HPV & Pregnancy

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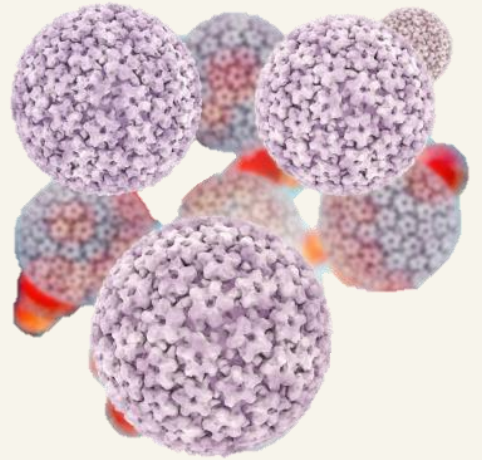
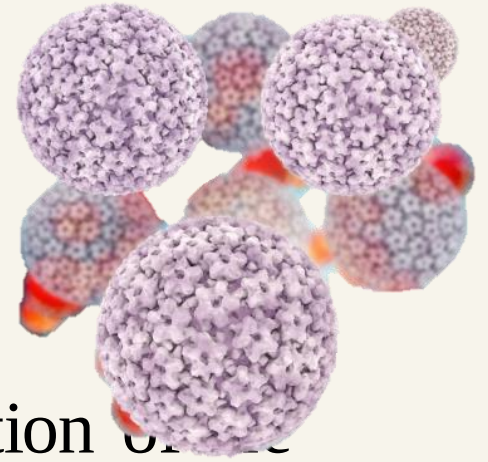
Human Papilloma Virus



- Double-stranded DNA
- > 200 types: Cutaneous/Mucosal
- Small, non-enveloped, capsid viruses 8 Kb circular genome, encoding 8 genes, including 2 encapsulating structural proteins, L1&L2
  - L1 protein, expressed recombinantly in a cell-culture system, self-assembles in the absence of the viral genome to form a **V**irus-**L**ike **P**article (VLP).
  - L1 VLP is the immunogen used in the HPV vaccines.
  - L2 is the minor capsid protein that along with L1 mediates HPV infectivity

Human Papilloma Virus



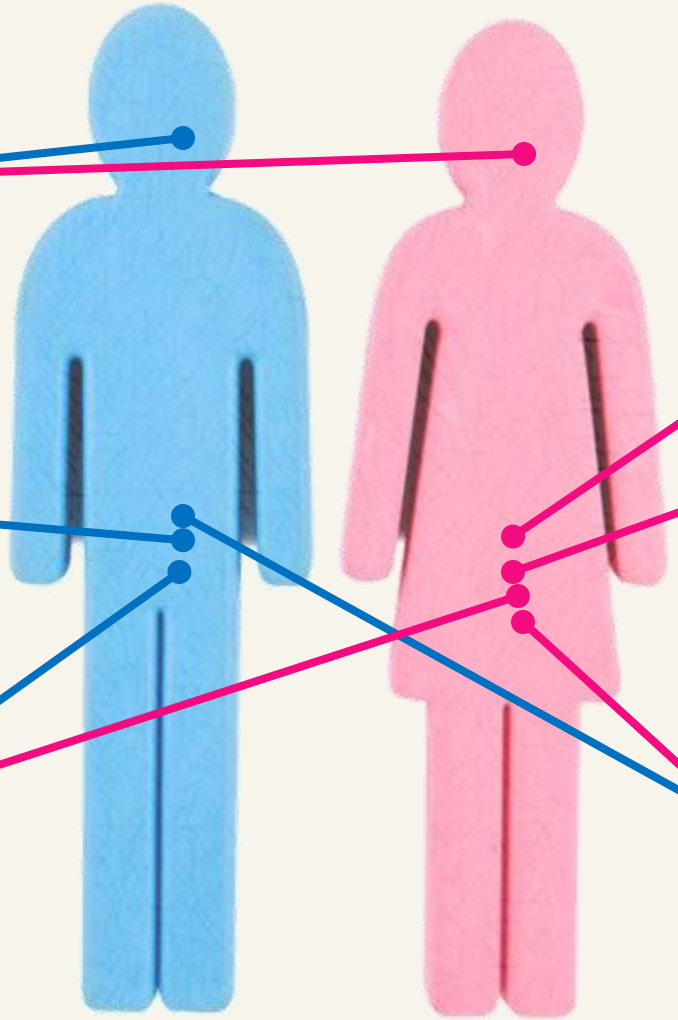
- Replication cycle linked to epithelial differentiation- Maturation of the keratinocyte.
- Initial infection of the basal stem cell occurs as the result of microscopic breaks in the epithelium .
- The infecting HPV virions appear to attach to the basal stem cell via tissue-specific heparan sulfate proteoglycans
- At the most superficial level, the genes for the L1, L2, and E4 genes are transcribed for assembly of the viral capsid into which the HPV genome is packaged.

HPV - Not Only Cervical Cancer:

13-72% of oropharyngeal cancers

~50% of penile cancers

~90% of anal cancers



Almost **ALL** (99.7%) cases of cervical cancers[12]

