

Prevention of intrapartal mother-to-child infection transmission

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mother - to - child transmission

MTCT



mother - to - child transmission

MTCT



Significant morbidity and mortality in perinatal outcome in these infections demonstrate the importance of preventing the intrapartal vertical transmission of infections

Svaka država bi trebala imati svoje smjernice, temeljene na nizu čimbenika koji su za nju specifični, na primjer: učestalost određene infekcije, cijene lijekova i postupaka, bruto nacionalni dohodak i drugo

Nažalost, u našoj se državi infekcije pri porodu u praksi najčešće ne prijavljuju pa pravo stanje i ne možemo znati

U Hrvatskoj postoje Smjernice o prenatalnom probiru trudnica na beta hemolitički streptokok skupine B. Koliko se iste sprovode u praksi ne znamo



mother - to - child transmission

Intraamniotic Infection (IAI)

Intraamniotic infection (Chorioamnionitis)

Intraamniotic infection = clinical diagnosis

•Fever in pregnant woman ($\geq 38^\circ\text{C}$)

And at least two additional conditions:

- leucocytosis ($> 15 \times 10^9/\text{L}$) •CRP \uparrow
- Tachycardia in pregnant woman ($\geq 100/\text{min}$)
- Fetal tachycardia ($\geq 160/\text{min}$)
- Uterine sensitivity
- Smelly amniotic acid

Newton ER. Chorioamnionitis and Intraamniotic Infection. Clin Obstet Gynecol 1993;38(4):795-808.

Intraamniotic infection

- Possible serious fetal, neonatal and maternal complications
- Treatment: antibiotics and fast delivery completion
- Polimicrobial infection
- Ampicilin 2 g iv. Every two hours and gentamycin 1,5 mg/kg every 8 hours** (only to women with normal kidney function)
- Equally effective is a single dose gentamycine in a dose of **5,1 mg/kg**
- Antibiotics are necessary also one day after delivery
- It is not necessary to follow with oral antibiotic therapy

mother - to - child transmission

BHSB

β hemolytic streptococcus group B (BHSB)

•*Streptococcus agalactiae*

•Gramm positive diplococcus

•The most common cause of neonatal sepsis

Hager WD, Schochat A, Gibbs R et al. Prevention of perinatal group B streptococcal infection: current controversies. J Perinat Med 2006;9(6):141-5.

β hemolytic streptococcus group B (BHSB)

- Asymptomatic colonization of gastrointestinal and genital system into 40% of pregnant women
- Mother-to-child transmission occurs during vaginal delivery or after the rupture of membranes (RVP) in about 50% of babies of colonized women
- After transmission, 1-2% of newborns will develop BHSB sepsis
- Elective (before RVP) lowers the risk of sepsis
- Still, cesaren section is not indicated, because colonization is fairly common and there is an effective, non invasive and much cheaper option, by screening and intrapartal antibiotic prophylaxis.

Hansen S, Van Wijk FH, Mol BW et al. Risk indicators for neonatal early-onset GBS-related disease. A case-control study. J Perinat Med 1997;25:469-75.

β hemolytic streptococcus group B (BHSB)

•Croatian Society of Perinatal Medicine – has recently published National Guidelines for antibiotic prophylaxis of early neonatal sepsis caused by beta hemolytic streptococcus group B

Hrvatsko društvo za perinatalnu medicinu (Hrvatsko Društvo Žena, Nacionalno preporuke za antibiotičku profilaksu rane neonatalne sepsis uzročnicom beta hemolitičkim streptokokom grupe B^o). Gynocol Perinatol 2016;16:119-26.

•It is advised to screen all pregnant women between 35. and 37. week of gestational age, in any case, not longer than weeks before term.

•Smears are obtained from the lower third of vagina without speculum, and then from anal sphincter. It must be noted that the smear is for BHSB.

β hemolytic streptococcus group B (BHSB)

In case of BHSB isolation, intrapartally is administered:

- penicillin G 5 x 10⁶ ij. iv. + 2,5 x 10⁶ ij. iv. every 4 h till delivery or
- ampicilin 2g iv. + 1g iv. Every 4 h till delivery

In case of penicillin allergy, with a small risk of anaphylaxis, the suggested treatment is:

- cephasoline 2 g iv. + 1 g iv. Every 8 hours till delivery

In case of high anaphylaxis risk:

- klindamycine 900 mg iv. Every 8 hours till delivery or
- eritromycine 500 mg iv. + 600 mg every 6 hours till delivery
- vankomycine 1g iv. Every 12 hours till delivery in case of klindamycine or eritromycine resistance (ventilator ili klindamycin ili eritromycin)

Th. Based on screening or risk factors: SIAL, preterm birth, BHSB in urine, cervix

