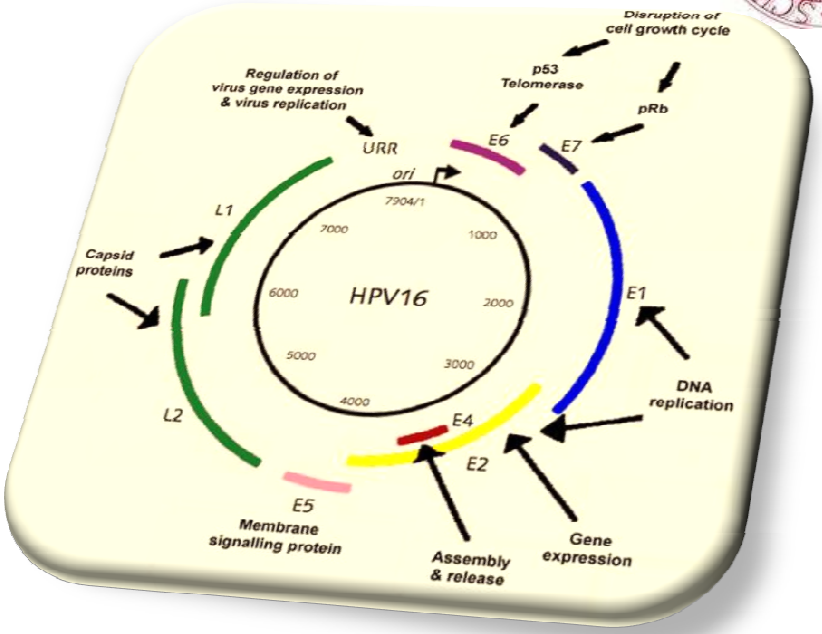
Università degli Studi di Padova
Dipartimento di Scienze Ginecologiche e della Riproduzione Umana
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

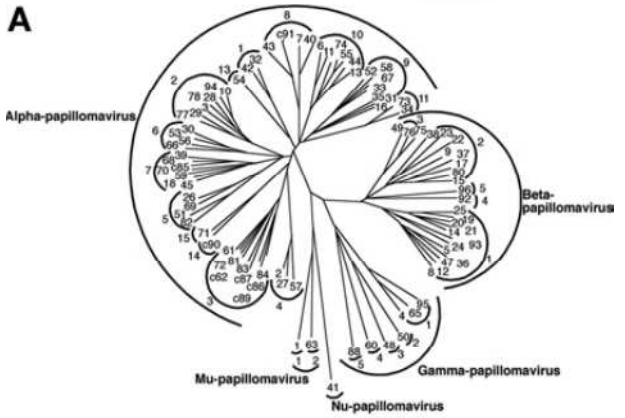
HPV-DNA sperm infection and infertility: Systematic review.

Dott. Marco Noventa

HPV molecular biology

Genus + Species	Type Species	SCC Cervix	Adeno Cervix	Category
Alpha 1	HPV32			low risk
	HPV42			low risk
Alpha 2	HPV3			cutaneous
	HPV10			cutaneous
	HPV28			cutaneous
	HPV29			cutaneous
	HPV77			cutaneous
	HPV78			cutaneous
	HPV94			cutaneous
Alpha 3	HPV61			low risk
	C62			
	HPV72			low risk
	HPV81	0.04%		low risk
	HPV83	0.04%		low risk
	HPV84			low risk
	C86			
	C87			
	C89			
Alpha 4	HPV2			cutaneous
	HPV27			cutaneous
	HPV57			cutaneous
Alpha 5	HPV26	0.22%		high risk
	HPV51	0.75%	0.54%	high risk
	HPV69			
	HPV82	0.26%		high risk
Alpha 6	HPV30			
	HPV53	0.04%		high risk
	HPV56	1.09%		high risk
	HPV66	0.19%		high risk
Alpha 7	HPV18	11.27%	37.30%	high risk
	HPV45	5.21%	5.95%	high risk
	HPV59	1.05%	2.16%	high risk
	HPV39	0.82%	0.54%	high risk
	HPV68	0.37%		high risk
	HPV70			
	C85			
Alpha 8	HPV7			cutaneous (mucosal)
	HPV40			cutaneous (mucosal)
	HPV43			cutaneous (mucosal)
	C91			
Alpha 9	HPV16	54.38%	41.62%	high risk
	HPV31	3.82%	1.08%	high risk
	HPV33	2.06%	0.54%	high risk
	HPV35	1.27%	1.08%	high risk
	HPV52	2.25%		high risk
	HPV58	1.72%	0.54%	high risk
	HPV67			
Alpha 10	HPV6	0.07%		low risk
	HPV11	0.07%		low risk
	HPV13			low risk
	HPV44			low risk
	HPV55	0.04%		low risk
	HPV74			
Alpha 11	HPV34			high risk
	HPV73	0.49%		high risk
Alpha 12				
Alpha 13	HPV54			low risk
Alpha 14	C90			low risk
Alpha 15	HPV71			low risk