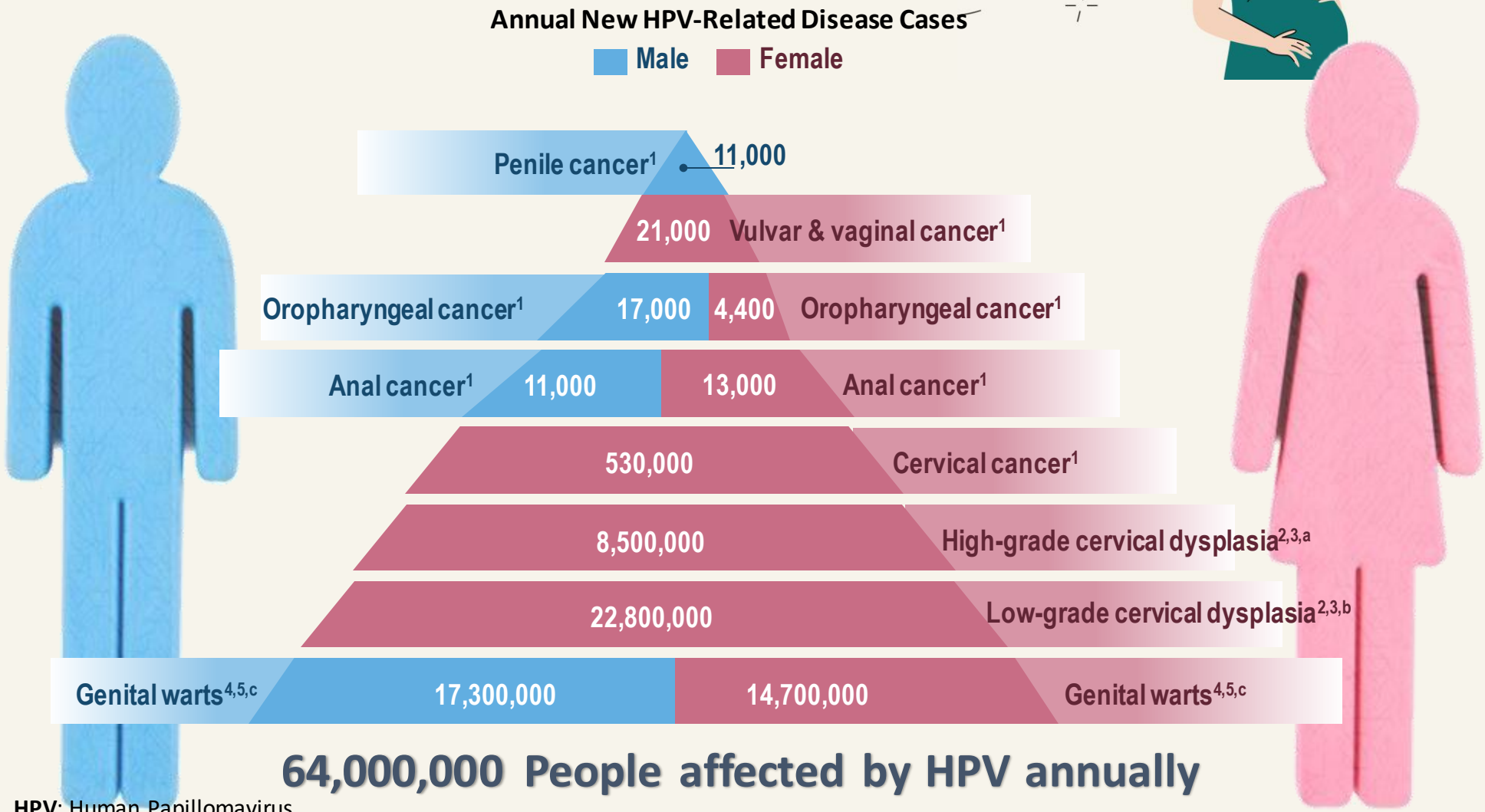
65-70% of of vaginal and vulvar cancers

> 90% of anogenital warts in males and females

HPV: Human Papillomavirus

Adapted from **1.** Joura E, et al. Cancer Epidemiol Biomarkers Prev 2014; 23:1997–2008.**2**. Alemany L, et al.Eur Urol 2016; doi:10.1016/j.eururo.2015.12.007.**3.** Alemany L, et al.. Int J Cancer 2015; 136:98–107. **4**. Alemany M, et al. Euro J Cancer 2014; 50:2846–54. **5**. Castellsague X, et al. J Natl Cancer Inst 2016; doi:10.1093/jnci/djv403. **6**. De Sanjose S, et al. Eur J Cancer 2013; 49:3450–61. **7**. Gillison M, et al. Int J Cancer 2014; 134:497–507. **8**. de Martel C, et al. Lancet Oncol 2012;9:607–15. **9**. Ferlay J, et al. Int J Cancer 2010; 127:2893–917.**10**. D'Souza G, et al. N Engl J Med 2007; 356:1944–56.**11**. Chaturvedi AK, et al. J Clin Oncol 2011; 29:4294–301. **12**.Walboomers JM, et al J Pathol. 1999 Sep;189(1):12-9.