Chlamydia trachomatis

Chlamydia trachomatis

- The most common bacterial cause of STD and PID
 - Mostly asymptomatic (> 80%) silent infection (SILENT EPIDEMICS)
 - Diagnostics ?!!!!
 - **Serious complications:** infertility, ectopic pregnancy, newborn diseases (inklusion conjunctivitis, nasopharyngitis, pneumonia)
 - C. trachomatis 1% of PID cases, found in fallopian tubes or endometrium of 50 of PID cases
 - ≤40% of women with untreated (undiagnosed) Chlamydia infection develop PID, 20 % become infertile and 18% develop chronic pelvic pain
- Source: Textbook of public epidemiology 4th ed. Am J Obstet Gynecol 1991;163:1012-3.
 Nelson KE, Quinn MC, Johnson C, Koutsky T, Johnson VA, Stamm WE. Effect of treatment regimen for bacterial gonorrhoea on serological detection of Chlamydia trachomatis. J Gen Intern Med 1992;7:10-14.
- Chlamydia t. - CIN; serotypes G,F,K
 - Chlamydia t. - ca.cervikalis; serotypes G,I,D; ca ovarija

Chlamydia trachomatis

Newborns

- Nasopharyngitis
- Pneumonia
- Conjunctivitis
- Otitis media

Men

- Epididymitis
- Urethritis
- Infertility
- Reactive arthritis
- Conjunctivitis
- Proctitis
- Pharyngitis
- Sy Reiter
- Trachoma
- LGV

Women

- Mucopurulent cervicitis
- Bartholinitis/Salpingitis
- Endometritis
- Perihepatitis, Sy Fitz - Hugh-Curtis
- Urethritis
- Infertility
- Ectopic pregnancy
- Reactive arthritis (uroarthritis, Reiter disease)
- RVP, ab., preterm birth
- Conjunctivitis
- Proctitis
- Pharyngitis
- Sy Reiter
- Trachoma
- LGV

Serotypes D-K

Serotypes A-C

Serotypes L₁₋₃

Symptoms 1-3 weeks after transmission

Chlamydia trachomatis

Pregnancy- predisposing factor for infection because of physiologic immunosuppression and cervical ectopy

Older studies often linked Chlamydia Infection to:

- Preterm birth
- Low birth weight
- Premature rupture of membranes

It was in fact a bad study method, because the patients often had vaginosis, i.e. infection with *Mycoplasma hominis* and *Ureaplasma urealyticum*. Later studies, performed on more than 10,000 pregnant women, showed significant correlation between vaginosis and preterm birth and low birth weight.

WILLER RJ, ROBERT AP, COCHRAN DA J. et al. REPRODUCTIVE HEALTH, VAGINOSIS AND PRETERM DELIVERY IN A POPULATION-BASED STUDY. The vaginal infections and Preterm Birth Study Group. N Engl J Med 1992;327:1355-1361.

EBM: Chlamydia infection has minimal effect on perinatal outcome, but it is clear that it can lead to postpartal endometritis and salpingitis, in as high as 20% of women.

FLUMBERG LA, LARA R. INCIDENCE OF POSTPARTUM ENDOMETRITIS AND SALPINGITIS. JAMA 1979;241:110-114.

Chlamydia trachomatis

60-70% - risk of newborn infection during vaginal delivery from an infected mother:

- Asymptomatic newborn
- Colonization of nasopharynx
- Positive serology

In non treated pregnant women, 20 - 50% of newborns will develop:

- conjunctivitis 5 - 12 day after delivery
- 10 - 20% afebrile pneumonia 1-3 months after delivery
- 30% of all pneumonias in the first 6 months is caused by Chlamydia

VOGELS HW, VAN VOORST VADER PG, SCHOUER JF. Chlamydia trachomatis infection in a high-risk population: Correlations of postpartum breast carriage and cell culture for diagnosis and infection. J Clin Microbiol 1992;35:1192-7.

Chlamydia trachomatis



Screening

Recommendations and Reports

- Before any intrauterine procedure
- Once a year for all sexually active women ≤ 25
- Once a year or more often for all sexually active women > 25 with risk factors (irregular use of barrier contraceptive methods, new seks partner in the last 3 months)
- Control screening 3-4 months after the treatment
- Screening of pregnant women in the first trimestre, and in those at high risk, repeat the test in third trimestre

Chlamydia trachomatis (KT)

The Centers for Disease Control recommends C. trachomatis diagnostic testing, if possible, at the first prenatal visit for all pregnant women, and again in the third trimester for those at high risk

The American College of Obstetricians and Gynecologists recommends targeted screening of high risk populations

Cunningham FG et al. Williams Obstetrics

mother - to - child transmission

HPV

Human Papillomavirus (HPV)



Epidemiology

- Genital infection caused by Human Papillomavirus
- The most common sexually transmitted disease
- 80% of women by the age of 50 get in contact with HPV

Styers EA, McChesney DC, Nicola S, Ederlin L, Waldman DR. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *American Journal of Epidemiology*. 2000; 151(12):1196-1197.

- In Croatia, 60% of sexually active women have HPV in cervical smear

Avoglin G, Ono M, Maggioni P, et al. Comparison of the different polymerase chain reaction (PCR) methods for detection of human papillomavirus (HPV) in cervical cell specimens. *Virus Research*. 2002; 81:15-24.



