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Pathophysiology, diagnosis and treatment of fetal CMV

Stephen L Pedron, MD, MBA

Perinatal Medicine

Stephen L. Pedron, MD, MBA

Stephen Pedron, MD, MBA is a fellow of the American College of Obstetricians and Gynecologists, and a member of the Society for Maternal-Fetal Medicine. He is board certified by the American Board of Obstetrics and Gynecology (ABOG) in MFM and Obstetrics and Gynecology.

He earned his medical degree from St. Louis University School of Medicine, served his Obstetrics & Gynecology residency in Phoenix, his MFM subspecialty training at the University of Wisconsin, and earned his MBA at the University of Chicago Booth School of Business. He lives and works as a hi-risk OB subspecialist in Cedar Rapids, Iowa.

Dr. Pedron regularly delivers instructional seminars to working groups, on expert panels, and at conferences. He has taught and rendered care during missions work in Haiti and China. He is heavily embedded in community work. His other passions include family, travel, cooking, racing (anything that uses motive force) and German Shepherds, among others. Dr. Pedron has a gaggle of children and grandchildren.

Disclosures

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- **Content Disclosure**: This learning event does not focus exclusively on any specific product or service.
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Learning Outcomes

After this course, participants will be able to:

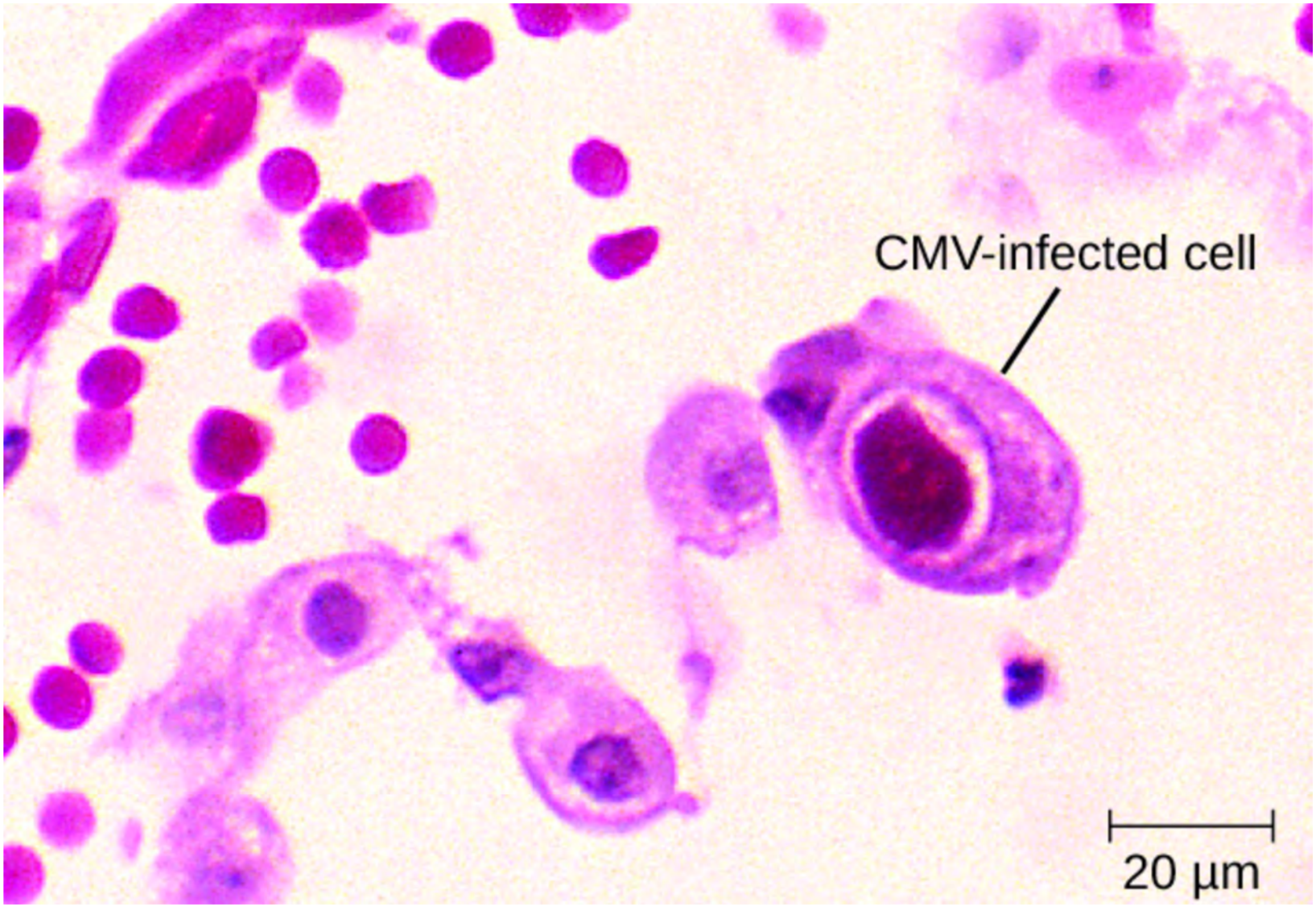
- Describe the pathophysiology of CMV infection in pregnancy.
- List the diagnostic options for identifying fetal CMV.
- List the treatment options available for CMV in pregnancy

Resources

- Patients
- Other professionals
  - Pathology, Immunology, Pediatric Infectious Diseases, Obstetrics & Gynecology, Maternal Fetal Medicine
- Literature