Global Annual HPV-Related Disease Burden



64,000,000 People affected by HPV annually

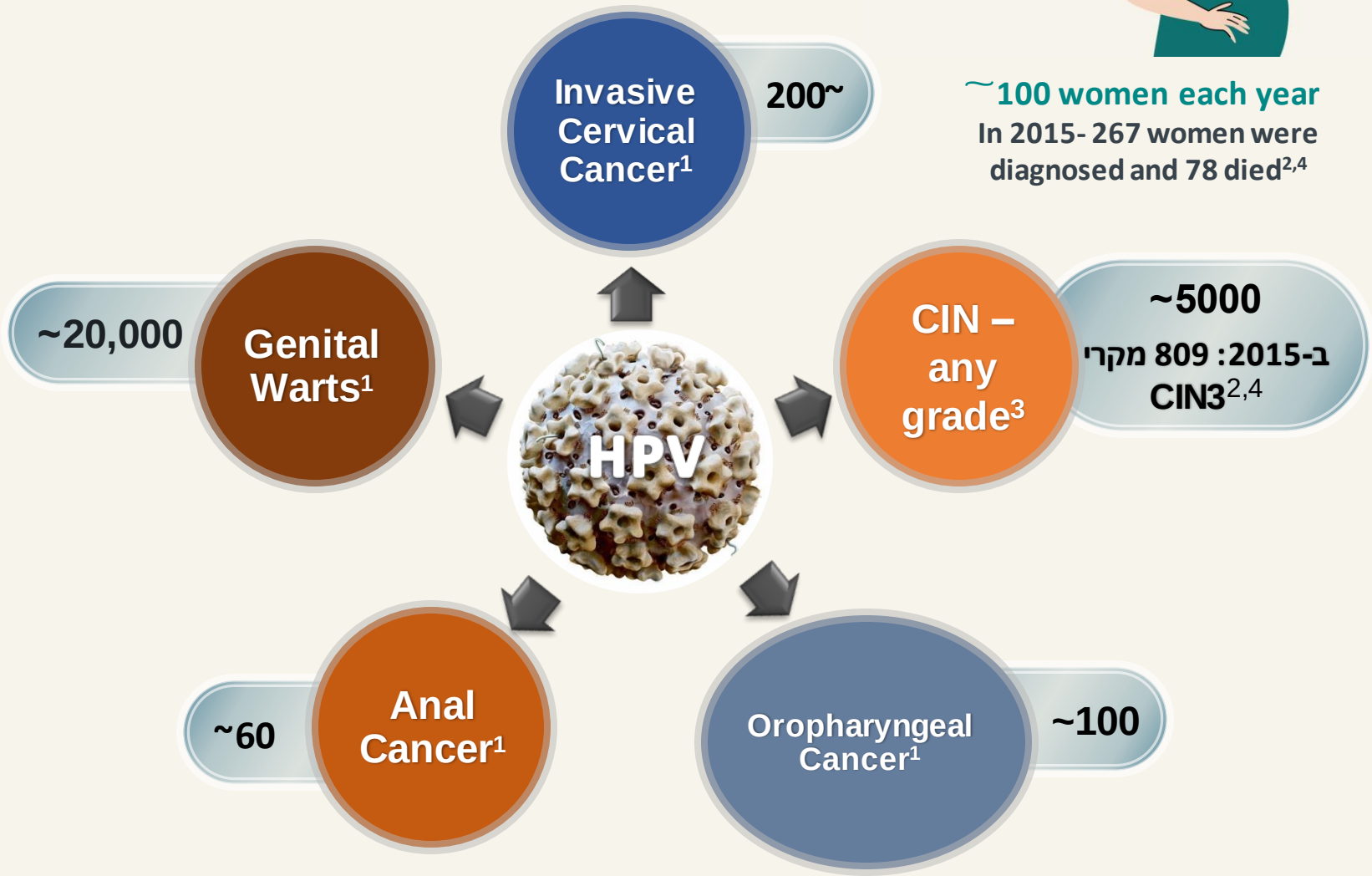
HPV: Human Papillomavirus

Adapted from **1.** ddForman D et al. *Vaccine*. 2012;30 Suppl 5:F12-23. **2.** World Health Organization. The current status of development of prophylactic vaccines against human papillomavirus infection. Report of a technical meeting, Geneva, 16-18 February 1999. Geneva, Switzerland: World Health Organization; 1999. http://www.who.int/vaccine_research/documents/en/hpv1.pdf. Accessed July 15, 2013. **3.** Guan P, et al. *Int J Cancer*. 2012;131(10):2349-2359. **4.** Executive summary: the state of world health, 1995. World Health Organization website. http://www.who.int/whr/1995/media_centre/executive_summary1/en/index.html. Accessed March 12, 2013. **5.** Greer CE et al. *J Clin Microbiol*. 1995;33:2058–2063. **6.** Public Health England. Health Protect Rep. 2013;7:9–15. http://www.hpa.org.uk/hpr/archives/2013/hpr2313.pdf. Accessed July 15, 2013.

Annual HPV-Related Disease Burden in Israel

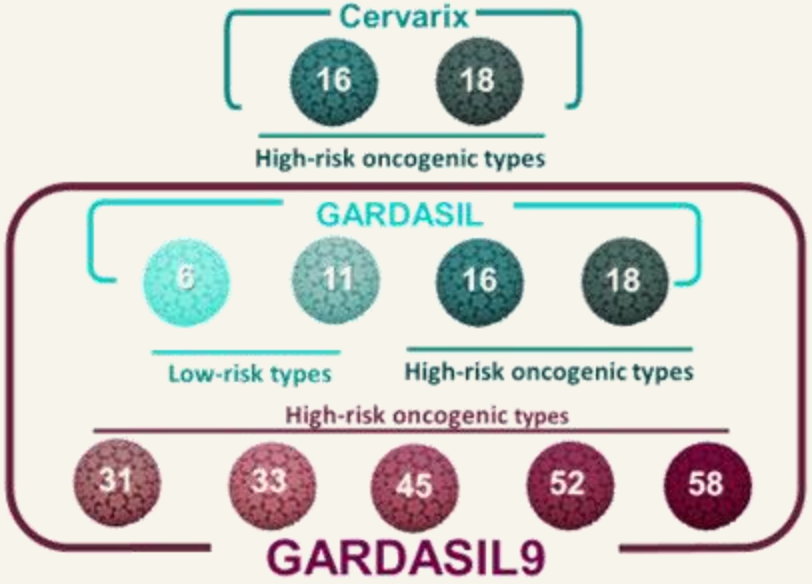
~100 women each year

In 2015- 267 women were diagnosed and 78 died[2,4]