The incidence is highest at the age of 20 to 24 years

Human papillomavirus

HPV



Biology

- > DNA virus
- > Family Papovaviridae
- > Gender Papillomavirus
 - papova* = papilloma + polioma + vacuola (pathologic changes that these viruses cause)
 - papiloma* = *papilla* (lat. wart) + *oma* (grč. tumor)
- > Viral particle is icosahedral in structure (T=7), size about 55-60 nm
- > Protein capsid is made of 72 capsomeres.
- > Virus is resistant to ether, 70% ethanol, acid and heat, because the capsid contains no lipids.



Ljudski papilomavirus (HPV)

- > Nowadays, more than 150 different types of the virus are known
- > More than 40 affect the urogenital tract

Human papillomavirus (HPV)

• Low risk
6, 11, 30, 42, 43, 44

• Medium risk:
31, 33, 35, 39, 51, 52,
58, 61

• High risk:
16, 18, 31, 33, 35, 45, 52, 56

HPV types

Human papillomavirus (HPV)

CERVICAL CANCER



Human papillomavirus (HPV)

Division based on the site of changes

- Skin
 - *Verruca vulgaris*
 - Plantar v.
 - Plantar (juvenile)
 - *Epidermodysplasia verruciformis* - develops in childhood, and 1/3 of the goes through malignant alteration in 30s or 40s
- Anogenital
 - *Condylomata acuminata*
 - Buschke-Lowenstein tumor (giant condyloma)
 - Premalign-malign changes
- Other
 - Recurrent respiratory papillomatosis (5. months -10. years, obstruction of upper respiratory tract - areorespiratory exposure in delivery)
 - Heck's disease: focal epithelial hyperplasia of oral mucose

TRANSMISSION

CONTACT:

- Sexual (penis/cervix, scrotum/vulva, penis/anus...)
 - Digital/anal, digital/vaginal
 - Fetus coming out through the infected birth cannal (recurrent respiratory papillomatosis)
 - By objects (towels, sponges, surfaces)
-
- Virus enters through damaged parts of skin or mucose, for example, places of traumas (micro) formed during sexual intercourse.
 - Perianal lesions may be found in both genders, but are more common in homosexual men.
 - **The probability of infection through single intercourse is around 26%**

Human papillomavirus (HPV)

•Condylomas in child-bearing women increase the risk of recurrent respiratory papillomatosis (RPR) for 231 time. It is mostly diagnosed in children between 6 months and 10 years.

Silverberg MI, Thomson P, Lindberg H, Grant LA, Stoh XV. Condyloma in pregnancy is strongly predictive of perinatal recurrent respiratory papillomatosis. *Gynecol Oncol*. 2003;101:645-52.

•RPR is manifested by signs of respiratory obstruction of upper respiratory tract including hoarseness, stridorous breathing and respiratory distress.

•Most common types are HPV 6 | 11, rarely 16

Human papillomavirus (HPV)

- Till 2003. in proven HPV infection or present condylomas
 - Caesarean section was an absolute indication
 - The prevention of mother to child transmission and development of RPR

- But, since 2003. and. 2004.
- Silverberg and colleagues and Smith and colleagues
- Caesarean section does not reduce the chance of transmission
- HPV as an indication for Caesarean section was gone
- Caesarean section is indicated only if condylomas form a mechanical barrier on the babies way out of the birth canal

Silverberg MI, Thomson P, Lindberg H, Grant LA, Stoh XV. Condyloma in pregnancy is strongly predictive of perinatal recurrent respiratory papillomatosis. *Gynecol Oncol*. 2003;101:645-52.

Smith DA, Scholtz JH, Yarbrough J, Jernstedt A, Wang D, Hagan YL. The risk of human papillomavirus persistence and type in newborns and parent, concordance and modes of transmission. *Sex Transm Dis*. 2003;101:314-21.

Sectio caesarea
To operate or not to operate?

Human papillomavirus (HPV)

•Lately, the way of delivery is becoming controversial due to RPR prevention

•Meta-analysis of current seven studies performed on 2 111 pregnant women shows that vaginal delivery poses greater risk for HPV transmission in comparison to cesarean section (18,0% : 8,0%; RR: 1,8; 95% CI: 1,3-2,4)

•One of main flaws to these studies is the question whether it is about the neonatal HPV infection or contamination with infective maternal cells

•In expectation of better designed studies, currently there are no guidelines that indicate cesarean section in case of condylomas or HPV in cervical smear.

Medford LR, Ether AD, Hildert JB et al. Vertical transmission of the human papillomavirus: a systematic quantitative review. *Cad Stand Publica*. 2003;11:1906-15.