Doorbar Jet al. Vaccine. 2012

HPV prevalence

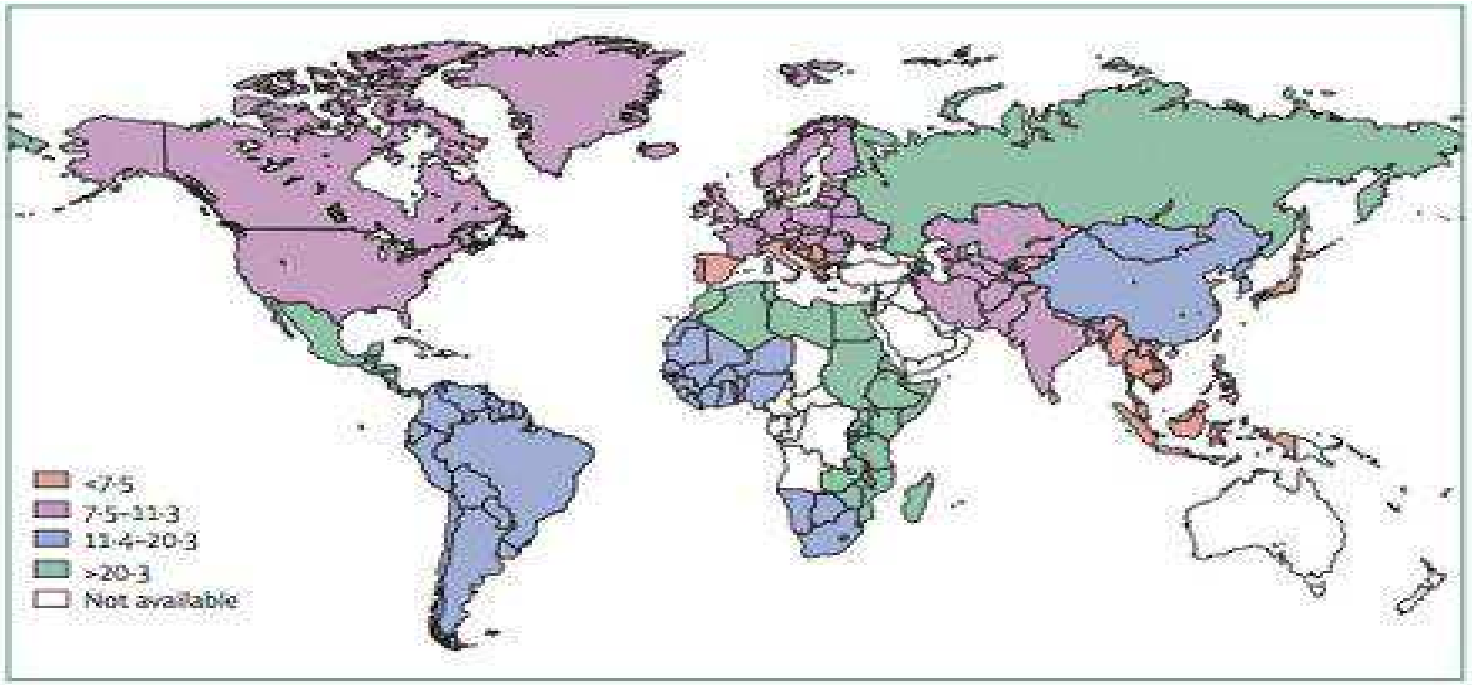


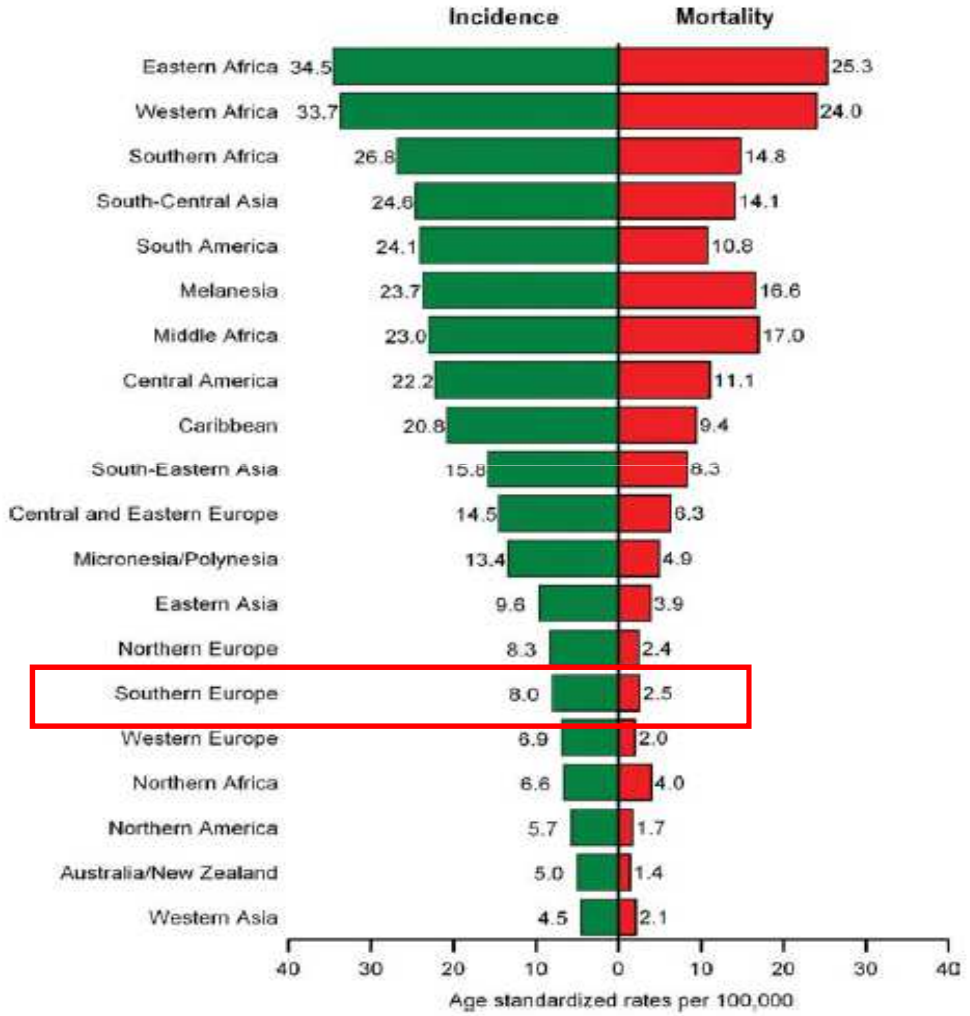
Figure 1: Estimated HPV DNA prevalence in the world regions
Estimates are based on a meta-analysis of 78 studies including 157 879 women with normal cytology. Colours represent the adjusted prevalence in the region and denote the quartile distribution of all the estimates.

Worldwide prevalence : 40% (male and female)

Barzon L et al. J Med Virol. 2010 Aug

HPV and Cervix neoplasia

	Estimated New Cases	Estimated Deaths
Developed Countries	**Female**	**Female**
	Breast 692,200	Breast 189,500
	Colon & rectum 337,700	Lung & bronchus 188,400
	Lung & bronchus 241,700	Colon & rectum 153,900
	Corpus uteri 142,200	Pancreas 79,100
	Stomach 102,000	Stomach 70,800
	Ovary 100,300	Ovary 64,500
	Non-Hodgkin lymphoma 84,800	Liver 39,900
	Melanoma of the skin 81,600	Leukemia 38,700
	Pancreas 80,900	Non-Hodgkin lymphoma 33,500
	Cervix Uteri 76,500	Corpus uteri 33,200
	All sites but skin 2,584,800	All sites but skin 1,223,200
Developing Countries	**Female**	**Female**
	Breast 691,300	Breast 268,900
	Cervix uteri 453,300	Cervix uteri 242,000
	Lung & bronchus 272,000	Lung & bronchus 239,000
	Stomach 247,000	Stomach 202,900
	Colon & rectum 232,400	Liver 177,700
	Liver 186,000	Colon & rectum 134,100
	Corpus uteri 144,900	Esophagus 115,900
	Esophagus 137,900	Ovary 75,700
	Ovary 125,200	Leukemia 75,100
	Leukemia 93,400	Brain, nervous system 50,300
	All sites but skin 3,453,600	All sites but skin 2,122,600