Objectives

- Review the pathophysiology, diagnosis and treatment of congenital cytomegalovirus (CMV) infection

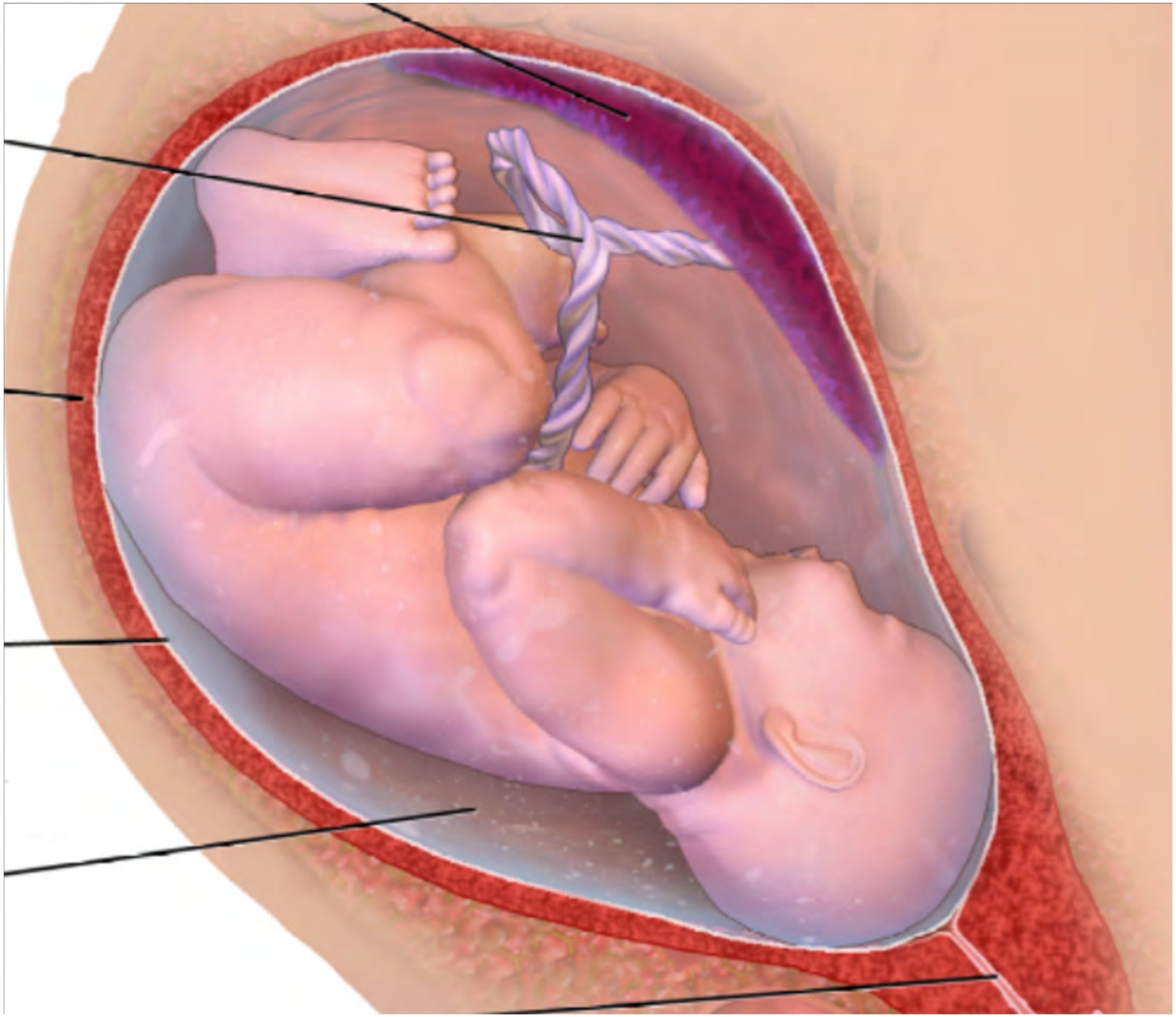

CMV-infected cell
20 µm

Terminology

- CMV – cytomegalovirus, member of the herpes virus family
    - As such, shares viral characteristics of other herpes viruses
        - Primary infection, latency, recurrence, etc.
        - Proclivity for neurons
- IgM, IgG
- Avidity
    - Roughly speaking, strength of association
- T-cells
    - For our discussion, generally the type of WBC that contends with viruses