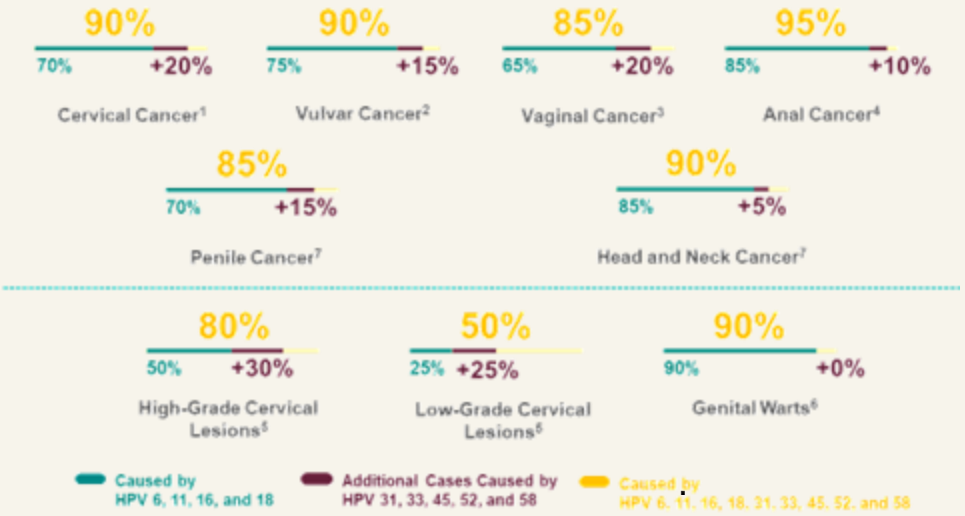


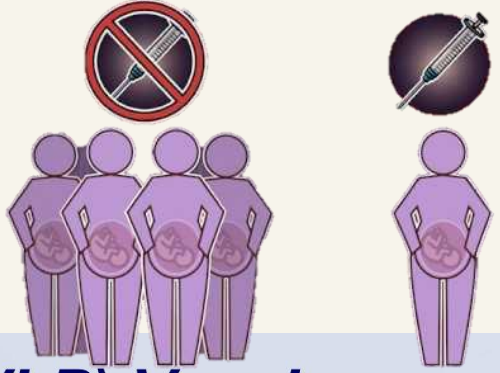
Adapted from **1.** אתר משרד הבריאות - חיסון נגד נגיף הפפילומה HPV https://www.health.gov.il/Subjects/vaccines/HPV/Pages/default.aspx. Accessed 14 Jan 2019. **2.** מערכת רישום נתוני סרטן (לשנת 2015) https://public.tableau.com/views/_5224/sheet2?:embed=y&:showVizHome=nhttps://public.tableau.com/views/_5224/sheet2?:embed=y&:showVizHome=no&:showTabs=y&:display_count=y&:display_static_image=y#%21 ע
Accessed 14 Jan 2019. **3.** https://www.health.gov.il/PublicationsFiles/HPV_presentation.pdf **4.** סרטן צוואר הרחם בישראל – עדכון הנתונים -ינואר 2019:
http://www.e-med.co.il/emed/new/usersite/content.asp?CatID=30&ContentID=730333&dacc=1&utm_source=EmedMail&utm_medium=SectionNewsItem&utm_campaign=NewsletterOfMador30

HPV Vaccines

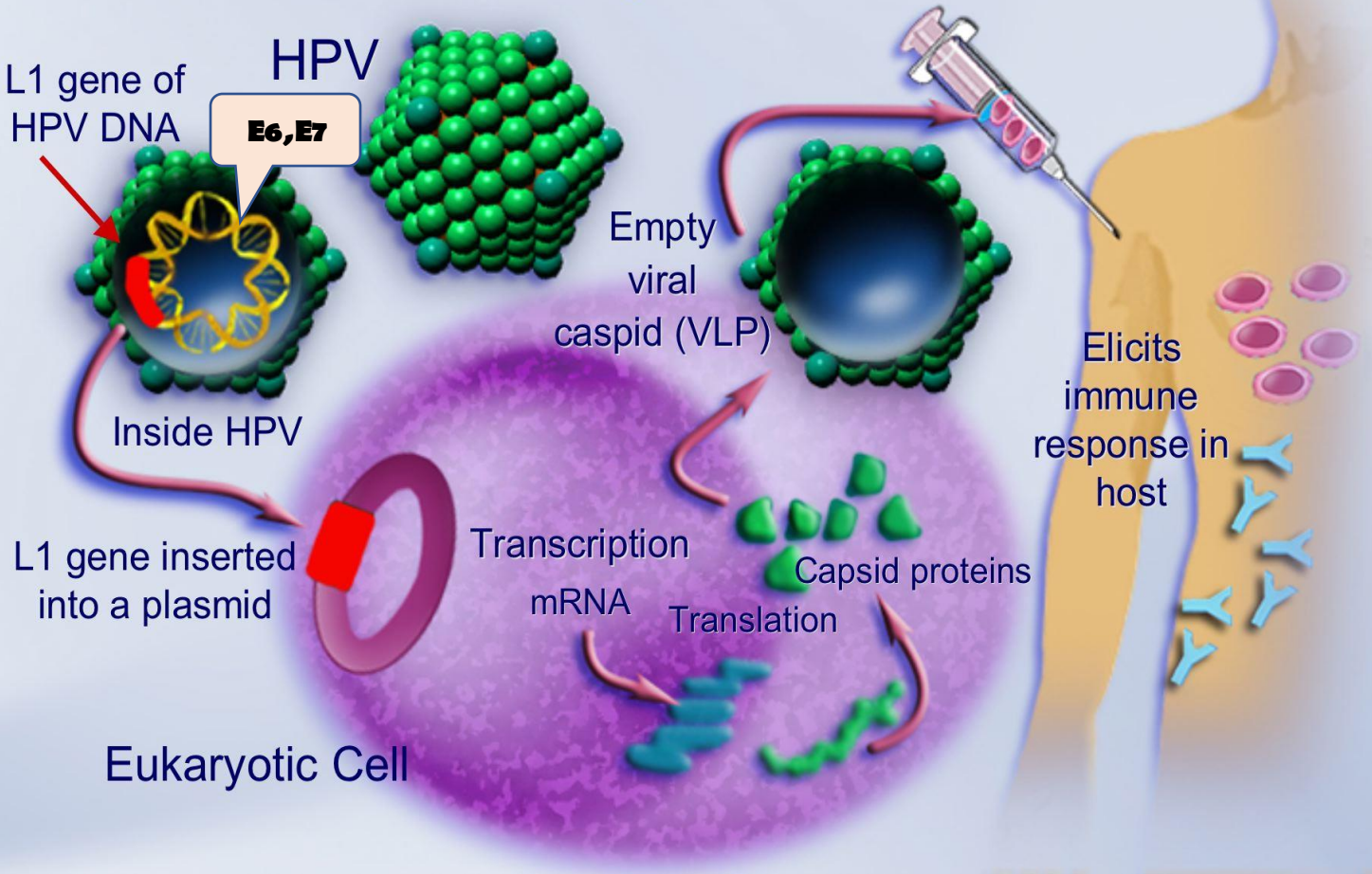


Nearly All HPV-Related Cancers and Diseases Are Caused by 9 HPV Types





HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis



First Evidence: HPV Vaccination Protects Against Invasive HPV-Associated Cancer

Malignancy	HPV vaccinated women: Person years	*n*	Rate (95% CI)	Non-HPV vaccinated women: Person years	*n*	Rate (95% CI)
Cervix cancer	65,656	0	–	124,245	8	6.4 (3.2, 13)
Vulva cancer	65,656	0	–	124,245	1	0.8 (0.1, 5.7)
Oropharyngeal cancer	65,656	0	–	124,245	1	0.8 (0.1, 5.7)
Other HPV cancers[1] (Vaginal carcinoma, Anal carcinoma)	65,656	0	–	124,245	0	–
All HPV associated invasive cancers	65,656	0	–	124,245	10	8.0 (4.3, 15)