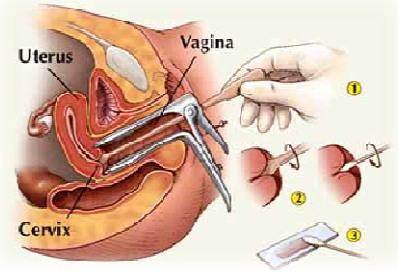


Jemal A et all Global cancer statistics. CA Cancer J Clin. 2011

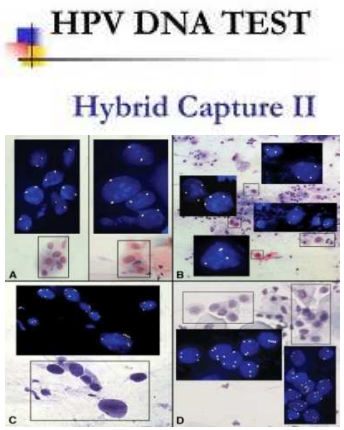
Screening

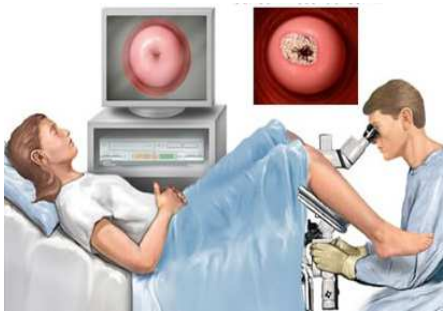
Prevention

I Livello



II Livello





Raccomandazioni per la qualità nella diagnosi, terapia e follow up delle lesioni cervicali, nell'ambito dei programmi di screening. GISCI 2010

Società italiana di Colposcopia e Patologia Cervico Vaginale: Gestione delle pazienti con Pap-test anormale.Anno XXI-N° 1 Dicembre 2006

Screening

Relation to ano-genital warts and different type of neoplasia (cancers of penis, anal canal, oral cavity, head and neck)

Prevalence of HPV in male: 1.3–72.9% (higher than that in females)

It does not tend to decline with age

Relation to Infertility in some cases?

Lenzi *et al. BMC Public Health* 2013, **13**:117
http://www.biomedcentral.com/1471-2458/13/117

BMC Public Health

CORRESPONDENCE Open Access

Rome consensus conference - statement; human papilloma virus diseases in males

Andrea Lenzi[1*], Vincenzo Mirone[2], Vincenzo Gentile[3], Riccardo Bartoletti[4], Vincenzo Ficarra[5], Carlo Foresta[6], Luciano Mariani[7], Sandra Mazzoli[8], Saverio G Parisi[9], Antonio Perino[10], Mauro Picardo[11] and Carla Maria Zotti[12]

Nielson CM et al. Human papillomavirus prevalence and type distribution in male anogenital sites and semen. Cancer Epidemiol Biomarkers Prev. 2007

Giuliano AR et al. Age-specific prevalence, incidence, and duration of human papillomavirus infections in a cohort of 290 US men. J Infect Dis. 2008

Garolla et al. Human papillomavirus sperm infection and assisted reproduction: a dangerous hazard with a possible safe solution. Hum Reprod. 2012

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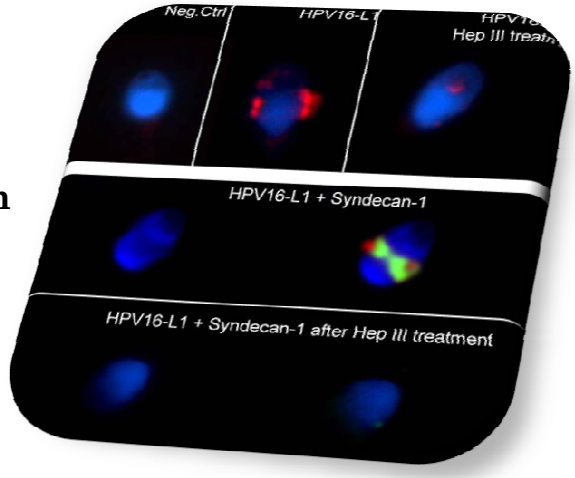
HPV Sperm Infection

- Prevalence highly variable from 3% to 65% (18-40 years)
- HPV binds two distinct site along the equator of the sperm head (Sydecan-1)
- Related to spermatic parameters modification?
  - sperm motility reduction
  - pH alterations
  - spermatozoa DNA fragmentation.
- HPV-infected sperm is able to fertilize oocyte transferring the viral genome?
- Infected oocytes interfere with implantation and pregnancy development?



Pérez-Andino J. Adsorption of human papillomavirus 16 to live human sperm. PLoS One. 2009 Jun

Foresta C. Human papillomavirus found in sperm head of young adult males affects the progressive motility. Fertil Steril. 2010

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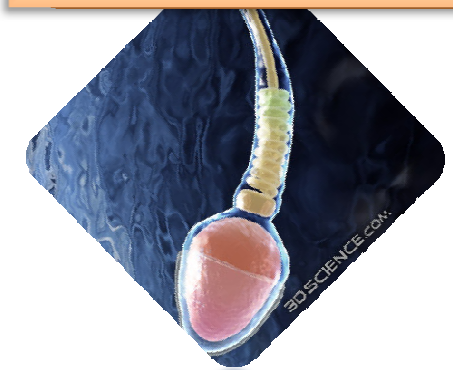
Aim of the Review

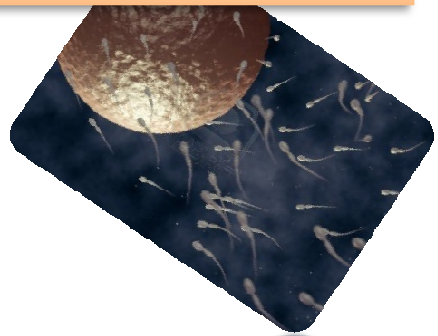
Investigate the HPV sperm infection implications on male and couple fertility

Clinical impact of HPV infection on early pregnancy development and pregnancy loss

Impact of HPV-infected sperm on fertilized oocyte, blastocyst implantation, apoptosis.