Human papillomavirus (HPV)
HPV genital infection in pregnant woman


Sectio caesarea
... to operate or not to operate

Because of prevention of recurrent respiratory papillomatosis (RRP)

YES $\xrightarrow{2003.}$ NO $\xrightarrow{2005.}$??? \rightarrow NO

DIAGNOSTICS

Molecular diagnostics



- In situ hybridization (ISH)
- Southern transfer hybridization (STH)
- Hybrid Capture (HC)
- Dot blot (DB)
- Filter hybridization (FH)
- Polymerase chain reaction (PCR)

***Digene HC* is the only FDA approved method for cervical HPV detection**
 (United States Food and Drug Administration – march 2000.)

Human papillomavirus (HPV)
Overview of removal and recurrence of condylomas related to the treatment choice

Treatment	Condylomas removed	recurrence (%)	
		3 months	≥ 6 mths
Cryotherapy	63-88	63-92	0-39
Electrocauterisation	93-94	78-91	24
Interferon intralesion	19-62	36-62	0-33
Interferon systemic	7-51	18-21	0-23
Interferon locally	6-90	33	6
Laser	27-89	39-86	< 7-45
Podophylline	32-79	22-73	11-65
Podophilotoxine	42-88	34-77	10-91
Imiquimod	50-62	50-62	13-19
Surgical excision	89-93	36	0-29
Trikloroacetic acid	50-81	70	36
5-fluorouracil epinephrine	61	50 - 60	

Legend: Lesmer KR, Wiley DJ. Recurrent external genital warts: a literature review. Papillomavirus Rep 1997;8:69-74.

mother - to - child transmission

HCV

Hepatitis C virus (HCV)

- There are around 1-5% HCV seropositive pregnant women
- Transmission may occur *in utero* or *Intrapartally*
- MTCT risk is estimated at 5% (1) or 6,2% (2), but HCV viraemia or HIV coinfection significantly raises the risk (3)
- **Cesarean section is not advised as it does not have any protective effect in comparison to vaginal delivery**

1. Nishimura AK, Nakamura H. Transmission of hepatitis C virus infection to the pediatric population. *World J Gastroenterol* 2004;10:115-18.
 2. Estroff SM, Hagan H, Hagan H, et al. Risk of mother-to-child transmission of hepatitis C virus infection. *J Infect Dis* 2001;183:1175-8.
 3. Martin D, Soper M. The impact of maternal viraemia on transmission of hepatitis C virus to the neonate. *Exp Parasitol* 2004;147:49-54.

Nishimura AK, Nakamura H, Nakamura H. Cesarean section versus vaginal delivery for preventing mother-to-infant hepatitis C virus transmission. *Cochrane Database Syst Rev* 2006;4:CD005524.

mother - to - child transmission

HBV

Hepatitis B virus (HBV)

- Transmission from HB+ mother to child is 20-30% (vag. delivery)
- Lee and co. 1988. *Lancet*, child-bearing women that are chronic HBsAg carriers with high serum levels of HBV-DNA
 - Elective cesarean section is advised (ECR) and hepatitis B immunisation
- In this survey, 447 children of hepatitis B positive mothers were examined
 - Higher rates of transmission occurred in vaginal delivery (98/385, 24.9%), compared to cesarean section (6 / 62, manje od 10%)
 - Serum HBV-DNA, in delivery was found in 13 of 67 babies delivered vaginally and in 0 of 30 babies delivered by cesarean section

Lee SD, Lo KL, Tai YF et al. Role of cesarean section in prevention of mother-infant transmission of hepatitis B virus. *Lancet* 1988;283:4

Hepatitis B virus (HBV)

- Still,
- There are no guidelines that suggest ECR
 - Due to effective active and passive immunoprophylaxis vaccine and immunoglobulines that are given to the newborn after delivery

Stama D, Spearin P. The impact of cesarean delivery on transmission of infectious agents to the neonate. *Chn Pediatr* 2008;35:497-50

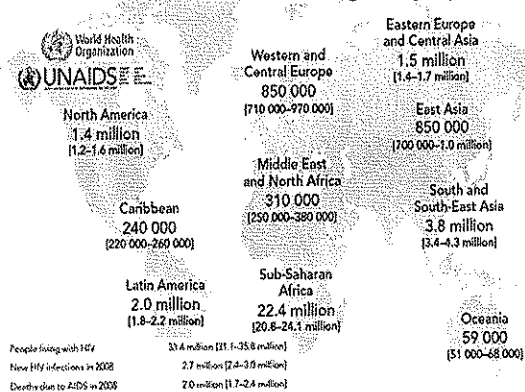
mother - to - child transmission

HIV-1

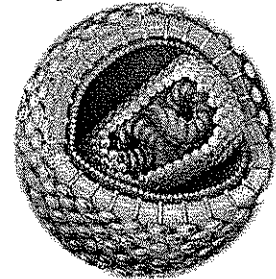
Human Immunodeficiency Virus (HIV-1)

- Human Immunodeficiency Virus - HIV, HIV-1
- Retrovirus responsible for AIDS pandemia

Virus humane imunodeficijencije (HIV-1)



Human Immunodeficiency Virus (HIV-1)



First child with AIDS was diagnosed in 1982.