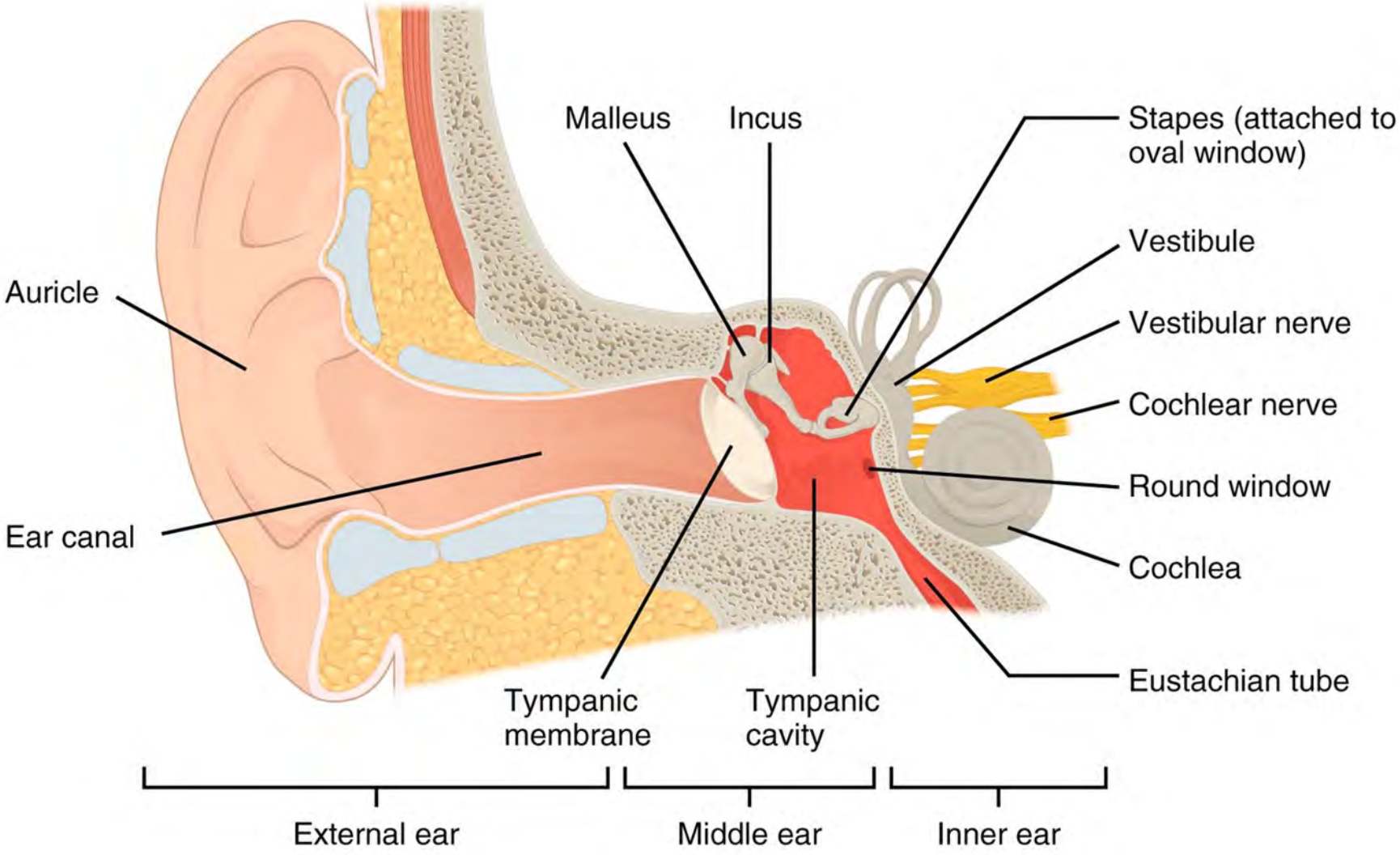
Pereira - why does CMV have such a proclivity for pregnancy?

- Infection, particularly uterine, in pregnancy is more virulent due to immune tolerance
  - Avidity rises slowly, and is somewhat unpredictable
  - A “tolerant” environment for CMV infection
- T cells are attracted to the uterus and placenta
  - Concentrates CMV infected cells in the uterus
  - CMV then grows into the decidua, where avidity rises even slower
  - CMV stays in the uterus, where avidity continues to languish
- Causes placental impairment, FGR, even if fetal infection not present