Spermatic parameters alteration and spermatozoa molecular changes HPV-related



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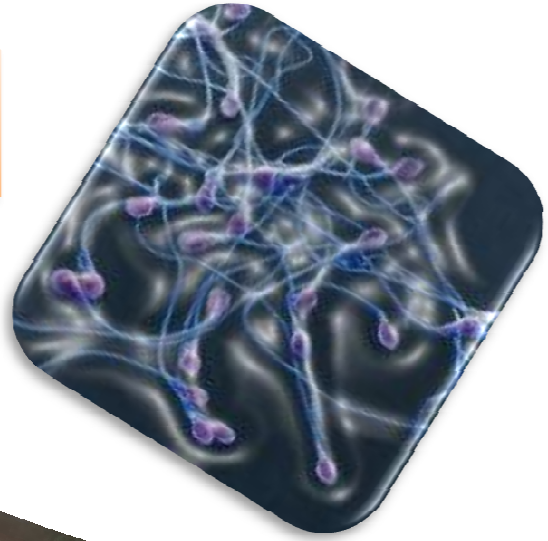
Aim of the Review

Feasibility and clinical efficacy of all the available options to detect and treat HPV-infected sperm.



Finally we evaluated the implication of all these data in relation to sperm banking and ART cycle.

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Data Sources

- **Interval time from 1994 to 2013**

- **Key search terms:**

- HPV sperm infection
- Male infertility and HPV
- Sperm parameters and HPV
- HPV infected sperm and fertilization
- HPV and fertility outcome
- HPV and sperm/blastocyst apoptosis

- **Outcomes**

- Clinical impact of HPV infection and fertility outcomes
- HPV-related spermatic modifications and their impact on fertility
- Ability of infected semen to vehicle exogenous HPV-DNA and its impact on pregnancy evolution

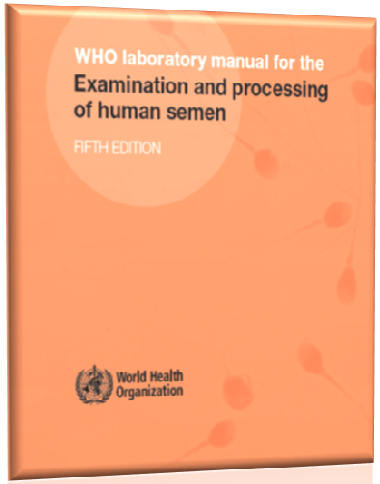
Available Methods

Clinical impact of HPV-DNA infection (in male, female and couples) in relation to :

spontaneous miscarriage rate

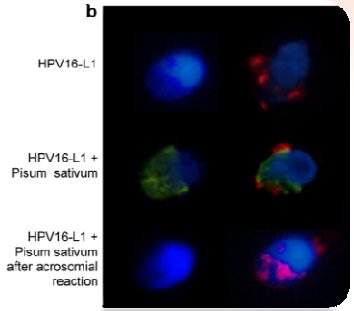
placental infection rate (at term or abortion)

Sperm parameters were analysed according to



HPV-DNA detection and localization

PCR



FISH

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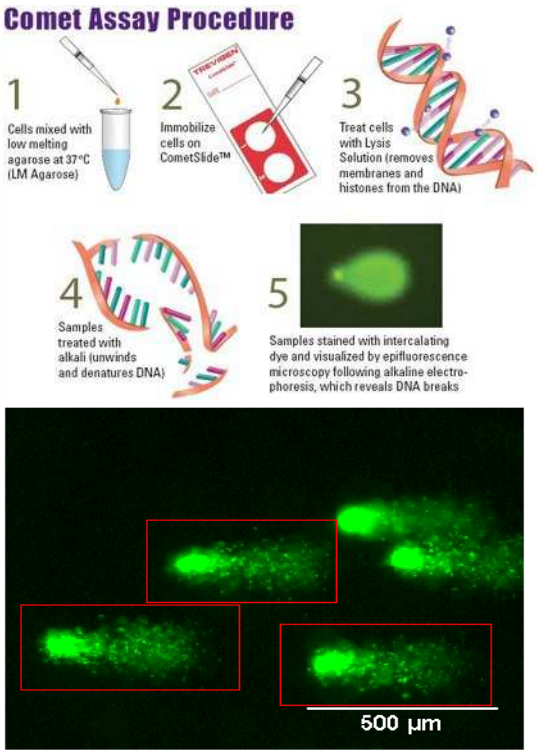
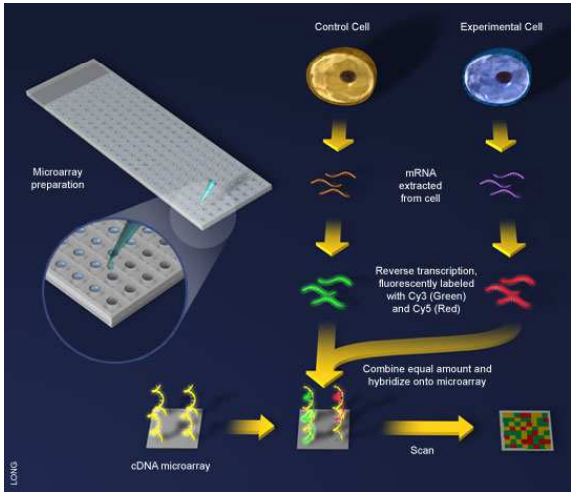
Available Methods

To detect HPV-related apoptosis

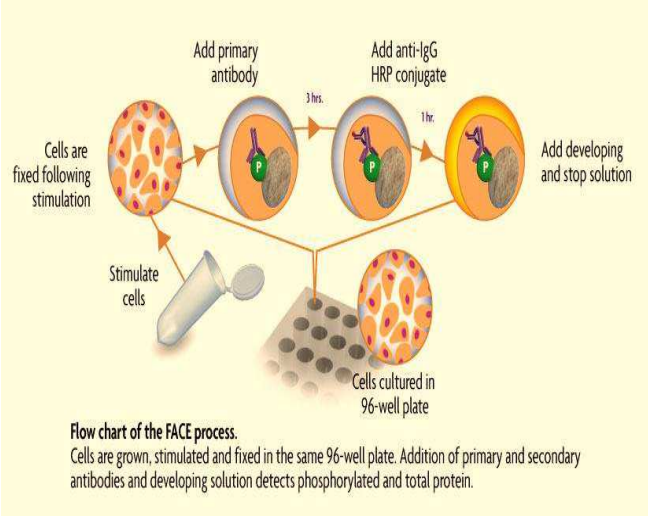
Comet assay



DNA disc chip assay



Cell Death Detection ELISA



Clinical impact of HPV infection and fertility outcomes

5 manuscript focused on this topic

Authors (Year)	N° of samples	Spontaneus aborted products: HPV +/HPV-	Electively aborted products: HPV +/HPV-	Incidence of miscarriages in pregnant exposure to Gardasil	Samples of placentas at term: HPV +/HPV-	Incidence of miscarriages in couple with male partner: HPV +/HPV-	Incidence of miscarriages in couple with female partner: HPV +/HPV-	Incidence of miscarriages in couple with both partner: HPV +/HPV-
Hermonat et al. (1997)	40	60%/40%	20%/80%					
Matovina et al. (2004)	108	7,4%/92,6%						
Dana et al. (2009)	517			6,9%				
Skoczynski et al. (2011)	129	17.7%/82,3 %			24,4%/75,6%			
Perino et al. (2011)	199 (couple)					66,7%/15%	40%/13%	100%/15,9%

Matovina M et al Fertil Steril. 2004 Mar

Hermonat PL,et al. Virus Genes 1997.