Human Immunodeficiency Virus (HIV-1)

EPIDEMIOLOGY

• In the world, more than 2000 babies get infected by mother to child transmission everyday, 750000/god.

Newell MG. Current issues in the prevention of mother-to-child transmission of HIV-1 infection. Trans R Soc Trop Med Hyg 2006;100:1-5

Read JB, Newell ML. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. Cochrane Database Syst Rev 2005;4:CD005419.

• MTCT - the most common way of children infection (1) and becomes more and more common (2)

1. Connor EM, Sperling RS, Gelber K, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine lamivudine. N Engl J Med 1999;341:1173-80.

2. Jamison DJ, Clark J, Kozlita AP et al. Recommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States. Am J Obstet Gynecol 2007;197(Suppl 3):S26-32.

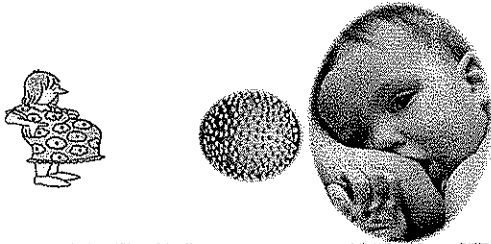
Human Immunodeficiency Virus (HIV-1) Predisposing factors of transmission (MTCT)

- **Mother's amount of virus** Prematurity
 - 6,6% <33 weeks. vs. 1,1% for term births
- **Prolonged period since membrane rupture**
- **Intrapartal interventions**
 - Fetal scalp electrode, drawing fetal blood



Human Immunodeficiency Virus (HIV-1)

In case the mother is HIV positive, chances for transmission are 15 - 30% or 30 - 40% in case of breast feeding



UNAIDS. Prevention of mother-to-child transmission of HIV. Available at: http://www.unaids.org/en/Data/296965_11173_11173 Accessed April 10, 2005.

Estimated Risk of Transmission of HIV Based on Exposure

Exposure	Risk (%)	Per 1000 Encounters
Transfusion of HIV+ blood	90	900
Needle sharing	0.6	6
Receptive anal sex	0.5	5
Needle stick, occupational	0.3	3
Receptive vaginal sex	0.1	1
Insertive anal sex	0.07	0.7
Insertive vaginal sex	0.05	0.5
Receptive oral sex	0.01	0.1

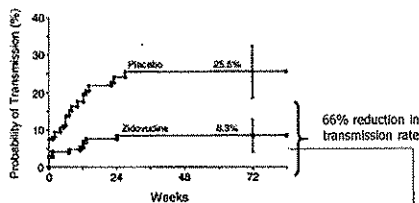
For mother-to-child transmission, the risk is 13-25%, excluding breast-feeding. The risk of breast-feeding 14-29% based on time of maternal infection, and length of breast-feeding: 0.7% per month up to age 5 months, 0.6% 6-11 months and 0.3% per month thereafter (therefore, at time of greatest risk, 7/1000 per month, or 2/1000 per day breast-feeding, or approximately 0.5-0.3/1000 each episode of feeding).^{1,3-29}

Adapted from MMWR 2005;54(No. RR-2):1-20.²⁰

• Ukoliko je trudnica HIV-1 pozitivna, vjerojatnost da će doći do MTCT-a je 15 - 30% tj. 30 - 40% ako dulje doji

Human Immunodeficiency Virus (HIV-1)

antiretrovira prophylaxis



Connor EM et al, NEJM 1994, 331: 1173-1180

Virus humane imunodeficijencije (HIV-1)

Measures of MTCT transmission prevention include:

- antiretroviral prophylaxis (during prenatal, intrapartal and neonatal period)

- Elective cesarean section and I

- No breast feeding



Newell ML. Current issues in the prevention of mother-to-child transmission of HIV-1 infection. Trans R Soc Trop Med Hyg 2006;100:1-5.

International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. N Engl J Med 1999;340:977-87.

• These measures result in MTCT rates of less than 2% cases

European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis 2005;40:455-65.

Virus humane imunodeficijencije (HIV-1)

Paths of MTCT transmission – most common is intrapartal (in 2/3 cases):

- maternal transfusion to fetus in delivery
- ascendent infection after membrane ruptures
- Direct contact with secretions or blood from, birth canals

- Meta-analysis of 15 prospective studies in USA and Europe
- Prophylactic elective cesarean section leads to 50% less transmission (vag. 19%; s.c. 10%)

•Intrapartal risk for HIV transmission is proportional to the amount of virus in maternal blood so
 •ACOG recommends to avoid cesarean delivery in case the amount of virus in maternal blood is less than 1000 copies / mL, because the risk of transmission is small, and risk of surgical complications, especially in these women, is significantly higher

Sharma D, Spearman P. The impact of cesarean delivery on transmission of infectious agents to the neonate. *Chin Perinatol* 2009;35:407-20.



