baseline cesarean section rate much differed with 13.0% in the study by Cohen et al[18] versus 43.7% in the present study. The recommendation regarding the route of delivery is cesarean section only when the tumor growth obstructs the maternal birth canal. In addition, the incidence of juvenile RPP does not differ between infants born to mothers with and without AGWs[27].

The largest sample size in literature review of the present study appears to be the first strength. Second, well-kept, complete electronic medical records in the authors institute dilute the weakness of retrospective chart-review study design. However, AGW's principal diagnostic method by direct inspection may result in the underestimate of the prevalence. In addition, as the present study was conducted in a single quaternary hospital, the finding may not be generalized worldwide due to the various disease prevalence among countries. However, it could be used as a guidance to counsel pregnant women with active anogenital lesions at the time of delivery regarding the possible maternal and neonatal complications.

Pregnant teenagers, women with concurrent STIs, or women with DM were more likely to have AGW. The significant adverse pregnancy outcomes included LBW and VLBW.

Conclusion

Pregnant women in the anogenital wart group were more likely to have overt DM, concurrent STDs, and give birth to LBW newborn.

What is already known on this topic?

Anogenital wart is commonly found during pregnancy due to immune-compromised status of the pregnant women. Many modalities have been offered for the appropriate treatment to avoid the adverse events or grave outcomes during the pregnancy. Unfortunately, the information of perinatal outcomes of pregnancy with genital wart is still very limited for this critical issue.

What this study adds?

Incidence of anogenital wart at time of delivery was 0.54%, and 3.5% of these had a history of anogenital wart infection. Pregnant women with anogenital wart have a higher prevalence of LBW and VLBW newborn, overt DM, teenager status, syphilis, HIV, and hepatitis B infection.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Chen HC, Chang SW, Huang SF. Adjunctive treatment with interferon alpha-2b may decrease the risk of papilloma-associated conjunctival intraepithelial neoplasm recurrence. Cornea 2004;23:726-9.
2. Ball SL, Winder DM, Vaughan K, Hanna N, Levy J, Sterling JC, et al. Analyses of human papillomavirus genotypes and viral loads in anogenital warts. J Med Virol 2011;83:1345-50.
3. Dias EP, Gouvea AL, Eyer CC. Condyloma acuminatum: its histopathological pattern. Sao Paulo Med J 1997;115:1383-9.
4. Yang LJ, Zhu DN, Dang YL, Zhao X. Treatment of condyloma acuminata in pregnant women with cryotherapy combined with proanthocyanidins: Outcome and safety. Exp Ther Med 2016;11:2391-4.
5. Suzuki S, Sekizawa A, Tanaka M, Matsuda H, Okai T, Kinoshita K, et al. Current Status of Condylomata Acuminata in Pregnant Japanese Women. Jpn J Infect Dis 2016;69:347-9.
6. Garozzo G, Nuciforo G, Rocchi CM, Bonanno NM, Sampugnaro EG, Piccione S, et al. Buschke-Lowenstein tumour in pregnancy. Eur J Obstet Gynecol Reprod Biol 2003;111:88-90.
7. Costa MC, Bornhausen DE, Azulay DR, Perisse AR, Dias MF, Nery JA. Sexually transmitted diseases during pregnancy: a synthesis of particularities. An Bras Dermatol 2010;85:767-82.
8. Cho G, Min KJ, Hong HR, Kim S, Hong JH, Lee JK, et al. High-risk human papillomavirus infection is associated with premature rupture of membranes. BMC Pregnancy Childbirth 2013;13:173.
9. Bonde U, Joergensen JS, Mogensen O, Lamont RF. The potential role of HPV vaccination in the prevention of infectious complications of pregnancy. Expert Rev Vaccines 2014;13:1307-16.
10. Cotton-Caballero A, Dudley D, Ferguson J, Pettit K, Boyle A. Maternal human papillomavirus infection increases the risk of premature rupture of membranes [19M]. Obstet Gynecol 2017;129:S137.
11. Gomez LM, Ma Y, Ho C, McGrath CM, Nelson DB,

Parry S. Placental infection with human papillomavirus is associated with spontaneous preterm delivery. Hum Reprod 2008;23:709-15.
12. Huang QT, Zhong M, Gao YF, Huang LP, Huang Q, Wang W, et al. Can HPV vaccine have other health benefits more than cancer prevention? A systematic review of association between cervical HPV infection and preterm birth. J Clin Virol 2014;61:321-8.
13. Zuo Z, Goel S, Carter JE. Association of cervical cytology and HPV DNA status during pregnancy with placental abnormalities and preterm birth. Am J Clin Pathol 2011;136:260-5.
14. McDonnold M, Dunn H, Hester A, Pacheco LD, Hankins GD, Saade GR, et al. High risk human papillomavirus at entry to prenatal care and risk of preeclampsia. Am J Obstet Gynecol 2014;210:138-5.
15. Niyibizi J, Zanre N, Mayrand MH, Trottier H. The association between adverse pregnancy outcomes and maternal human papillomavirus infection: a systematic review protocol. Syst Rev 2017;6:53.
16. Houpt ER, Rein MF. Sexually transmitted disease and obstetric and gynecologic infections. In: Betts RF, Chapman SW, Penn RL, editors. A practical approach to infectious diseases. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 541-86.
17. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003;101:645-52.
18. Cohen E, Levy A, Holcberg G, Wiznitzer A, Mazor M, Sheiner E. Perinatal outcomes in condyloma acuminata pregnancies. Arch Gynecol Obstet 2011;283:1269-73.
19. Lee SM, Park JS, Norwitz ER, Koo JN, Oh IH, Park JW, et al. Risk of vertical transmission of human papillomavirus throughout pregnancy: a prospective study. PLoS One 2013;8:e66368.
20. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008;118:1236-47.
21. Gallagher TQ, Derkay CS. Recurrent respiratory papillomatosis: update 2008. Curr Opin Otolaryngol Head Neck Surg 2008;16:536-42.
22. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122-31.
23. Chayachinda C, Boriboonhirunsarn D, Thamkhantho M, Nuengton C, Chalermchockcharoenkit A. Number of external anogenital warts is associated with the occurrence of abnormal cervical cytology. Asian Pac J Cancer Prev 2014;15:1177-80.
24. Ambühl LMM, Leonhard AK, Widen Zakhary C, Jørgensen A, Blaakaer J, Dybkaer K, et al. Human papillomavirus infects placental trophoblast and Hofbauer cells, but appears not to play a causal role in miscarriage and preterm labor. Acta Obstet Gynecol Scand 2017;96:1188-96.
25. Kornete A, Pumpure E, Zodzika J, Rezeberga D, Puksta-Gulbe L, Jermakova I. Human immunodeficiency virus and human papillomavirus co-infection in pregnant woman. Acta Chirurgica Latviensis 2016;16: 26-7.
26. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 1999;26:259-65
27. Gilson R, Nugent D, Werner RN, Ballesteros J, Ross J. 2019 European guideline for the management of anogenital warts [Internet]. 2018 [cited 2019 Aug 22]. Available from: https://www.iusti.org/regions/europe/pdf/2019/IUSTIguidelinesHPV2019.pdf.