



Herpesvirus infections in pregnancy

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Case 1

- ▶ Baby develops fever, thrombopenia, hepatitis and then sepsis-like syndrome from 6th day p.p.
- ▶ History: delivery by cesarean section in 38th week of pregnancy (mother developed flu-like illness with oesophagitis)
- ▶ "TORCH" serology "normal"

- ▶ After 4 days without specific findings and despite empiric antibiotic treatment situation deteriorates and baby finally dies
- ▶ Histology shows inclusion bodies in hepatocytes
- ▶ PCR from liver and blood: HSV-1-DNA highly positive
- ▶ HSV-IgG negative

What had happened?

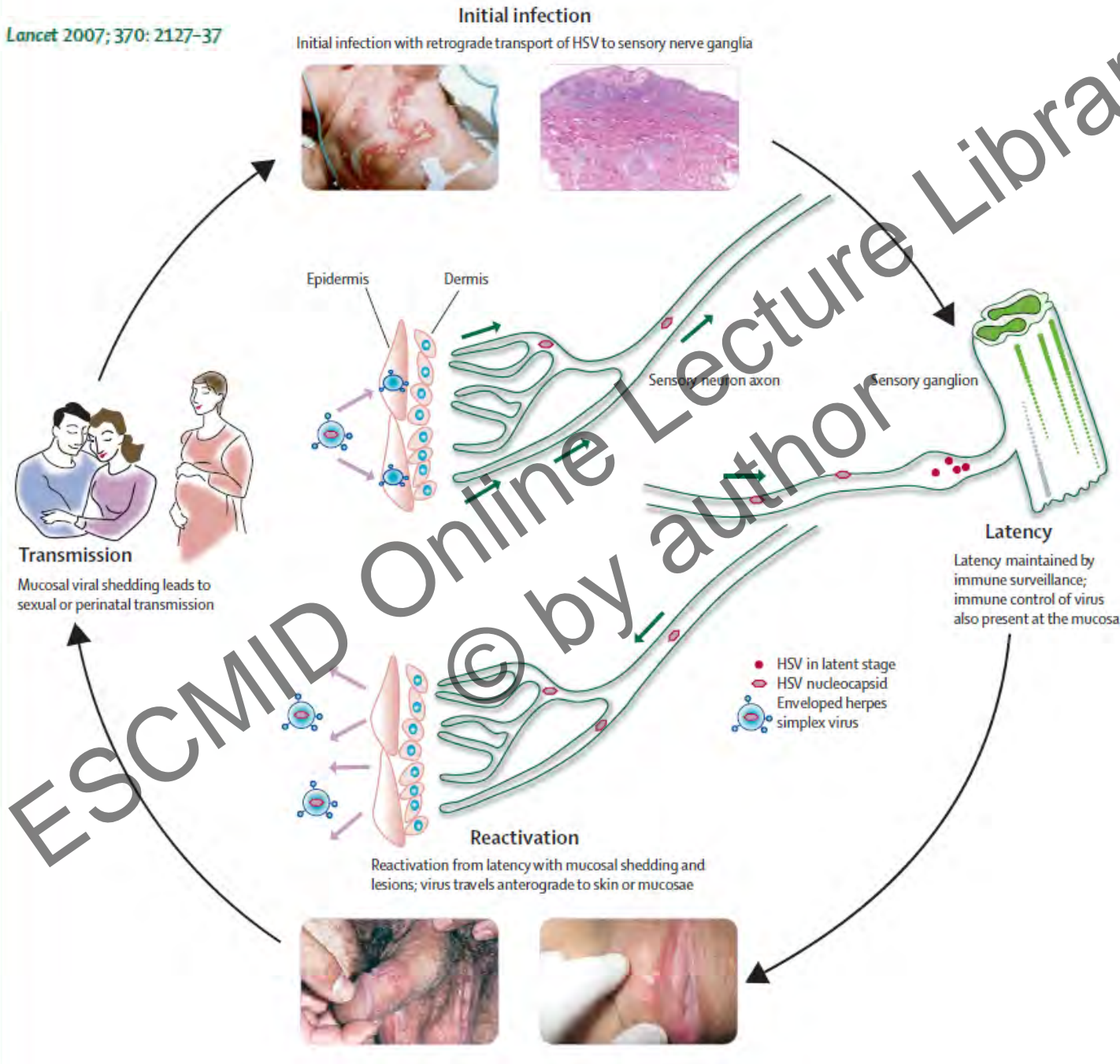
- ▶ Primary infection with HSV-1 during late pregnancy, complicated by oesophagitis
 - TORCH Serology of patient: negative HSV-antibodies
- ▶ Infection possibly acquired postnatally (saliva of mother highly infective) or via blood stream with viraemia