IMPORTANCE

- Important public health problem
- Sexual and perinatal transmission
- HSV-2 infection increases the risk of HIV-1 infection for 2 times¹
- Fetal anomalies, abortion, neonatal and conatal infection

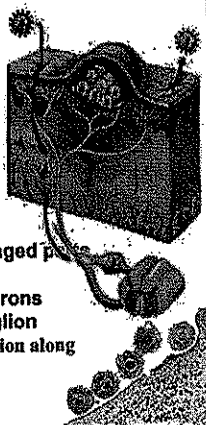
- Neonatal transmission (in delivery)
- 1 / 3200 liveborn²
- Can lead to severe complications:
- Bleeding, psychomotor retardation, spasticity, disability and death²

1. World A, Link K. *J Infect Dis* 2002;185:45-52
 2. Brown Z et al. *JAMA* 2003;289:203-209

RESISTANCE

- Resistant to temperatures up to 256°C during 20,5h
- Inactivated at pH<4
- Ultraviolet and gama rays inactivate it fast
- Sensitive to: ether, alcohol, disinfectants and proteolytic enzymes
- Prevention: soap hand washing and wearing gloves

PATOPHYSIOLOGY



- Virus enters through mucose or damaged part of skin
- Infection and replication in cells - neurons
- Latent infection in dorsal spinal ganglion
- Stress – recurrentna – retrogradeinfection along the sensory nerves

EPIDEMIOLOGY

Most seropositive patients are found among prostitutes (in USA 75%) and male homosexuals (83%)

Nahmias AJ, Lee FK, Bachman-Hamilton S. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis* 1990; 69:19.

Newly infected yearly 5,1/100

National Health and Nutrition Examination Survey (NHANES study)

Men: 18%

Women: 26%

Total: 22% older than 12 years

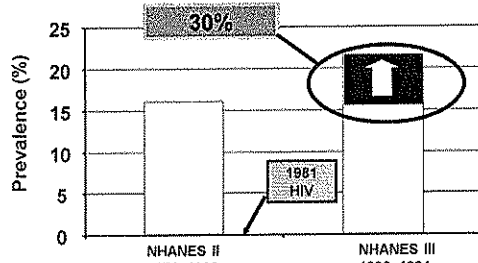
90% does not know about the infection

1:4

Fleming DT, et al. *N Engl J Med*. 1997;337:1105-1111.

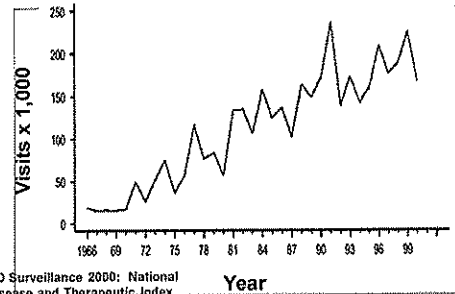
Herpes simplex virus (HSV)

Serological Prevalence of Genital Herpes



Fleming DT et al. N Engl J Med. 1997;337:1105-1111.

Genital Herpes: Initial Visits to Physician's Offices, 1966-2000



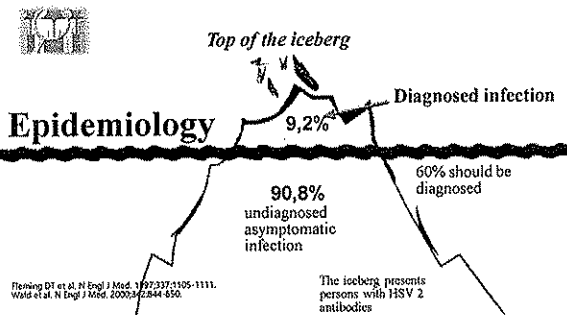
STD Surveillance 2000: National Disease and Therapeutic Index

Viral transmission, in contact with:

- Fluid inside of the vesicles
- Excretions (saliva, lesions)
- Ulcerose lesions
- Vaginal discharge
- Objects (glasses, plates...)

More common in women for 5%

Most infections are not manifested (subclinical), and clinically manifested ones are most often not reported thus the real incidence is not known



Fleming DT et al. N Engl J Med. 1997;337:1105-1111.
Wald et al. N Engl J Med. 2000;342:844-850.

The iceberg presents persons with HSV 2 antibodies

Herpes simplex virus (HSV)

HERPES GENITALIS - SIGNS AND SYMPTOMS

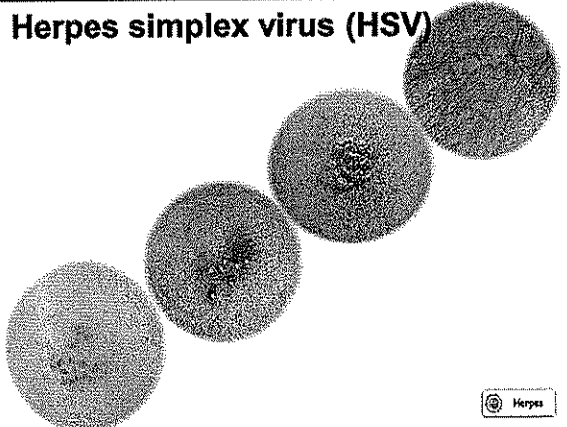
First episode is usually more severe and longer than recurrent infection
Lesions in women are usually on vulva, cervix or perianal