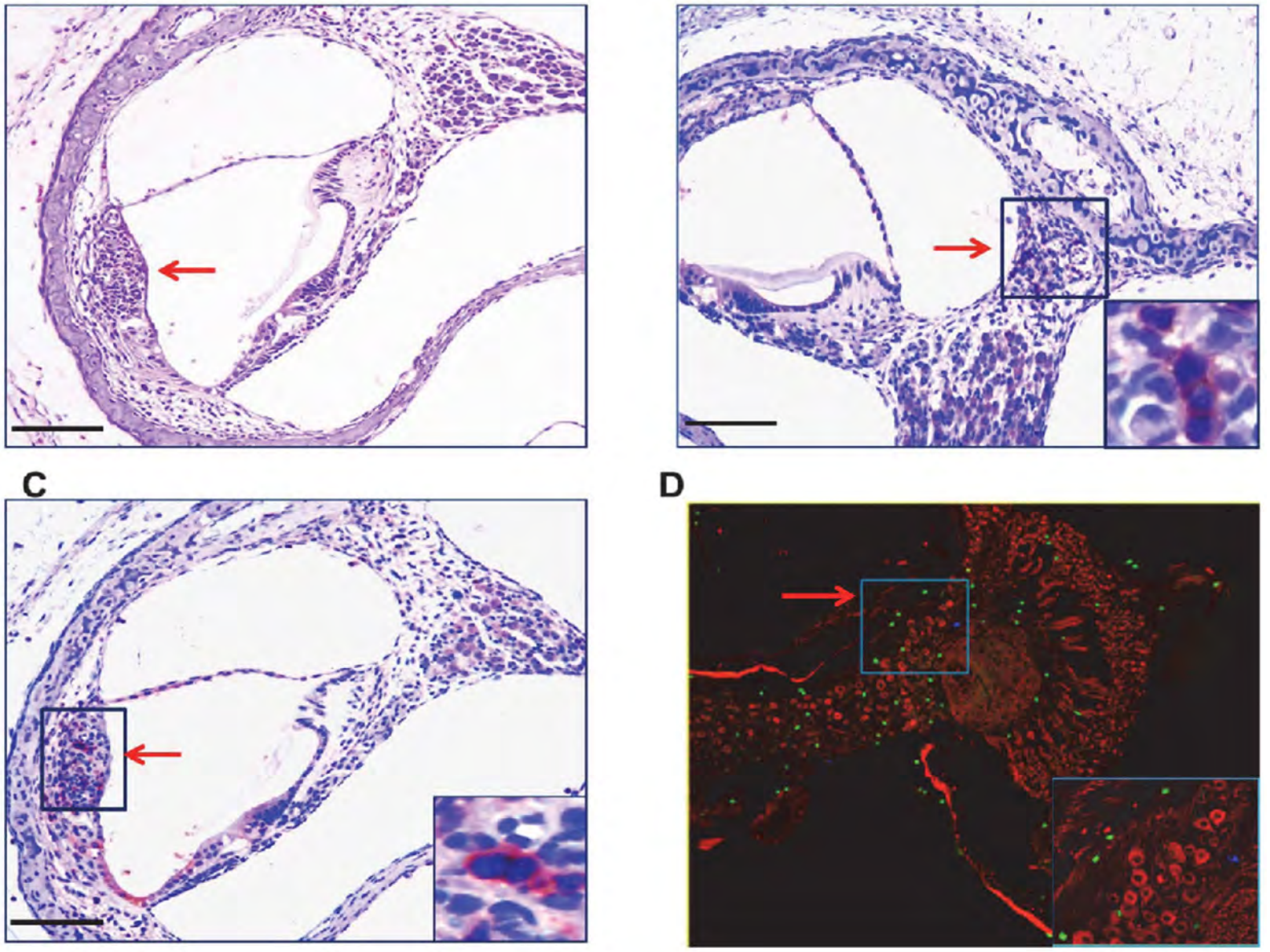
Auriti – on CMV infection in pregnancy

- "A key issue emerged in the last years is the key role of placental impairment in the pathogenesis of congenital CMV infection"
- Although CMV-associated congenital disorders are attributed to a direct infection of the fetus, abnormal development and function of the placenta may also strongly contribute to disease development and severity
- CMV replicates in cytotrophoblasts
  - Interferes with cytotrophoblast differentiation and invasion and proper development of new villi
  - Leads to placental edema/fibrosis and impaired transport of oxygen and nutrition to the fetus
    - May in some cases lead to FGR even if the fetus per se is not infected


Malleus
Incus
Stapes (attached to oval window)
Vestibule
Vestibular nerve
Cochlear nerve
Round window
Cochlea
Eustachian tube
Auricle
Ear canal
Tympanic membrane
Tympanic cavity
External ear
Middle ear
Inner ear

Zhuang - how does CMV cause sensorineural hearing loss (SNHL) in fetuses?

- "Little is known regarding the factors that initiate the inflammatory process in SNHL induced by CMV"
- Their group has shown that downstream inflammatory factors are activated in CMV-infected cochleae
- Spiral ganglion neurons (SGN) convey electric signals to the brain
- Inflammation and apoptosis
  - Inflammation may damage the SGN of the inner ear through the round window membrane leading to SNHL
  - Bradford has reported that cochlear SGN apoptosis occurs in murine CMV infection, leading to SNHL

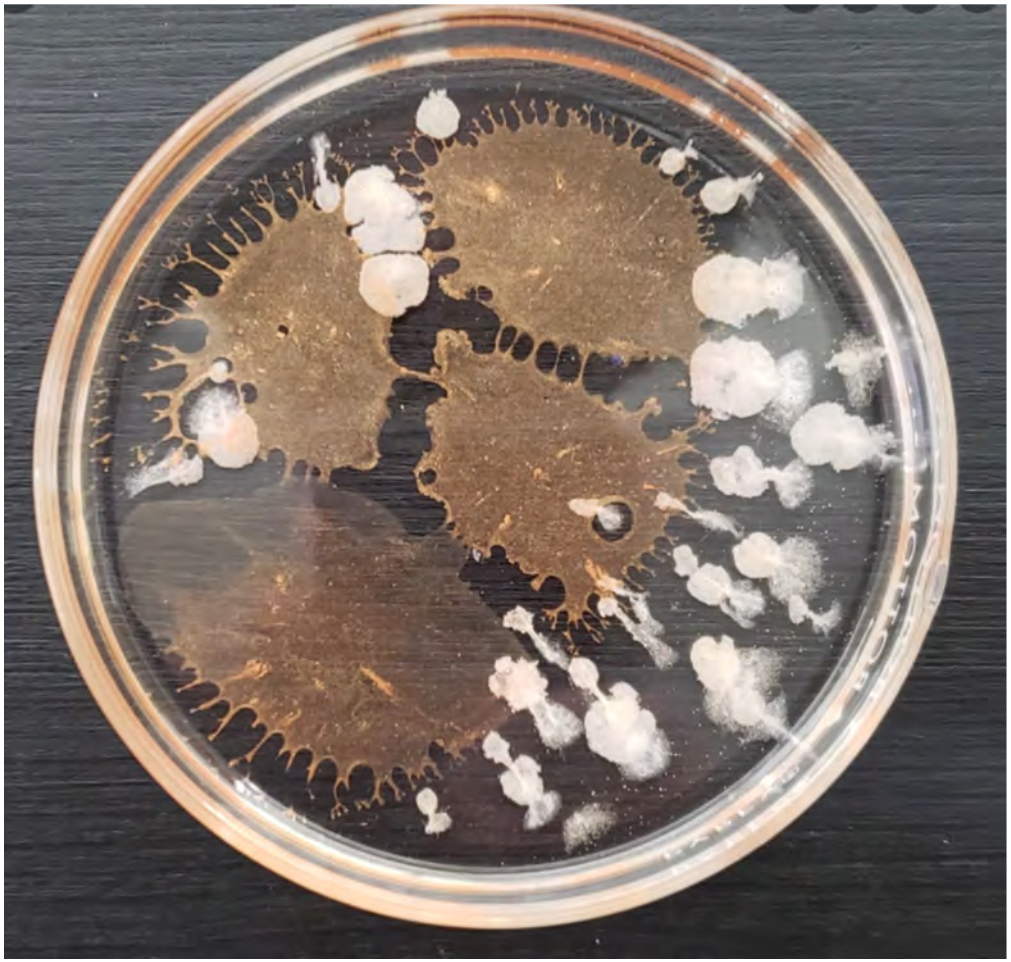

C
D

Who is harboring and transmitting CMV?