Herpes simplex virus 1+2

Risk in pregnancy and at birth

- ▶ HSV-1 primary infection has higher risk of complications during pregnancy
- ▶ Intrauterine infection possible (very rare, only with primary infection in early pregnancy)
- ▶ Perinatal infection (very dangerous for the baby)
 - Herpes genitalis during pregnancy
- ▶ Postnatal infection

Lancet 2007; 370: 2127-37



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Genital Herpes

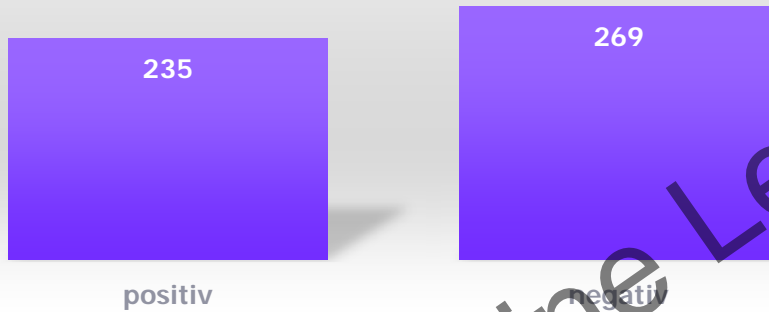
- ▶ ~5% of women of childbearing age report history of genital herpes
- ▶ HSV-2 originally called herpes genitalis (HSV-1 herpes labialis)
- ▶ Changing epidemiology over the last 20 years



Changing Epidemiology of Genital Herpes

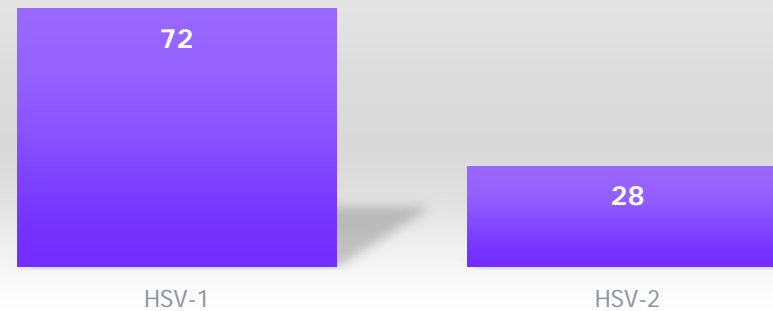
- ▶ Retrospective analysis of genital herpes isolates in USA/Vaccine studies
 - Proportion of HSV-1 in newly diagnosed genital infection increased from 31% in 1993 to 78% in 2001
 - Vaccine studies: More than twice primary HSV-1 infections compared to HSV-2 infections
 - Seroprevalence of HSV-2 decreasing

Detection of HSV (PCR/cell culture) in women with genital/perianal lesions (n)



Freiburg University
2009-2016

Frequencies of HSV-1 and HSV-2 in genital/perianal lesions (%)



Reasons for epidemiological change

- ▶ Decreasing seroprevalence for HSV-1 in adolescents
- ▶ Other routes of primary infection: HSV-1 becomes STD
- ▶ But: Seroprevalence may be underestimated in recent studies:

Sex Transm Infect. 2016 Jun;92(4):257-60. doi: 10.1136/sextrans-2015-052213. Epub 2016 Jan 11.

False-negative type-specific glycoprotein G antibody responses in STI clinic patients with recurrent HSV-1 or HSV-2 DNA positive genital herpes, The Netherlands.

van Rooijen MS¹, Roest W², Hansen G¹, Kwa D³, de Vries HJ⁴.