Cluster randomized female cohorts altogether:

- **HPV vaccinated: 9,529** women **14-17 year old** (2vHPV or 4vHPV vaccine recipients)
- **non-HPV vaccinated: 17,838** originally **14- 19 year-old** women,

10 years of passive follow-up:

- Population-based cancer-registry follow-up of two Finnish vaccination trials and unvaccinated control
- Individually randomized sub-cohorts, age-aligned, from country-wide Finnish Cancer Registry based 7-year periods of passive follow-up

n: number of cases; **Rate:** incidence rates per 100,000 woman-years

Adapted from T. Lehtinen et al., Vaccination protects against invasive HPV-associated cancers. International Journal of Cancer: 00, 00–00 (2018) © UICC . DOI: 10.1002/ijc.31251

Finland 2018

106,579 females
16-59 years old
2006-2013
Follow up:
up to 8 years

Included in NIP in 2007

Belgium 2015

Included in NIP in 2012

Sweden

n=1,333,691 females;
Aged 13-29;
follow-up:
Up to 8 years
2006 to 2013

Denmark 2009

Efficacy of Gardasil (4vHPV) Against High-Grade Cervical and External Genital Lesions

High effectiveness of Gardasil (4vHPV) Vaccination Against Genital Warts

Rate per 100,000 per year

Age at First Dose

- Register-based popul
- Three time frame intervals: 2006–2008 (pre-vaccination) , 2009–2012 (early post-vaccination effect period), 2013–2015 (late post-vaccination effect period)
- Averaged annual number of members of 1,765,481, 1,906,774 and 2,042,678 in the years 2006–2008, 2009–2012 and 2013–2015, respectively

NIP: National Immunization Program

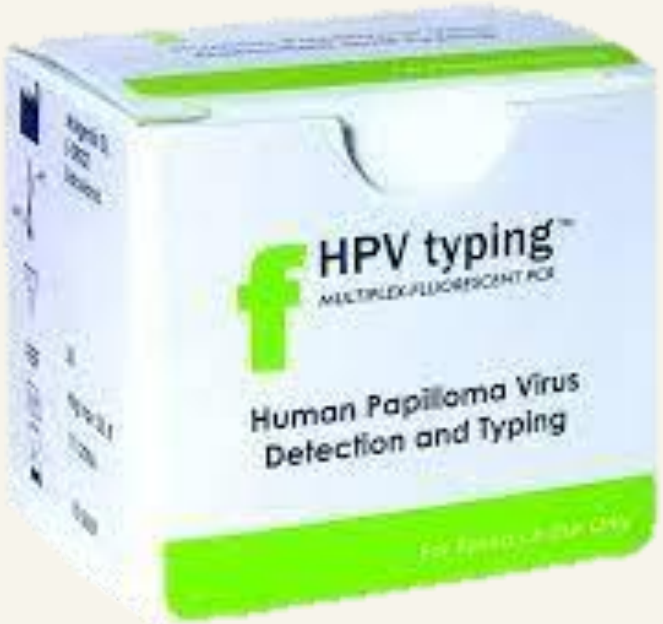
n = number of vaccinated women with lesion in each group, ** Pvalue < 0.001,* Pvalue < 0.05

NIP: National Immunization Program; CIN2+:CIN2 or worse, adenocarcinoma in situ (AIS) or worse; CIN3+:CIN3 or worse, AIS or worse

Adapted from S. Lurie, et al., Impact of quadrivalent human papillomavirus vaccine on genital warts in an opportunistic vaccination structure, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.06.001

Adapted from Herweijer E, Sundstrom K, Ploner A, Uhnoo I, Sparen P, Arnheim-Dahlstrom L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study.

The triage today:



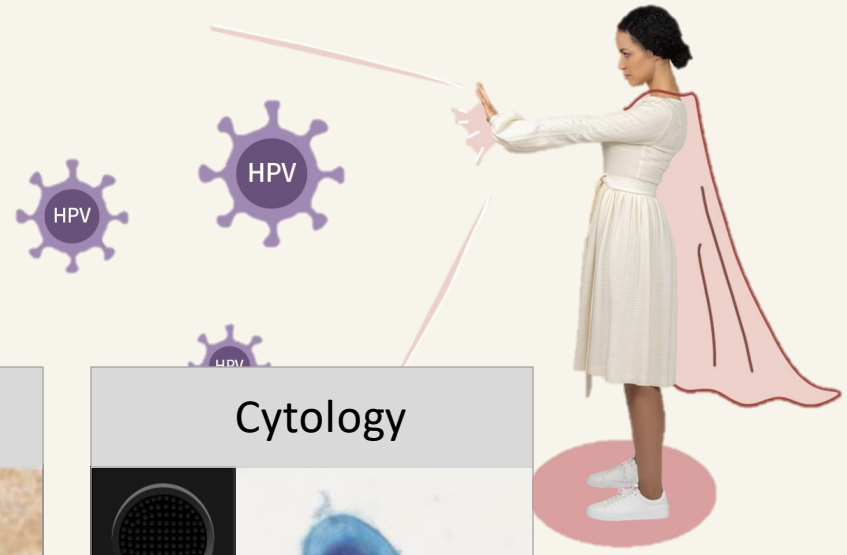
Facts

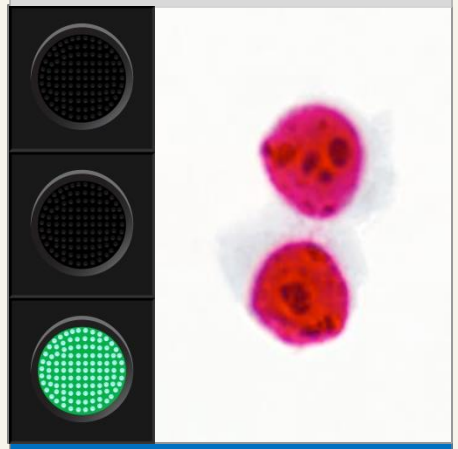
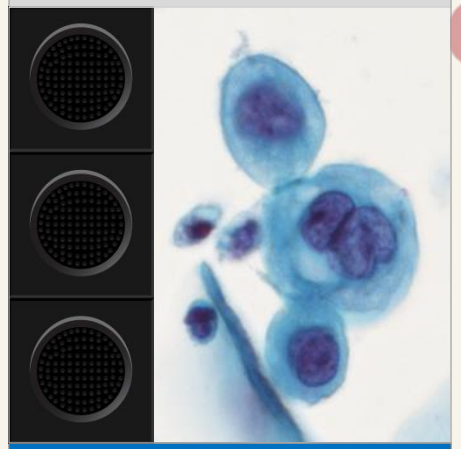
The process