- Everyone, but especially toddlers
- Person to person
- Non-sexual contact – secretions
- Also
  - Sexual activity
  - Lactation
  - Transfusion
  - Transplantation


snotty-noses.com

Children =



Transmission summary

- In US, primary infection is the concern, though most infections are probably recurrent (less virulent)
  - In other cultures, secondary infection, reinfection, etc. may predominate
- If 1st trimester infection occurs, the perinatal transmission rate is lower, but the consequences are higher
- If 3rd trimester infection occurs, the perinatal transmission rate is higher, but the consequences are lower
- Of course, there is a continuum

How common is seroconversion (primary infection)?

- Depends on the demographic (Hyde)
  - All pregnancies – about 2%
  - Day care workers – at least 8%
  - Parents of a shedding toddler – about 24%
- 40-50% with primary infection transmit to fetus
  - Highest in 3rd trimester
  - Fetal illness worst in 1st and 2nd trimesters
  - Overall, 25% risk of symptomatic disease with primary infection

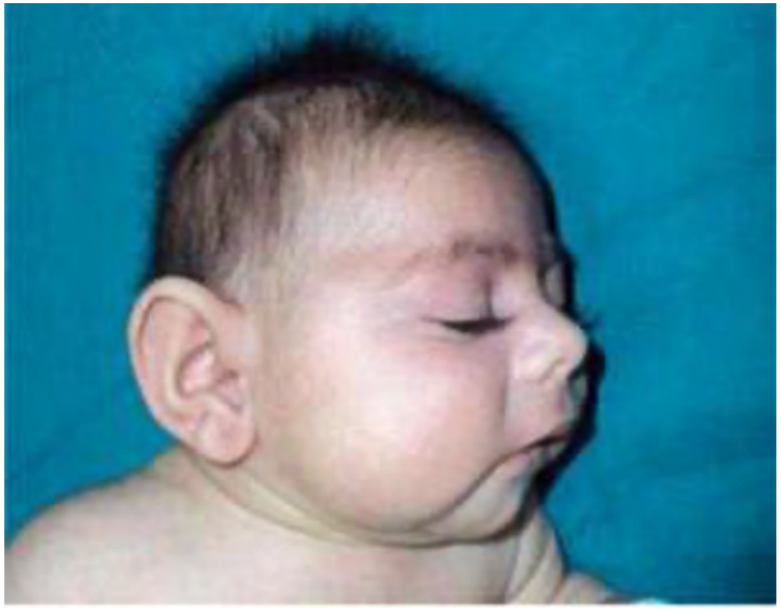
Asymptomatic phenotype - SNHL

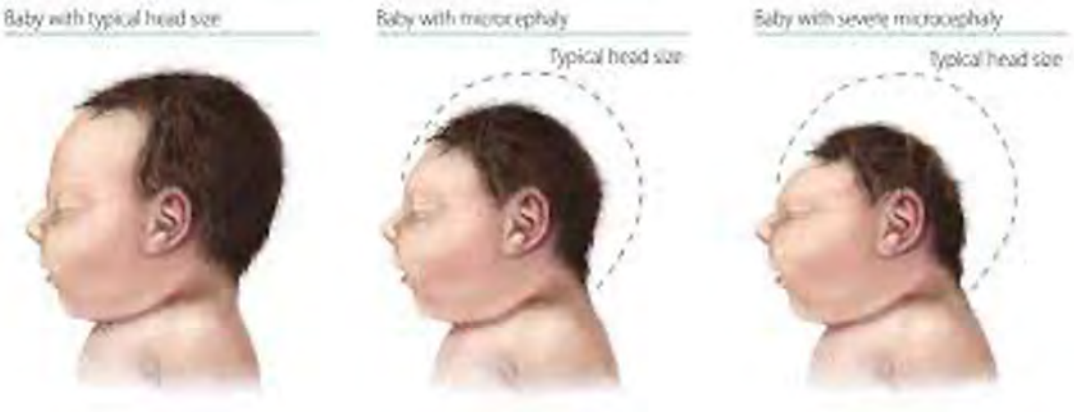
- Note: this slide is only here to state the obvious enormous personal and public health problem
  - This baby looks perfect, but nothing to stop him (or her) from having SNHL due to CMV