Dana A et al Obstet Gynecol. 2009

Skoczyński et al. Acta Obstet Gynecol Scand. 2011

Results

Human papillomavirus infection in couples undergoing in vitro fertilization procedures: impact on reproductive outcomes

A prospective study was performed to assess the relationship between human papillomavirus (HPV) infection in 199 infertile couples and outcome of assisted reproductive technologies (ARTs). A highly statistically significant correlation between pregnancy loss rate (proportion of pregnancies detected by β-hCG that did not progress beyond 20 weeks) and positive HPV DNA testing in the male partner of infertile couples, compared with HPV negatives, was observed (66.7% vs. 15%). (Fertil Steril® 2011;95:1845–8. ©2011 by American Society for Reproductive Medicine.)

Key Words: Abortion, ART, HPV infection, infertility, pregnancy loss

TABLE 1

Frequency of miscarriage by sociobehavioral and clinical characteristics: univariate and multivariate analyses.

Characteristic	No. of pregnancies (total = 66)	No. of miscarriages n	%	OR (95% CI)	Adjusted OR (95% CI)
Age of men (y)					
≤38[a]	54	8	14.8	1.00	1.00
>38	12	5	41.7	4.11 (0.80–19.5)	5.36 (1.20–24.0)
Age of women (y)					
≤35[a]	41	6	14.6	1.00	
>35	25	7	28.0	2.27 (0.55–9.42)	
No. of oocytes					
≥3[a]	23	4	17.4	1.00	
<3	43	9	20.9	1.26 (0.30–6.33)	
Cause of infertility[b]					
Unexplained	10	1	10.0	1.00	
Female	15	0	0	22.7 (3.46–149.3)	
Male	38	8	21.1	2.40 (0.26–21.80)	
Couple	3	0	0	0.90 (0.03–27.86)	
HPV + male					
No	60	9	15.0	1.00	1.00
Yes	6	4	66.7	11.33 (1.32–134.9)	14.72 (2.11–102.7)
HPV + female					
No	51	7	13.7	1.00	
Yes	15	6	40.0	4.20 (0.91–18.50)	
HPV + couples					
No	63	10	15.9	1.00	
Yes	3	3	100.0	35.8 (1.7–742.8)	

Note: OR = odds ratio; CI = confidence interval.

increase in the risk of pregnancy loss when HPV infection was diagnosed in sperm cells of the male partner. When both partners resulted infected, the miscarriage rate detected was 100%

Perino A et al Fertil Steril. 2011

The presence of HPV in semen sample can be associated with an impairm

Results

HPV-related spermatic modifications and their impact on fertility.

9 eligible studies aimed on this field

AUTHORS (YEAR)	TYPE OF STUDY	PATIENTS	TOTAL MOTILITY (%)	PROGRESSIVE MOTILITY %	AMPLITUDE LATERAL HEAD (MM)	PERCENTAGE HYPERACTIVE (%)	STRAIGHT-LINE VELOCITY (MM/SEC)	CURVILINEAR VELOCITY (M/S)	AVERAGE PATH VELOCITY (MM/SEC)	LINEARITY (%)
Lee et al (2002)	case control study	control subjects	74.0 ± 0.6	17.3 ± 0.2	3.0 ± 0.0	2.3 ± 0.1		58.4 ± 0.2		
		Patients HPV-DNA 16	38.4 ± 1.1	6.0 ± 0.2	1.3 ± 0.1	1.4 ± 0.1		40.1 ± 0.7		
		Patients HPV-DNA 18	56.1 ± 0.5	9.1 ± 0.2	2.9 ± 0.0	2.3 ± 0.1		53.0 ± 0.2		
		Patients HPV-DNA 6/11	47.1 ± 0.5	7.0 ± 0.2	2.1 ± 0.0	3.3 ± 0.1		51.4 ± 0.4		
		Patients HPV-DNA 31	53.4 ± 0.6	8.6 ± 0.1	2.7 ± 0.0	2.4 ± 0.1		52.0 ± 0.4		
		Patients HPV-DNA 33	46.0 ± 1.3	10.8 ± 0.4	3.0 ± 0.0	2.9 ± 0.1		47.3 ± 1.3		
		controls DQA1	47.0 ± 0.6	6.5 ± 0.1	2.7 ± 0.0	4.3 ± 0.3		49.6 ± 1.0		
Brossfield et al (1999)	case control study	L1 HPV DNA	51.5 ± 0.15	15.5 ± 0.11	1.9 ± 0	0.5 ± 0.02	23.5 ± 0.02	43.5 ± 0.02	34.0 ± 0.04	57.0 ± 0.04
		Control sperm washed	75.0 ± 0.45	19.0 ± 0.04	3.1 ± 0	4.0 ± 0.09	24.5 ± 0.07	57.5 ± 0.02	41.0 ± 0	44.5 ± 0.11
		Transfected centrifuge-washed	90.0 ± 0	38.5 ± 0.61	4.1 ± 0.03	8.0 ± 0.38	31.5 ± 0.2	73.5 ± 0.05	47.5 ± 0.05	44.5 ± 0.14
		Transfected Isolate-washed	93.0 ± 0.10	33.5 ± 0.05	3.6 ± 0.12	1.0 ± 0.10	26.0 ± 0.10	56.5 ± 0.25	37.5 ± 0.25	47.0 ± 0
		Transfected, TYB-washed	94.0 ± 0.40	37.0 ± 0.70	3.7 ± 0.01	4.0 ± 0	26.0 ± 0.10	58.5 ± 0.05	36.0 ± 0.20	46.5 ± 0.35
Connelly et al (2001)	case control study	Patients HPV-DNA 16	48.0 ± 0.2	5.5 ± 0.2	1.8 ± 0	1.0 ± 0.1		38.5 ± 0.3	28.0 ± 0.1	56.0 ± 0.2
		Patients HPV-DNA 18	47.5 ± 0.1	11.0 ± 0.2	2.7 ± 0	1.0 ± 0.1		55.5 ± 0.7	36.0 ± 0.5	47.5 ± 0.2
		Patients HPV-DNA 6b/11	36.5 ± 0.1	6.5 ± 0.1	1.8 ± 0	0 ± 0		31.5 ± 0.1	23.0 ± 0	57.0 ± 0.2
		Patients HPV-DNA 31	55.0 ± 0.5	14.5 ± 0.1	2.8 ± 0.1	2.0 ± 0		45.5 ± 0.3	30.5 ± 0.1	52.5 ± 0.5
		Patients HPV-DNA 33	48.5 ± 0.7	13.0 ± 0.3	2.7 ± 0	0 ± 0		42.5 ± 0.4	28.5 ± 0.3	52.5 ± 0.2
		Patients DQA1	37.5 ± 0.2	11.0 ± 0.4	3.1 ± 0	2.0 ± 0		47.5 ± 0.2	31.5 ± 0.1	49.0 ± 0.4