Moral

CINtec *PLUS* Cytology removes subjectivity from interpretation

- Co-expression of p16/Ki-67 biomarkers indicates transforming HPV infections



CINtec *PLUS*	CINtec *PLUS*	CINtec *PLUS*	Cytology
			
Negative	**Negative**	**Positive**	**Subjective**
Expression of p16 (brown) signals halting of cell division	Expression of Ki-67 (red) signals progression of cell division	Co-expression of p16 & Ki-67 (brown & red) indicates cell cycle dysregulation	Reliant on interpretation of morphology only

Source: CINtec PLUS Cytology package insert for the US market

CINtec *PLUS* Cytology test – FDA approved intended use summary

- Approved by the FDA for the triage of **cobas®** 4800 HPV(+) results in 2 screening scenarios

Primary HPV screening (age 25-65)

cobas® HPV TEST

HPV16/18(+)*

+

12 other hrHPV(+)

CINtec® PLUS CYTOLOGY

+ Colposcopy*

− Follow-up*

*For HPV16/18+ use as additional information in conjunction with the physician's assessment of patient screening history, other risk factors, and professional guidelines to guide patient management.

LBC/HPV co-testing (age 30-65)

cobas® HPV TEST

HPV16/18(+)*

+

12 other hrHPV(+)

LBC Cytology

−

CINtec® PLUS CYTOLOGY

+ Colposcopy*

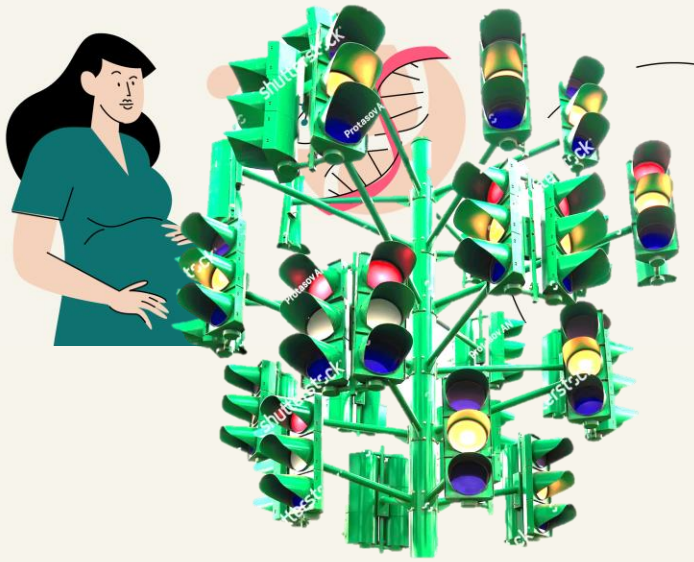
− Follow-up*

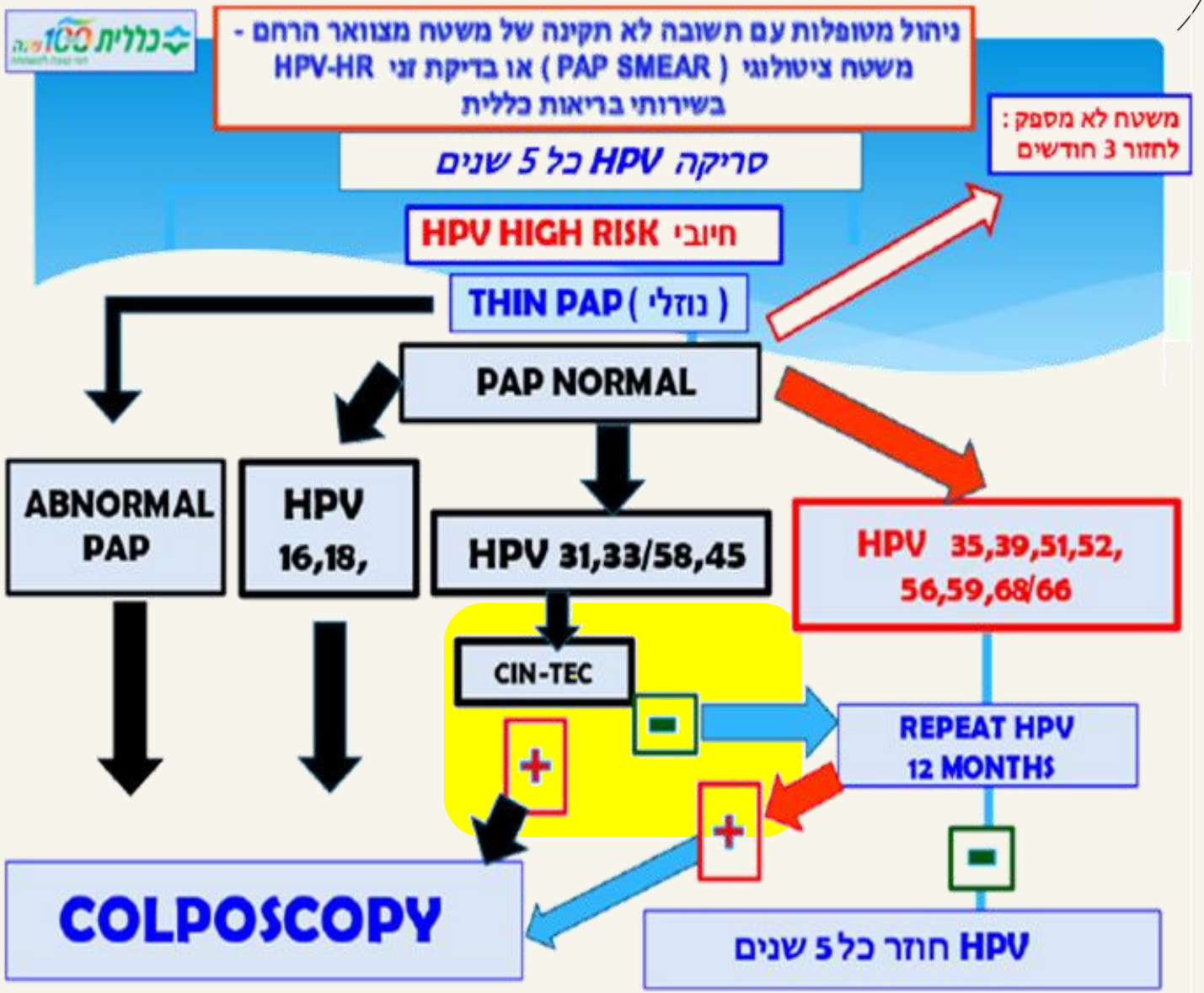
*For HPV16/18+ use as additional information in conjunction with the physician's assessment of patient screening history, other risk factors, and professional guidelines to guide patient management.