Clinical presentation of genital herpes

- ▶ Dependent on infection status
 - Primary
 - ▶ First infection with Herpes simplex 1 or 2 without preexisting antibodies
 - Non-primary first episode
 - ▶ First infection with HSV 2 in HSV 1 seropositive women
 - Recurrent
 - Asymptomatic viral shedding

Herpes genitalis primary infection

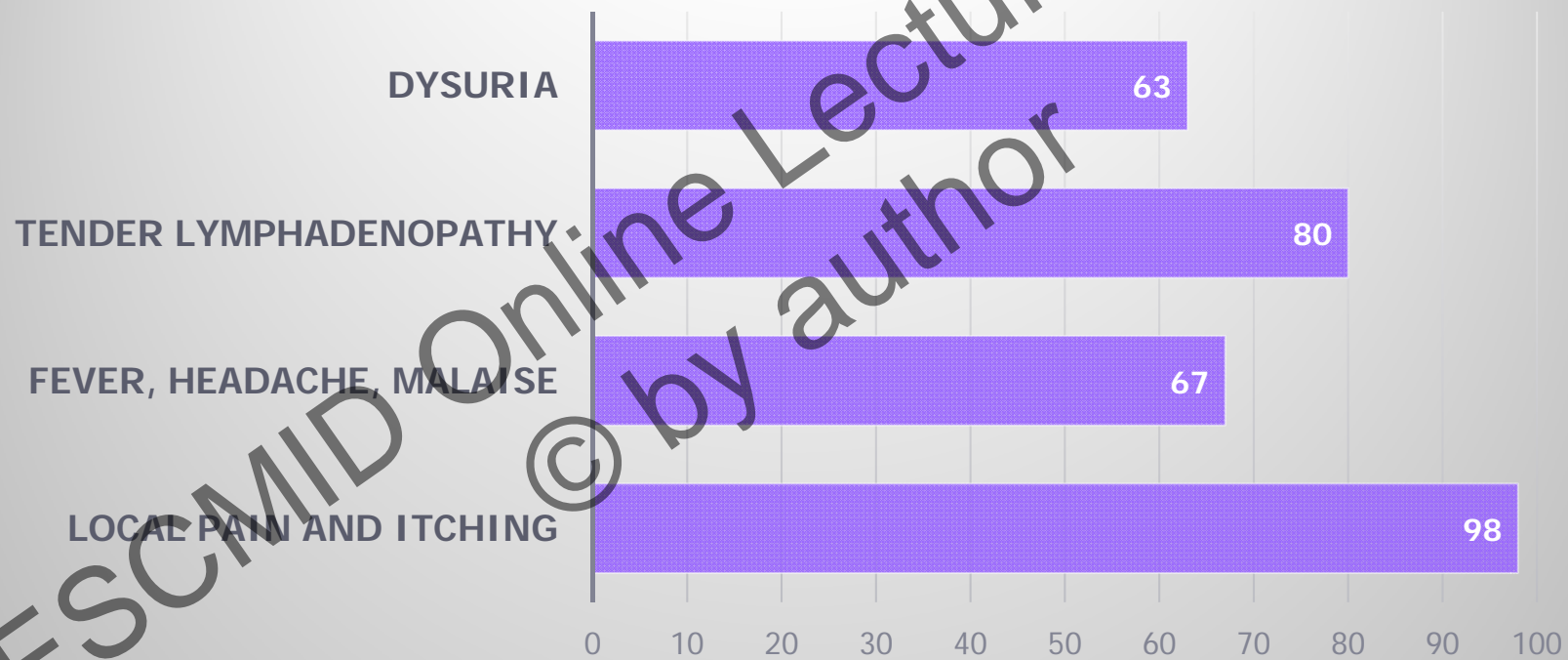
- ▶ Around 2/3 of patients subclinical infection
 - Symptoms in 37% of HSV-2 cases in prospective study
- ▶ Average incubation time 4 days (2-12)

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Symptoms of Primary Herpes Genitalis Infection (96)





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- ▶ Reduction of ulcers without therapy after 19 days
- ▶ Complications
 - Meningitis
 - Myelitis (cauda syndrome with bladder paralysis)

Non-primary first episode

- ▶ Partial protection from HSV-1-antibodies
 - Coinfection/Superinfection possible
- ▶ Less often symptomatic
- ▶ Duration of symptoms and shedding shorter

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Recurrent HSV infection

- ▶ Homologous antibody present when symptoms appear
- ▶ Most symptoms localized
- ▶ Lower viral load, shedding few days (4), symptoms shorter (9 days)
- ▶ HSV-2 recurrence 60%, HSV-1 only 14%
 - Most recurrent infections are HSV-2
 - Most primary infections are HSV-1

Asympomatic shedding

- ▶ First 3 months after primary infection 3x more frequent than later
- ▶ 26% of days during first year after primary, 9% in later years
- ▶ Coinfecion with HIV increases asymptomatic shedding