- | | |
|---|--|
| <ul style="list-style-type: none"> • Classic <ul style="list-style-type: none"> - Painful vesicles - pustular lesions - Genital ulcer (painful) - crust - heals without scar - Perineal and anal ulcerations • Atypical, usually not recognised <ul style="list-style-type: none"> - Vulvar or perineal fissures and irritation - Cervicitis, proctitis - Dysuria - Urethral, vaginal or rectal discharge - Painful ulcerations | <ul style="list-style-type: none"> • Primary and recurrent infections are usually followed by: <ul style="list-style-type: none"> - high temperature - malaise - headache - Ingvinal lymphadenopathy - Sometimes neck pain and stiffness • Dysuria 63% • Systemic symptoms 67% • Ingvinal lymphadenopathy 80% • Local: pain, pruritus 98% |
|---|--|

• Asymptomatic (only 9% HSV-2 seropositive patients confirm the infection in medical history)

Fleming DT et al. N Engl J Med. 1997; 337:1105-1111.

Herpes simplex virus (HSV)



© Herpes

Herpes simplex virus (HSV)

Clinical classification of HSV-2 infection (genital herpes)

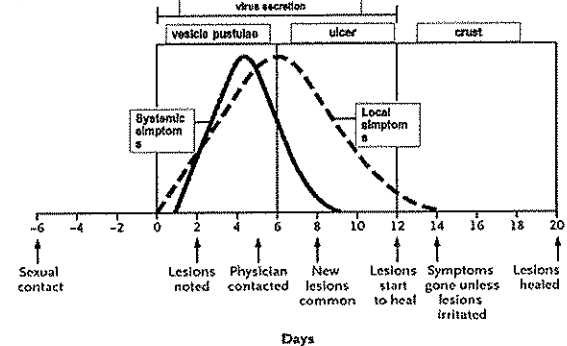
- First episode, primary infection, (seronegative for HSV-1 and HSV-2)
- First episode, not primary infection (previous HSV-1 infection, positive antibodies)
- Recurrent infection (symptomatic, asymptomatic) (Undiagnosed, asymptomatic infection – most common)

Latent infection - asymptomatic

Baker DA and the ACOG Committee on Practice Bulletins – Obstetrics. Int J Gynecol Obstet.

Herpes simplex virus (HSV)

Course of infection: first episode



Corey L, Adams HO, Brown ZA, Holmes RK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med. 1983;99: 900-72

Herpes simplex virus (HSV)

How women usually interpret the

symptoms

- Yeast infection
- Vaginitis
- Uroinfection
- Menstrual problems
- Hemorrhoids
- Allergy to:
 - condom
 - tights
 - Spermicide
 - Sperm
 - Partner
- Irritation from:
 - Bike seat
 - depilation
 - swimming
 - Sex

Ashley RL, Wald A. Clin Microbiol Rev. 1999;12:1-8.

Herpes simplex virus (HSV)

How men usually interpret the

symptoms:

- Folliculitis
- 'Normal' itchiness
- Hemorrhoids
- Condom allergy
- Irritation from:
 - Tight pants
 - Sexual intercourse
 - Bike seat
- Insect bite
- Bite

Ashley RL, Wald A. Clin Microbiol Rev. 1999;12:1-8.

Herpes simplex virus (HSV)

HSV-1 causes:

- labial herpes
- gingivostomatitis
- chertoconjunctivitis, but more often it is found as a cause of
- genital ulcer – growing incidence – in over 80% of women

ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. No. 82 June 2007. Management of herpes in pregnancy. Obstet Gynecol. 2007;109:1469-78.

HSV-2 is mostly related to genital ulcers, which are sexually transmitted, and it is often the cause of neonatal herpes, in 1/4 - 2/3 of children.

Incubation is 2-12 days

Brown ZA, Wald A, Morrow EA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003;289:203-9.

Herpes simplex virus (HSV)

•> 2% of women have seroconversion during pregnancy

•Development of neonatal herpes in 1/3200 deliveries

•1500 affected newborns per year in USA

Herpes simplex virus (HSV)

Neonatal herpes

Neonatal herpes manifests in three forms:

- Disease of skin, eyes and/or mouth - SEM disease - 45%
- encephalitis - 30%
- Systemic (disseminated) disease - 25%



Neonatal mortality is (even today- antiviral treatment):

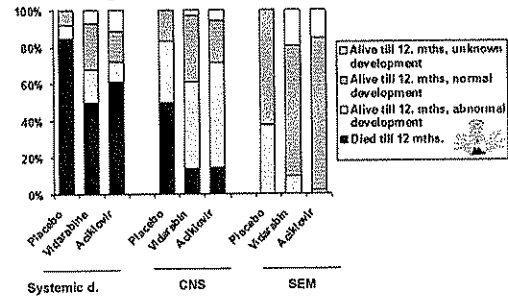
Systemic disease - 29%

Encephalitis 4% - *only 31% of affected newborns have normal neurological development*

SEM disease - almost non-existent

Herpes simplex virus (HSV)

Morbidity and mortality in 229 newborns with neonatal herpes infection (1974-1998.)