Source: Adapted from CINtec PLUS Cytology package insert for the US market. CINtec plus is also CE-IVD, for permitted uses under the CE-IVD marking please refer to CINtec PLUS CE-IVD Cytology package insert.

Clalit:

תרשים מס' 2:





Cervical cancer in pregnancy

- 2nd neoplasia diagnosed during pregnancy or postpartum
- 0.004–0.1% of pregnant and postpartum
- The incidence and persistence of HPV in women are higher during pregnancy and increase over the course of gestation,
  Hormonal variations? Local immunosuppression?
  (de Freitas, Pereira, Merçon-de-Vargas, & Spano, 2018)
- Diagnostic tools and the treatment are the same in pregnancy
- Pregnancy does not change the aggressiveness and the progression of cervical cancer
- Timing of therapy and delivery seems the most important factor for the health of both mother and fetus *(Ishioka et al., 2009; Morice et al., 2012; van Vliet, van Loon, ten Hoor, & Boonstra, 1998).*

Cervical cancer in pregnancy

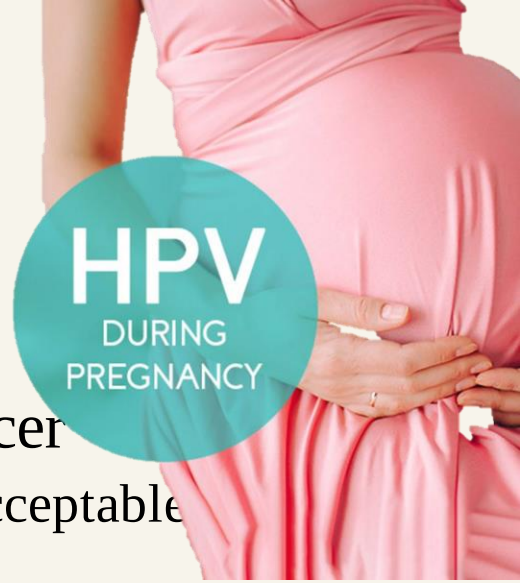


TABLE 1 Revision of the literature

Stages	No. of cases (References)	Histotype	Treatment in pregnancy	Obstetric outcome	Surgical treatment	Adjuvant	Oncological outcome	Neonatal outcome
IA1	2 (Favero et al., 2010)	SCC	LPS PL, 23 weeks	CS, 33 weeks	RH + PL (same time of CS)	None	NED, 32 months	ND
		AC	LPS PL, 18 weeks	CS, 36 weeks	RT (6 weeks after CS)	None	NA	ND
	4 (Yahata et al., 2008)	AC	4 Laser conization, 16–23 weeks + 1 reconization (positive margins)	2 CS 2 VD	3 RH + PL 1 conization (positive margins in pregnancy)	None	NED, 24–156 months	NA
	3 (Vercellino et al., 2014)	NA	LPS PL, mean, 17 weeks	CS, mean, 34 weeks	20 RH + PL (same time of CS) 1 RH + PL (6 weeks after CS) 6 RT (6 weeks after CS) 1 sectio parva + RH + PL (same time of CS)	NA	NED, 42 months	ND
	2 (Hecking et al., 2016)	SCC	Conization, 21 weeks	CS, 35 weeks	Hysterectomy	None	NED, 107 months	ND
		SCC	No treatment	CS, 36 weeks	Conization	None	NED, 52 months	ND
	1 (Lanowska et al., 2011)	AC	LPS PL, 19 weeks + conization + cerclage + NAC	CS, 34 weeks	RH (same time of CS)	None	NED, 1 month	ND
IA2	1 (Favero et al., 2010)	AC	LPS PL, 6 weeks	CS, 34 weeks	RT (6 weeks after CS)	None	NED, 8 months	ND
	7 (Vercellino et al., 2014)	NA	3 LPS PL, mean, 17 weeks + NAC	CS, mean, 34 weeks	20 RH + PL (same time of CS)	NA	NED, 42 months	ND
			4 LPS PL, mean, 17 weeks	-	1 RH + PL (6 weeks after CS) 6 RT (6 weeks after CS) 1 sectio parva + RH + PL (same time of CS)			
IB1	1 (de Lima et al., 2013)	AC	NAC	CS, 34 weeks	RH + PL (same time of CS)	CHT	NED, 24 months	ND
	2 (Kong et al., 2014)	AC	NAC	CS, 33 weeks	RH + PL + AL (same time of CS)	None	NED, 96 months	ND
		SCC	NAC	CS, 34 weeks	RH + PL + AL (same time of CS)	CHT	NED, 48 months	ND
	1 (Calusaerts et al., 2006)	SCC	NAC	CS, 32 weeks	RH + PL (same time of CS)	NA	NED 6 months	ND
	1 (Giacalone et al., 1996)	SCC	NAC	CS, 32 weeks	RH + PL + AL (same time of CS)	None	NED, 12 months	ND
	5 (Alouini et al., 2008)	SCC	LPS PL + RT, 12 weeks (same time of LPS)	Spontaneous abortion, 12 weeks	RH	None	NED, 132 months	-
		AC	LPS PL + RT, 15 weeks (same time of LPS)	CS, 30 weeks	RH (after CS)	RX	DOD, 36 months	ND
		SCC	LPS PL, 15 weeks	CS, 34 weeks	RH (7–10 weeks after CS)	None	NED, 26 months	ND
		AC	LPS PL, 20 weeks	CS, 35 weeks	RT (7–10 weeks after CS)	None	NED, 14 months	ND
		SCC	LPS PL, 22 weeks	CS, 34 weeks	RT (7–10 weeks after CS)	None	NED, 84 months	ND
	1 (Ayhan et al., 2012)	AC	NAC	CS, 32 weeks	RH + PL (same time of CS)	None	NED, 36 months	ND (Triplet pregnancy)
	13 (Favero et al., 2010)	AC	LPS PL, 15 weeks	abortion, 17 weeks	RH + PL 17 weeks	CHT + RX	NED, 128 months	-
		SCC	LPS PL, 14 weeks	CS, 32 weeks	RH + PL (same time of CS)	None	NED, 102 months	ND
		AC	LPS PL, 21 weeks	Abortion, 23 weeks	RH + PL 23 weeks	None	NED, 68 months	-
		SCC	LPS PL, 23 weeks + conization 26 weeks	CS, 33 weeks	RT (6 weeks after CS)	None	NED, 18 months	ND