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Results

Lee et al

Differential Effects of Human Papillomavirus DNA Types on p53 Tumor-Suppressor Gene Apoptosis in Sperm

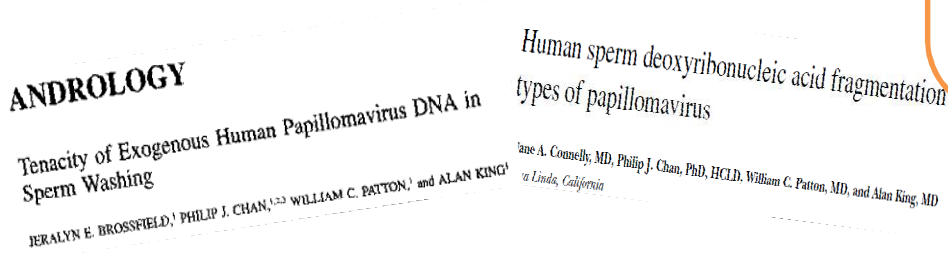
Cathy A. Lee, M.D.,* Christopher T. F. Huang, M.D.,* Alan King, M.D.,* and Philip J. Chan, Ph.D., H.C.L.D.*†‡

- **Sperm motility was reduced in the presence of hrHPV-DNA E6–E7 fragments,**
- **the percentages of progressive motility were lower in sperm exposed to the all HPV-DNA [except genotype 33],**
- **the amplitude of lateral head displacement was decreased after exposure to HPV-DNA type 16 and lr-HPV-DNA.**

Brossfield et al

Connelly et al

slight increase in motility



ANDROLOGY

Tenacity of Exogenous Human Papillomavirus DNA in Sperm Washing

JERALYN E. BROSSFIELD,[1] PHILIP J. CHAN,[1,2,3] WILLIAM C. PATTON,[1] and ALAN KING[1]

Human sperm deoxyribonucleic acid fragmentation by types of papillomavirus

ane A. Connelly, MD, Philip J. Chan, PhD, HCLD, William C. Patton, MD, and Alan King, MD

a Linda, California

- **Observation was made after two hours of incubation.**
- **This data suggests that HPV-DNA required an adequate interval time to determine molecular changes in regulation of sperm motility apparatus.**

Brossfield et al. J Assist Reprod Genet. 1999

Connelly DA et al Am J Obstet Gynecol. 2001
Lee CA et al . Gynecol Oncol. 2002

Results

Autors (year)	Study type	Patients	Sperm Concentration (10^6/ml)	Semen Volume (ml)	Total sperm count (10^6)	pH	Progressive motility %	Normal morpholgy %	Viability%
Garolla et al. (2013)	Cross-sectional clinical	Infertile HPV-infected patients n=61	32.0 ±11.2		94.2 ± 36.5		29.0±11.4	18.8 ± 6.2	80.0 ± 7.1
		Infertile non-infected patients n=104	34.6 ± 9.8		108.8 ± 44.5		47.8 ± 11.0	18.5 ± 4.3	83.2 ± 5.1
		Control subjects n=92	51.3 ± 8.4		156.0 ± 42.9		53.4 ± 11.4	21.3 ± 4.7	83.6 ± 5.1
Garolla et al. (2012)	Case- control	HPV-infected patients n =22	29.0 ± 10.3	3.1± 0.9	87.7 ± 36.3	7.6 ± 0.2	29.6 ± 14.2	19.0 ± 6.3	81.3+6.3
		Control subject n =13	30.5 ± 9.8	3.3± 1.0	98.8 ± 46.7	7.5 ± 0.3	42.4 ± 22.7	21.1 ± 7.5	83.8+8.3
		L1-incubated sperm (pool)					22.6 ± 8.7	20.9 ± 6.5	82.8+8.7
Foresta et al. (2010 a)	Cross-sectional clinical	sexually active subjects HPV(+) n=10	57.5 ± 30.4	2.9 ± 1.6	174.3 ± 115.8	7.7 ± 0.3	37.7 ± 16.8	31.5 ± 8	83.5 ± 7.9
		sexually active subjects HPV(-) n=90	60.2 ± 31.0	2.4 ± 1.6	175.8 ± 154.5	7.6 ± 0.2	53.7 ± 18.2	33.1 ± 11.1	84.6 ± 8.6
		virgin subjects n=100	58.3 ± 29.1	2.7 ± 1.5	174.5 ± 164.7	7.6 ± 0.3	53.7 ± 19.0	32.8 ± 10.6	83.6 ± 7.6
Foresta et al. (2011 c)	Cross-sectional clinical	infected infertile patients n=32	32.4 ± 21.1	3.0 ± 1.1	100.2 ± 73.4	7.6 ± 0.3	29.7±13.8	17.8 ± 9.1	78.3 ± 11.6
Foresta et al. (2010 b)	Cross-sectional clinical	Patients with genital warts HPV (+) n=14	53.5 ± 30.0	2.6 ± 1.7	167.6 ± 111.7	7.7 ± 0.2	36.2 ± 18.7	32.6 ± 10.7	80.2 ± 9.1
		Patients with genital warts HPV (-) n=12	56.2 ± 33.8	0.8 ± 1.8	177.1 ± 126.4	7.4 ± 0.3	56.2 ± 19.8	36.3 ± 14.4	81.3 ± 10.5
		subjects with HPV+ partner HPV(+) n=27	48.5 ± 23.0	2.8 ± 1.2	172.8 ± 110.2	7.6 ± 0.2	38.4 ± 13.2	31.8 ± 11.2	82.4 ± 8.8
		subjects with HPV+ partner HPV(-) n=39	50.1 ± 22.3	2.5 ± 1.3	178.4 ± 102.3	7.7 ± 0.4	53.8 ±16.5	31.8 ± 11.2	82.4 ± 8.8
		Infertile patients HPV (+) n=11	30.0 ± 21.5	2.9 ± 1.9	99.4 ± 88.8	7.7 ± 0.3	33.9 ± 15.9	32.9 ± 13.9	79.8 ± 8.6
		Infertile patients HPV (-) n=97	35.2 ± 23.0	3.0 ± 1.5	102.9 ± 100.9	7.6 ± 0.3	51.7 ± 16.2	33.1 ± 11.1	84.6 ± 10.7
		Fertile controls HPV (+) n=2	60.5 ± 31.5	2.5 ± 1.6	175.5 ± 131.6	7.6 ± 0.2	55.5 ± 17.6	33.5 ± 10.6	81.7 ± 9.4
		Fertile controls HPV (-) n=88	58.7 ± 30.8	2.6 ± 1.6	176.0 ± 139.6	7.7 ± 0.2	54.2 ± 17.9	33.0 ± 13.5	83.9 ± 8.0
Rintala et al. (2004)	case control	High-risk HPV DNA (+) n=10		3.07		7.37	54,2		65,2
		High-risk HPV DNA(-) n=55		4.03		7.51	56,5		69,6