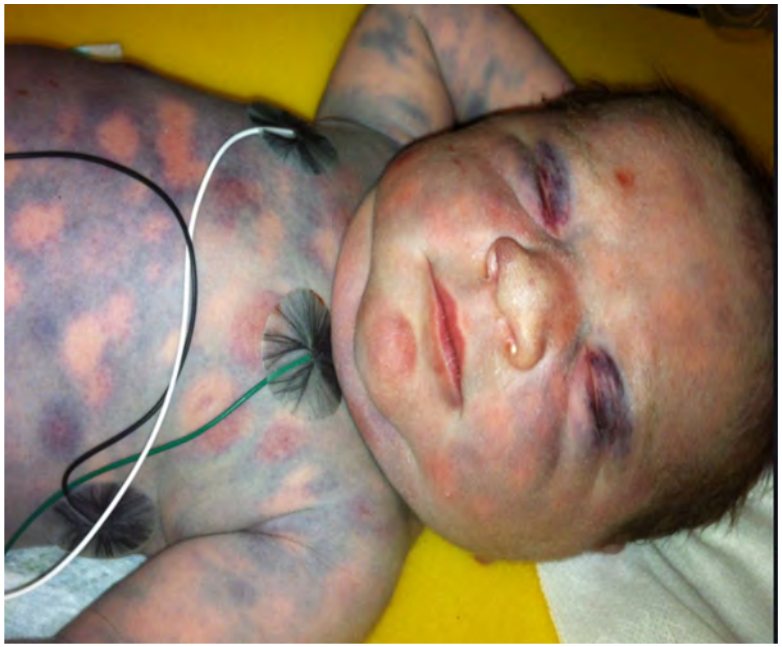
Symptomatic phenotype & prognosis

- Symptomatic with CNS or brain involvement (not at all subtle)
  - Microcephaly
  - Neurologic signs
    - Seizures, infantile spasms, hemiparesis, abnormal tone
  - Brain imaging
    - Ventriculomegaly, calcifications (periventricular), periventricular white matter lucencies, cortical maldevelopment (polymicrogyria, fetal brain disruption sequence), lenticulostriate vasculopathy, cysts, cerebral atrophy, etc.
  - Hepatitis, jaundice, thrombocytopenia, elevated CSF protein

Microcephaly







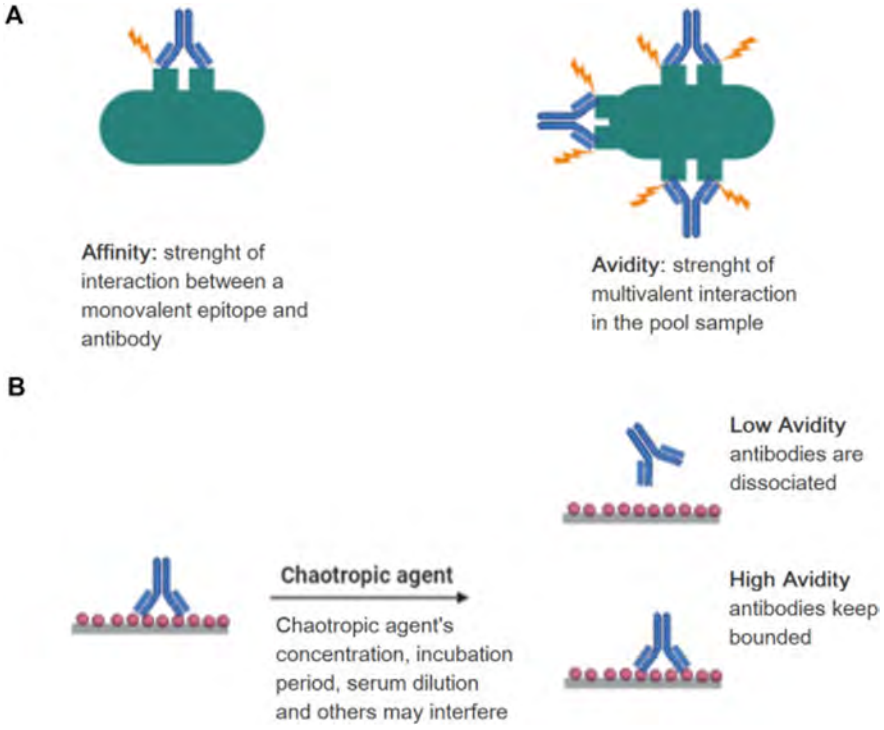
Recurrent or non-primary infection

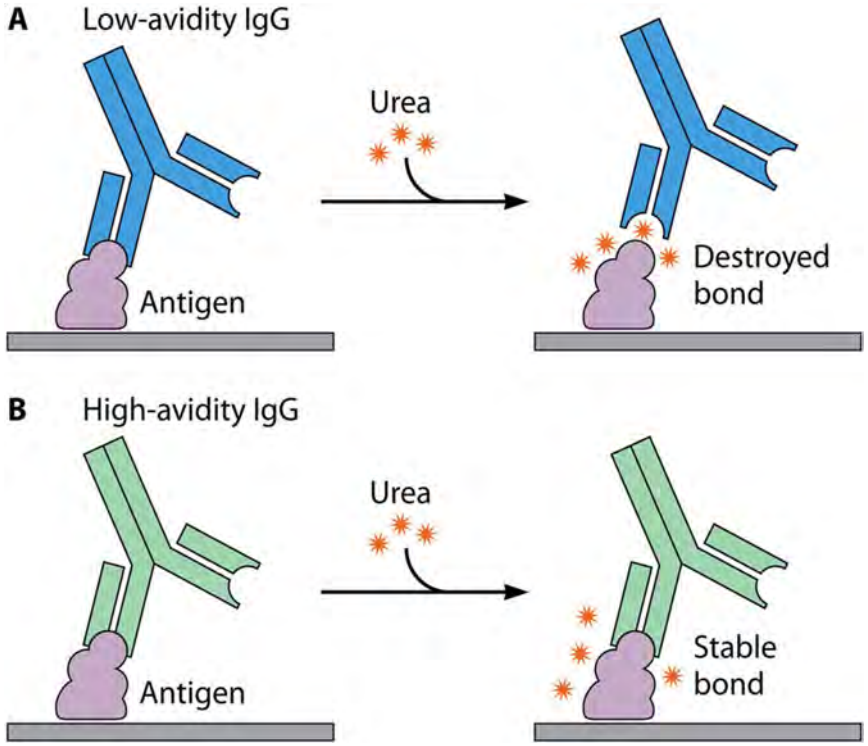
- Less severe phenotype
- Still a very common cause of hearing loss
  - Since it occurs more often, the numbers add up