(Continues)

mary treatment of early-stage cervical cancer

ge of 16 weeks for early-stage tumor could be an acceptable
th (5%; *Hunter, Tewari, & Monk, 2008)*

ancer patients did not promote tumor recurrence (Alouini,

al., 2010)

- Chemoradiotherapy is an optio
loss.

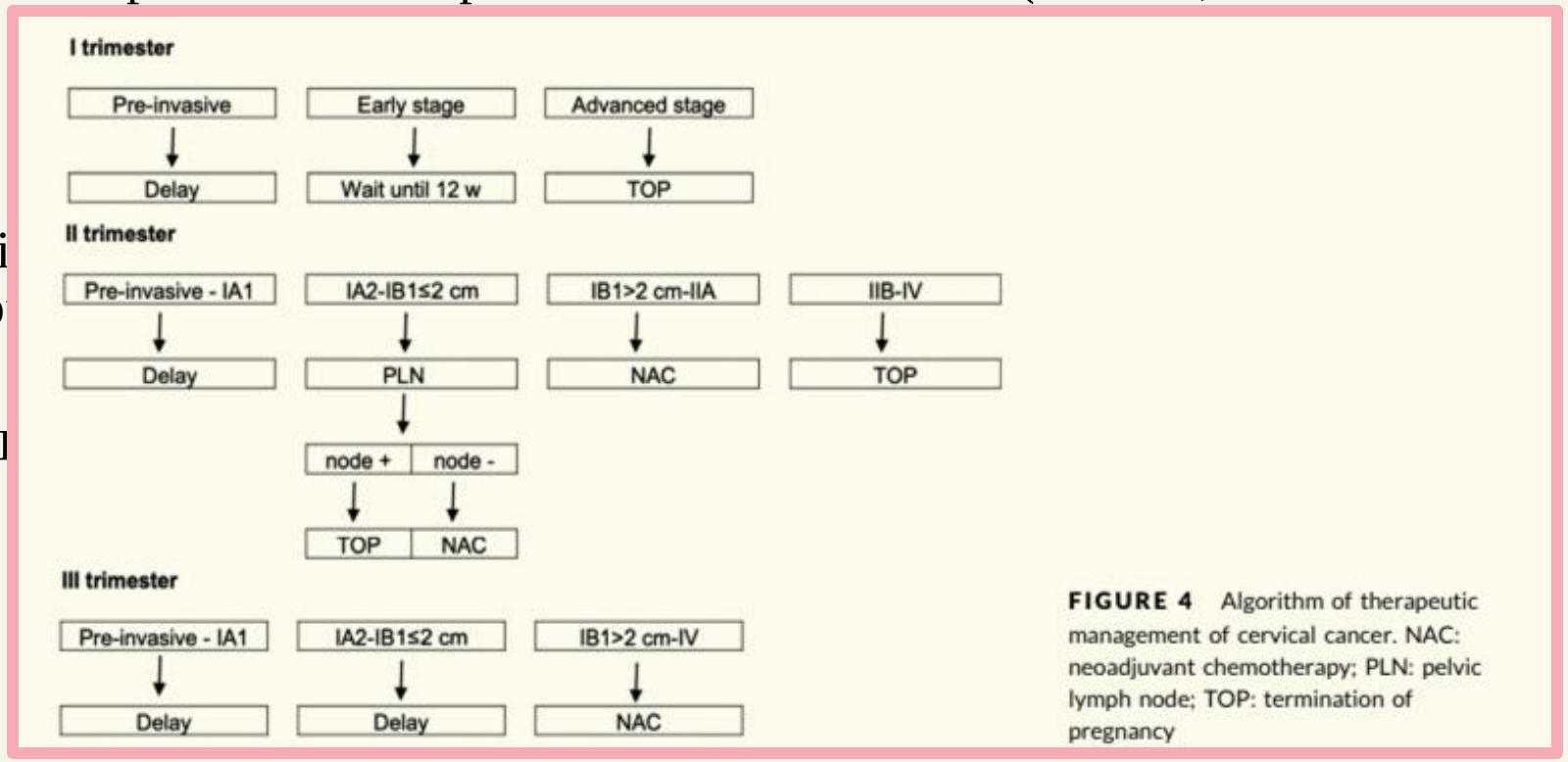


FIGURE 4 Algorithm of therapeutic management of cervical cancer. NAC: neoadjuvant chemotherapy; PLN: pelvic lymph node; TOP: termination of pregnancy

Still left to be talked about:

- Condylomas in pregnancy
- Conization in pregnancy
- Cerclage in pregnancy- after conization

But what can you do if -

- Can do in pregnancy:
  - PAPS
  - Colposcopy ±biopsy
  - Conization (1st trimester)
  - Deliver at 32-34w and treat/ termination of pregnancy (Sq cell ca or Adenoca)

Thank you for listening