Rintala et al. Detection of high-risk HPV DNA in semen and its association with the quality of semen. Int J STD AIDS. 2004 Nov

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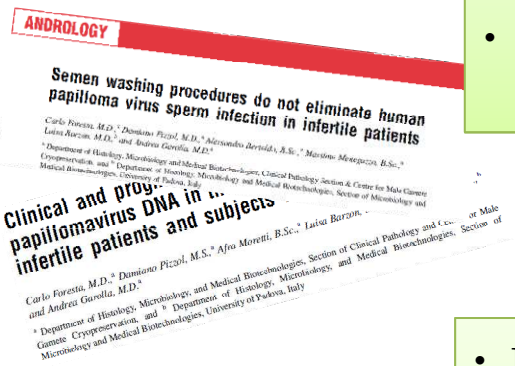
Results

Foresta et al


ANDROLOGY

Semen washing procedures do not eliminate human papilloma virus sperm infection in infertile patients

Clinical and prog... papillomavirus DNA in ... infertile patients and subjects

- **Significant reduction of sperm motility in HPV-DNA infected men**
- **HPV-DNA was detected frequently in exfoliated cells [77.8–100%]**
- **Spermatozoa infection was found in 72% of infertile men**
- **All the remaining spermatic parameters resulted comparable between infected or not-infected patients**

Garolla et al.


Association, prevalence, and clearance of human papillomavirus and antisperm antibodies in infected semen samples from infertile patients

- **Found a reduction of mean progressive motility in HPV-DNA positive sperm**
- **Infertile sperm men had ASAs (anti sperm antibodies) more frequently than fertile men**
- **HPV-DNA infected men with positive sperm-Mar test (ASAs presence) had at 24 months lower motility than negative ones.**
- **Many cases of reported idiopathic asthenozoospermia do not presented any risk factor except for the positivity to HPV-DNA genome**

Foresta C et al Fertil Steril. 2011
Garolla et al. Fertil Steril. 2013 Jan

Foresta C et al Fertil Steril. 2010 Feb
Foresta C et al. Fertil Steril. 2010 Oct

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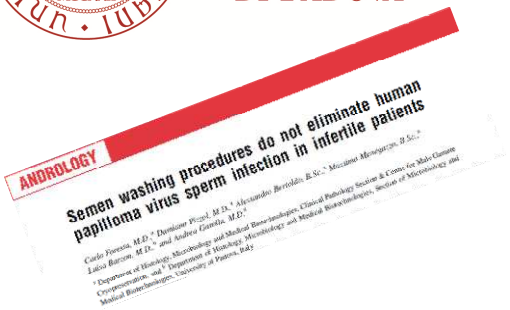
Results

Sperm washing procedures



Direct swim-up

reduces only 24% the HPV sperm infection

Discontinuous Density Gradients (Ficoll)

reduces only 30% the HPV sperm infection

Modified swim-up

slight decrease of sperm motility
viability and DNA integrity

sperm infection cannot be removed by classic washing procedures

IMPORTANT

Foresta C et al Fertil Steril. 2011

Garolla A et al. Hum Reprod. 2012

Ability of infected semen to vehicle exogenous HPV-DNA and its impact on pregnancy evolution.

11 studies (all in-vitro) analyzed the ability of sperm to carry exogenous HPV-DNA infection into oocyte and embryos, the blastocyst expression of viral genome and its impact in terms of fertility, implantation and embryonic effects.

Main Outcomes

- **Increased incidence of apoptosis (integrity of exon 5 and 8 of p53) in sperm cells exposed to E6/E7 region derived from the HPV-DNA types 16 and 18.(**Connely et al. 2001 and Lee et al 2001**)**
- **HPV-DNA infected sperm is able to transfer HPV-DNA into blastocyst and at cells of the reproductive tract.** (Chan et al 1996)
- **In the Blastocysts the exogenous HPV-DNA is present both in the the inner cell mass and throphoblast cells.** (Cabrera et al 1997)

Cabrera M et al J Assist Reprod Genet. 1997

Chan PJ. Et al. Mol Reprod Dev. 2000.

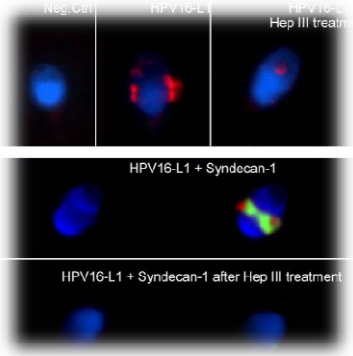
Connelly DA et al.Am J Obstet Gynecol. 2001

Lee et al. Gynecol Oncol. 2002

Results

Foresta et al

HPV is localized at the equatorial region of sperm head (interaction L1 and Sydecan-1)



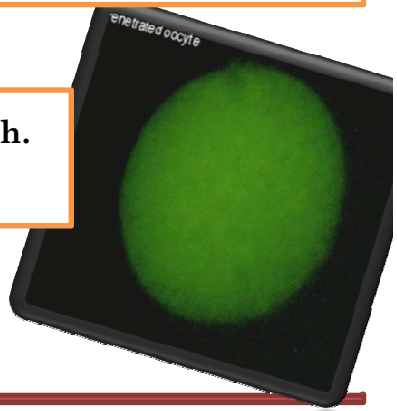
HPV infected sperm is able to transfer both the capsid protein L1 and E6/E7 viral genes to the oocyte with a subsequent gene expression by transfected blastocyst

Calinisan et al

Transfecting blastocysts with E6-E7 region of HPV genotype 16,18,31,33, observed the presence of DNA fragmentation only in subgroups of blastocysts infected by HPV-DNA type 16.