Maternal diagnosis

- CMV IgG & IgM
  - These may wax and wane
  - Technically should be several weeks apart, but the clock is ticking in pregnancy
  - IgM index ≥ 4.5
  - An increase in IgG *might* be informative
- The presence of IgG, with or without IGM, should suggest immunity
  - Almost all immunity presents as presence of both IgG & IgM
- Maternal CMV PCR

Affinity v avidity





Avidity

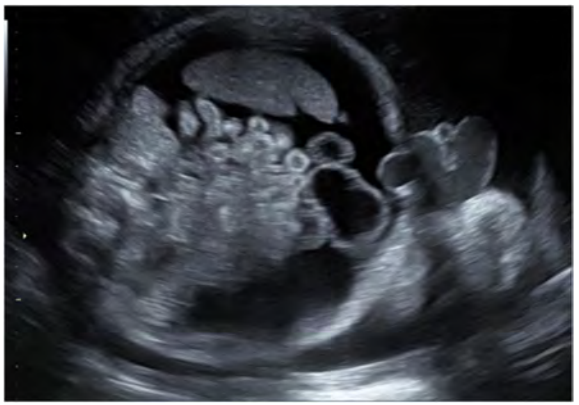
- Revello
  - Hi avidity suggests a longer, more enduring infection (immunity)
    - < 15% - < 6 weeks
    - < 35% - < 12 weeks
- Rouse
  - IgG avidity less than 32 %

MFM Units Network calculator

- Predictors of congenital infection after maternal primary infection
- Rouse, Obstetrics & Gynecology, 2022
  - Predictors
    - Government assisted insurance
    - IgM index 4.5 or greater
    - IgG avidity less than 32 %
    - Positive maternal CMV PCR
  - calculator

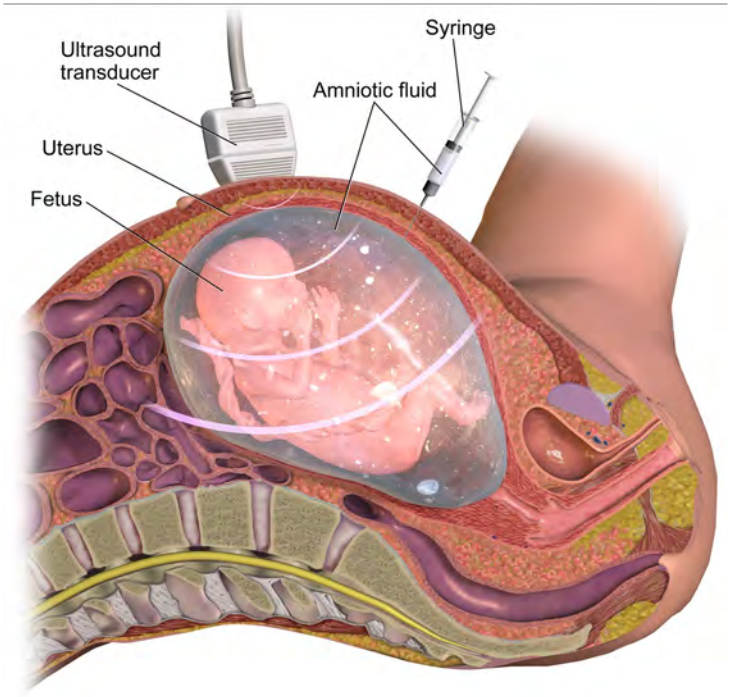
Antenatal ultrasound suspicion of fetal infection

- Echogenicities
  - Calcifications
- Fetal growth restriction
- Placentomegaly
- Hepatosplenomegaly
- Ascites, effusions, hydrops
- Microcephaly & other intracranial changes



Fetal diagnosis

- Amniocentesis
  - Amniotic fluid PCR
  - Might be a bit less accurate earlier in pregnancy



Strategies to decrease congenital CMV

- Prevention
- Screening
  - Newborn
  - Prenatal?
- Valaciclovir
- Novel therapies
  - Monoclonal antibodies
  - mRNA vaccine

Prevention - definitions

- Primary
  - Prevent maternal infection in the first place
- Secondary
  - Prevent perinatal transmission in the infected mother
- Tertiary
  - Newborn intervention

Primary prevention

- Avoid saliva & urine
- Hygiene
  - Hand washing
  - Avoid contact with secretions
  - Don’t share food, utensils, etc.

CMV Fact Sheet for Pregnant Women and Parents

Most people have been infected with cytomegalovirus (CMV), but do not have symptoms. If a pregnant woman is infected with CMV, she can pass it to her developing baby. This is called congenital CMV, and it can cause birth defects and other health problems.

For pregnant women

You can pass CMV to your baby
If you are pregnant and have CMV, the virus in your blood can cross through your placenta and infect your developing baby. This is more likely to happen if you have a first-time CMV infection while pregnant but can also happen if you have a subsequent infection during pregnancy.