Predictors of neonatal infection

- ▶ Highest risk with primary infection or first episode non-primary acquired near time of delivery
 - 40-44% Primary
 - 24-31% Non-primary
 - 1-3% recurrent
- ▶ If antibodies developed before labour similar risk as recurrent
- ▶ Asymptomatic shedding: risk increases with invasive fetal monitoring, preterm birth

Risk of primary/non-primary infection

- ▶ Vaccine trial Herpevac: Seroconversion for HSV-2 in seronegative women (18-30y)
1,6%
 - 3,7% for HSV-1, 84% genital infection*
- ▶ Transmission in couples with male partner having recurrent herpes: 17%
 - If antibodies to HSV-1 are present: 9%
 - HSV-negative: 32%
 - ▶ 70% asymptomatic shedding

(*Clin Infect Dis. 2013 Feb;56(3):344-51)

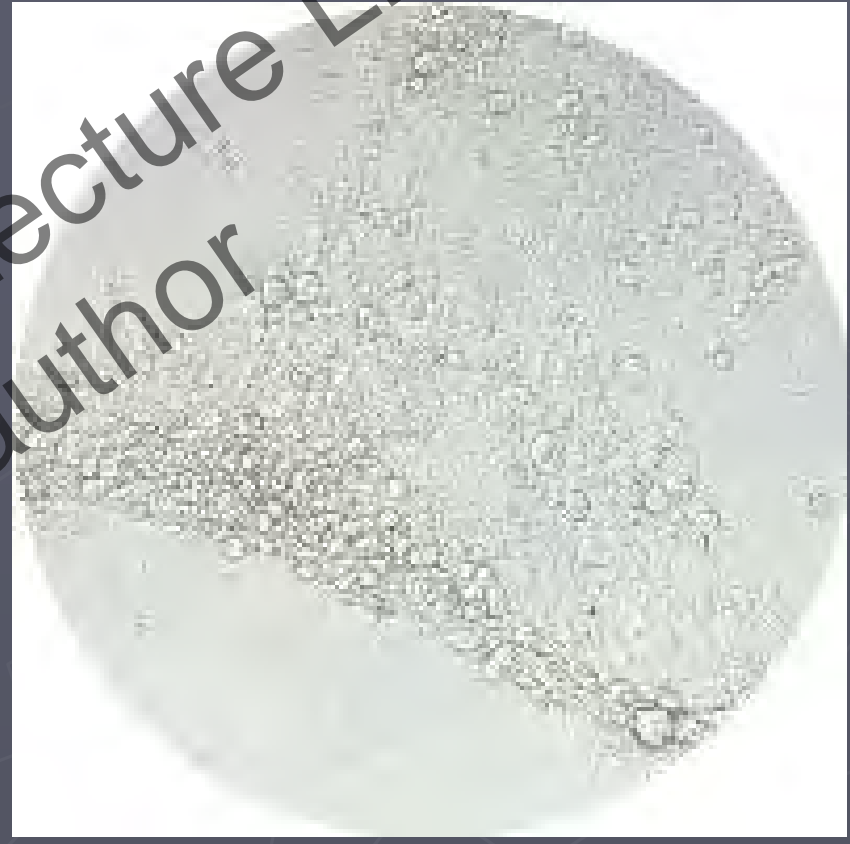
Diagnosis – Differentiation of primary/non-primary vs. recurrent infection

- ▶ Virus-Culture and typing or type-specific PCR from swab
- ▶ HSV-1/2-IgG Screening assay
 - If IgG negative and culture/PCR positive: Diagnosis of primary infection
 - If IgG and culture/PCR HSV-2 positive: typespecific serology (glycoprotein G ELISA or Westernblot/Lineblot)
- ▶ HSV-IgM not useful, no differentiation of primary non-primary, not type specific

Viral shedding

- ▶ If virus culture positive at labour: 5% transmission
- ▶ 0,02% if culture negative (OR346 for positive culture)
- ▶ No data on PCR, probably too sensitive!