You et al

HPV-16 oncogenes genes may be responsible of Throbhoblast death. (placenta alteration? ➡ Spontaneous miscarriage?)



You H, Liu Y et al Mol Cancer Res. 2002

Foresta C et al PLoS One. 2011
Calinisan et al J Assist Reprod Genet. 2002

Results

Hennemberg et al

Demonstrated the differences of HPV-DNA growth inhibition effects related to the embryo-stage cells.

- **25,9% less Blastocyst formed with HPV 16 exposure**
- **25.9-31.8% more degenerated embryos with HPV 16 exposure**
- **The direct effect of growth inhibition was found only at 2-cell embryo-stage but not at the 4–8 cells one**

Gomez et al

The rates of apoptosis in HPV transfected trophoblast cell were 3-fold [2.4–3.7] and 5.8-fold [5.6–5.9] greater if compared with negative controls at 3 and 12 days.

The invasion of transfected trophoblast cells progressively and significantly decreased from day 3 until 15 after transfection [25.2–57.6% lower than negative controls]

Henneberg et al J Assist Reprod Genet. 2006

Gomez LM et al Hum Reprod. 2008

Results

Sperm is able to vehicle the viral genome in fertilized oocytes and blastocysts

HPV genomes are expressed in fertilized oocytes, blastocysts and trophoblast cells.

Main Outcomes

The viral genome could induce cell changes such as:

- zygote growth inhibition
- blastocyst formation decrease
- DNA fragmentation and apoptosis, resulting often lethal for early embryo development

HPV extravillous trophoblast infection induces cell death and may reduce placental invasion into the uterine wall.

HPV infection may cause placental dysfunction and could be associated with adverse pregnancy outcomes, (such as early pregnancy loss)

It is unknown whether these in vitro findings might apply to in-vivo.

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Conclusion

In infected semen samples, HPV can be localized at different levels: in sperm, in exfoliated cells or in both sites.

HPV was present on the surface of sperm cells, located at two distinct binding sites along the equatorial region of the sperm head (L1-Sydecan-1)

A significant reduction of mean sperm motility was found in those subjects with HPV infected semen

No difference in seminal volume, viscosity, pH count, viability, and normal morphology in HPV-infected and non-infected semen samples.

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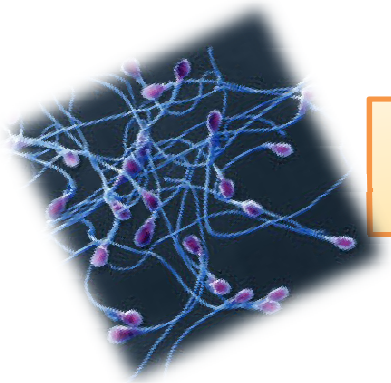
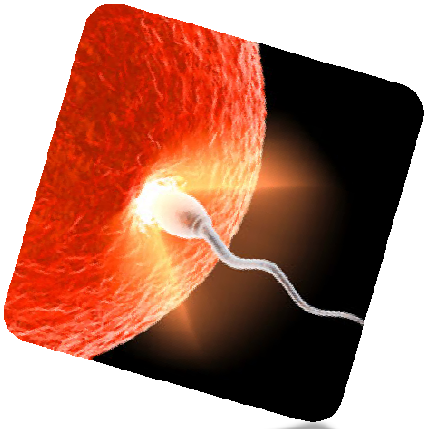
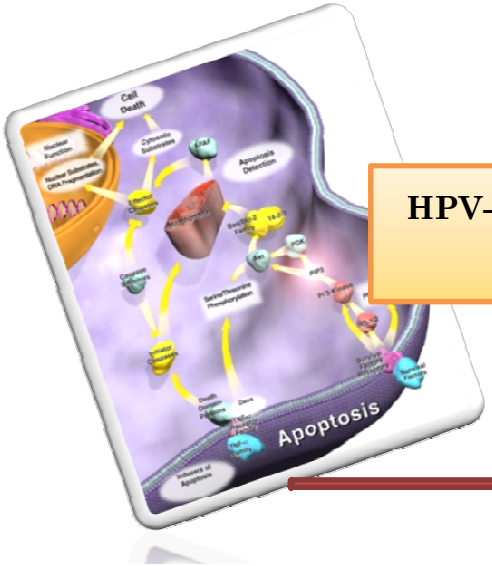
Conclusion



HPV, inducing an alteration of sperm motility, may play a major role in cases of idiopathic asthenozoospermia and thus in male infertility.



Oocytes penetrated by transfected sperm expressed the viral genes, suggesting an active transcription of viral genes by the infected oocyte



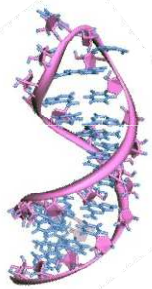
HPV-transfected blastocyst/trophoblast cells have an increased rate of apoptosis and a reduced placental invasion into the uterine wall compared with controls

Conclusion

Concerning ART cycles

Significant persistence of infected sperm after sperm washing procedures

HPV sperm infection cannot be removed by classic washing procedures



HPV-DNA semen screening (PCR) can help to define the best timing [regression of semen infection] to start ART cycles.

HPV male vaccination should be considered a possible strategy for the prevention of HPV semen impairment and improvement of couple fertility outcomes

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Thanks for your attention

Title page

Update on HPV-DNA sperm infection role on male and couple fertility: molecular mechanism, clinical outcomes and further implications. Systematic review.

IN PRESS

Salvatore Gizzo[1] M.D.; Marco Noventa[1] M.D.; Carlo Saccardi[1] M.D, PhD,

Tito Silvio Patrelli[2] M.D.; Michela Longone[1] M.D.; Anna Bertocco[1] M.D.; Lucia Vendemiati[1] M.D.;

Prof. Michele Gangemi[1] M.D Prof. Donato D'Antona[1] M.D & Prof Giovanni Battista Nardelli[1] M.D.

1 - Department of Woman and Child Health – University of Padua (ITALY)
2 - Department of Obstetrics, Gynecological and Neonatology Sciences– University of Parma (ITALY)

Grazie