Kimberlin D. Rev Med Virol 2001;11:167-168.

Herpes simplex virus (HSV)

•HSV transmission:

- In 85% vcases Intrapartally
- Rarely Intrauterine or
- postnatal

•Risk of HSV transmission to the fetus:

- 50% If pregnant woman gets primary genital herpes during third trimestre
- 3% or less In case of recurrent Infection kod rekurentne infekcije iznosi

•More than 75% newborns born with HSV Infection were delivered by completely asymptomatic women

Herpes simplex virus (HSV)

•It is a practice today to perform an elective cesarean section

- To prevent mother-to-child transmission
- In every pregnant woman with genital lesions suspicious to herpes
- With prodromal symptoms (vulvar pain or burning) with genital herpes in medical history

•Nevertheless, not even then, we cannot exclude the possibility of transmission (1,2%), although significantly less than in vaginal delivery (7,7%)



Herpes simplex virus (HSV)



•Cesarean section – electively is best

•In case of RVP-a as soon as possible

Herpes simplex virus (HSV)

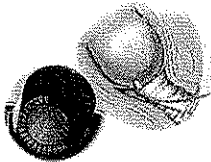
Risk of transmission relative to the duration of RVP

Delivery	N
Vaginal delivery	9/18 (50%)
Cesarean section RVP ≥ 6 h	4/4 (100%)
Intact membranes or RVP ≤ 4 h	0/4 (0%)

Nohmias A. Am J Obstet Gynecol 1971;110:926-934

Herpes simplex virus (HSV)

- SC is advised today
- Even regardless of time/duration of RVP
- By placing the scalp electrode on fetal head, the risk of transmission increases 6 times



Herpes simpleks virus (HSV)

- The only prospective study that examined the success of cesarean section in prevention of neonatal herpes
- Brown and co. 2004. on more than 58 000 pregnant women
- The use of cesarean section in prevention of neonatal herpes was proven
- Positive HSV cultures in the moment of delivery were found in 202 women (202 /58000)
- Neonatal herpes developed in 5% (10/202) of newborns
- Only one child, of those delivered by cesarean section, developed the disease, which is 1,2% (1/65), relative to 9 of those delivered vaginally, or 7,7% (9/117) (P = 0,047)

Herpes simplex virus (HSV) Pregnant women that have arecurrent genital herpes in history and no visible lesions in delivery

- No point in performing SC
- Risk of transmission is 2/10 000
- This practice would increase perinatal maternal morbidity and mortality
- Every prevented neonatal herpes by SC in the USA would cost 2,5 million dollars and around 1580 cesarean section should be done for one prevented neonatal herpes
- When, SC is performed in women with primary HSV infection, 9 cesarean sections more would be performed to prevent one neonatal herpes
- To all pregnant women with recurrent genital herpes in medical history
 - Antiviral prophylaxays from 37th week
 - This decreases the recurrence risk for 75% and
 - Percentage of cesarean sections for 40%
 - although aciklovir may cause neutropenia

Herpes simpleks virus (HSV)

CDC guidelines on antiviral therapy in pregnancy



Indication	Aciclovir	Valaciclovir
Primary infection or first episode	400 mg po, 3 x 1 / 7-10* days	1g po, 2/day / 7-10* days
Symptomatic recurrent episode	400 mg po, 3 x 1 / 5 days or 800 mg 2 x 1 / 5 days	500 mg po, 2 x 1 / 5 days or 1g po 1x / 5 days
Suppressive therapy	400 mg po, 3 x 1 from 37th week till delivery	500 mg po, 2 x 1 from 37th week to delivery
Herpes systemic disease	5-10 mg/kg, iv, 3x/24-7 days followed by 400 mg po, 3 x 1 / 10 days	

Herpes simplex virus (HSV)

- There is no indication for cesarean section in women with lesions on other than genital regions
- Cover with clothes
- Around 10% of women that are HPV-2 seronegative have seks partners which are positive:
 - Use of condoms is advised or
 - Sexual abstinence

Herpes simplex virus (HSV)

Predisposing factors of HSV transmission

- Active genital herpes lesions
- Transplacental antibodies
- Fetal scalp electrode
- Duration of RVP
- Way of delivery (vaginal)



Herpes simplex virus (HSV) PREVENTION

- Hand washing
- Using gloves
- Abstinence from seks during infection
- Condom is advised but is not an absolute protection
- Cesarean section in women with active genital herpes
- Vaccine, still in experimental phase, would prevent infection, latency and decrease recurrence
- Suppressive antiviral therapy (Valaciclovir decreases the transmission risk 75%) – transmission decrease

Corey L et al. Abstract LB-3, ICAAC 2002, September 27-30, 2002.