Cell culture



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Management of genital herpes in pregnancy

Scope: Reducing risk of perinatal infection

- ▶ Serologic screening not recommended
 - Increasing number of HSV-1 infections
- ▶ Although type of HSV affects risk of transmission and neonatal sequelae (Transmission HSV1 > HSV2, Sequelae HSV2 > HSV1), clinical management does not take HSV-type into account

Maternal monitoring

- ▶ Weekly cultures/PCR not recommended
 - No prediction of shedding during labour
- ▶ Transcervical procedures should be avoided
- ▶ Transabdominal procedures not contraindicated

Type of delivery

- ▶ Caesarian section is recommended in active genital infection or with history of genital herpes and prodromal symptoms (pain, burning)
 - Evidence for CS: OR=0,14
- ▶ Some recommend CS if primary infection in the last weeks before delivery
- ▶ Utility of rapid PCR before delivery not clear
- ▶ CS does not completely rule out neonatal infection

Therapy

- ▶ Therapy should be offered to all patients with primary/non-primary episode
- ▶ Acyclovir safe at all stages, Valacyclovir seems to be safe
 - Reduction of symptoms, complications and duration of shedding
- ▶ Suppressive therapy: recurrent herpes from 36 weeks o.G.
 - Effect on transmission not shown
 - Cases of neonatal infection with suppressive therapy documented

Herpes neonatorum

- ▶ Defined as herpes infection in the first month of life
- ▶ Transmission
 - Intrauterine – very rare
 - Perinatal – 85%
 - Postnatal – 10% (US, other countries no actual data)
 - ▶ Caretaker or sibling with HSV lesion and neonate antibody negative

Herpes neonatorum - Symptoms

- ▶ Up to 50% without skin lesions
- ▶ Uncharacteristic symptoms at the beginning
- ▶ Different pictures
 - SEM – localized to skin, eye and mouth: 30-45%
 - CNS infection with or without SEM: 35%
 - Disseminated disease – hepatitis, pneumonitis, encephalitis, sepsis: high mortality
 - ▶ More than 20% without skin vesicles



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Herpes neonatorum - diagnosis

- ▶ History of genital herpes in pregnancy and vaginal delivery: swab from mouth, eye, anus 24h post partum – PCR
- ▶ With lesions: swab from lesion
- ▶ Without lesion: Blood and cerebrospinal fluid – PCR
 - Should be included in neonatal sepsis work-up
- ▶ Serology not usefull!!!!!!

Case 2

- ▶ One twin girl from day 7 uncharacteristic symptoms with hepato-splenomegaly, sucking weakness, hypothermia
- ▶ Beginning with antibiotic therapy, no effect, liver enzymes rising, abdominal distension
- ▶ Weekend, empirical start of Acyclovir 45mg/kg/ 8h („looks like viral disease“)
- ▶ Monday: virological work-up (HSV, enterovirus, parechovirus)

- ▶ HSV-1-DNA in blood (from Friday) 14 mio copies/ml
- ▶ Oral swab from beginning of symptoms retrospectively analyzed: HSV-1 positive
- ▶ Baby gets better every day
- ▶ After 3 weeks of therapy baby well and healthy

Herpes neonatorum - Therapy

- ▶ Suspect of infection (don't wait for result):
45mg/kg/day i.v. (8h) for localized symptoms, 60mg for CNS or disseminated disease
 - 14 days/21 days
- ▶ If PCR post partum positive: 14 days
- ▶ CNS: >80% sequelae
 - Debate: Suppressive therapy for 3-6 months
- ▶ Mortality of disseminated disease despite therapy 56%

Follow-up of case 2

- ▶ Mother, father and grandmother of baby HSV-seronegative – nosocomial infection!
- ▶ 65-80% of adults (age dependent) seropositive for HSV-1
- ▶ HSV shedding in 1% of days of infected children and 5-10% of days of infected adults!

The last case or: The importance of laboratory diagnosis

- ▶ Pregnant women, second pregnancy, 38y, comes in 38 weeks o.G. with genital blisters to the hospital
- ▶ Suspect of primary herpes genitalis
- ▶ Call Friday morning in Virology: urgent PCR, cesarian section?

Patient history

- ▶ Patient is happily married
- ▶ Husband seems happily married too
- ▶ Question of patient and colleague: possible infection from toilet seat?



Let's have a closer look at patient history

- ▶ Beginning with pain in the pelvis and right thigh
 - At that time feeling sick, maybe fever
- ▶ Popping up of blisters at the right labia 2 days later
- ▶ New blisters on the inner side of the right thigh
- ▶ Extremely painful, itching and burning

I believe it's another virus...

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- ▶ PCR HSV1+2 negative
- ▶ Routine PCR is tripple PCR HSV1+2+VZV
- ▶ VZV positive
- ▶ Vaginal zoster
- ▶ Probably more often than you think
(Dermatomes S2/S3, Sacral plexus)
- ▶ Different management (higher dose of acyclovir but normal birth mode)
- ▶ Think of it!

Thank you for your attention