You are not likely to be tested for CMV
It is not recommended that doctors routinely test pregnant women for CMV infection. This is because laboratory tests cannot predict which developing babies will become infected with CMV or have long-term health problems.

You may be able to reduce your risk
You may be able to lessen your risk of getting CMV by reducing contact with saliva and urine from babies and young children. The saliva and urine of children with CMV have high amounts of the virus. You can avoid getting a child's saliva in your mouth by, for example, not sharing food, utensils, or cups with a child. Also, you should wash your hands after changing diapers. These cannot eliminate your risk of getting CMV, but may lessen the chances of getting it.

For parents

About 1 out of every 200 babies is born with congenital CMV. About 1 out of 5 of these babies will have birth defects or other long-term health problems.

Babies with congenital CMV may show signs at birth
Some signs that a baby might have congenital CMV infection when they are born are:

- Small head size
- Seizures
- Rash
- Liver, spleen, and lung problems

Tests on a baby's saliva, urine, or blood done within two to three weeks after birth can confirm if the baby has congenital CMV.

Early treatment may help
Babies who show signs of congenital CMV at birth may be treated with medicines called antivirals. Antivirals may decrease the severity of health problems and hearing loss but should be used with caution due to side effects.

Long-term health problems may occur
Babies with signs of congenital CMV at birth are more likely to have long-term health problems, such as:

- hearing loss
- intellectual disability
- vision loss
- seizures
- lack of coordination or weakness

Some babies with congenital CMV but without signs of disease at birth may still have or develop hearing loss. Hearing loss may be present at birth or may develop later in babies who passed their newborn hearing test. Sometimes, hearing loss worsens with age.

Hearing checks and therapies are recommended
Children with congenital CMV should have regular hearing checks. Children with hearing loss should receive services such as speech or occupational therapy. These services help ensure they develop language, social, and communication skills.

The earlier your child can get hearing checks and therapies, the more he or she can benefit from them.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

For more information, visit:
www.cdc.gov/cmv

National Center for Immunization and Respiratory Diseases (NCIRD)

What is CMV?

Cytomegalovirus (CMV) is a common virus that's a member of the herpes virus family. In fact, it's estimated that over half of adults will have CMV by age 40[1]. Once in the body, it stays there for life.

Most people don't know they have CMV because it rarely causes symptoms in healthy people. However, when a pregnant woman is infected with CMV, it may cause serious health problems for her unborn baby.

What is Congenital CMV?

When a baby is born with CMV infection, it's called congenital CMV infection.

CMV is the most common congenital infection in the United States. According to the CDC, roughly 1 in 200 babies are born each year with congenital CMV.

Based on this statistic, it's estimated that about 115 babies born in Idaho each year may have congenital CMV infection.

Of those born with congenital CMV, about 1 in 5 (roughly 23 in Idaho per year) may develop long-term health problems due to the infection[2]

If pregnant or planning to become pregnant, consider these steps to reduce your chances of getting CMV.

Wash your hands for at least 20 seconds after changing diapers, feeding children, wiping a child's nose or drool, or handling children's toys.

Wear gloves when changing diapers or touching bodily fluids such as urine, vomit, or saliva.

Don't put a child's pacifier in your mouth.

Don't share food, drinks, eating utensils, or a toothbrush with a child.

Regularly disinfect toys, counter tops, and other surfaces that may have a child's saliva or urine on them.

Avoid contact with a child's saliva when kissing or snuggling.

Helpful information for mothers, those expecting, and child care workers.

Anyone who works closely with children in settings such as child care facilities and church nurseries may be at greater risk for CMV infection as CMV is common in these settings. Young children tend to shed the virus in high amounts in saliva and urine, even if they themselves have no signs of infection. If you are pregnant and work in these settings, you can help reduce your risk of getting CMV by following the steps outlined in this brochure.

Because CMV is a very common virus and is widespread in the community, children and adults known to have CMV should not be excluded from attending or working in child care settings or schools. To lessen the chance of infection, good personal hygiene is needed at all times.

CMV is a common virus | **Protect your baby and yourself** | **Visit cmv.dhw.idaho.gov**

The maddening under recognition and inattention to congenital CMV

- Provider knowledge
  - Pesch 2020
    - OB provider knowledge is low
- Demmler-Harrison
  - The elephant in the room

Do not screen

- CDC
- ACOG
- SMFM
- Billette de Villemeur
  - No proven treatments
  - Screening results in increased death due to termination
  - Emphasize hygiene instead
- Across the board, the rationale for ignoring the problem is that there is no known treatment for perinatal disease

CDC's position on screening

- Routine screening for primary CMV infection during pregnancy is not recommended in the United States for several reasons:
  - Most laboratory tests currently available to identify a first-time infection can be difficult to interpret
    - True, unless you invest in understanding some immunology
  - Current tests cannot predict if the fetus may become infected or harmed by infection
    - True, but also prognosis difficult to assign for many fetal disorders we evaluate
  - The lack of a proven treatment to prevent or treat infection of the fetus reduces the potential benefits of prenatal screening
    - Current state of play – may be untrue

Treatment per se - valaciclovir

Leruez Ville, 2016

- Treated 43 patients with fetal infection & mild ultrasound features
  - Valaciclovir 8 grams/day
- Majority of neonates were asymptomatic
- Higher platelet counts
- Lower viral levels
- Results indicate that high-dosage valacyclovir given in pregnancy is effective for improving the outcome of moderately symptomatic infected fetuses
- Although not a randomized controlled trial, this was the first study reporting the efficacy of an antiviral drug to treat cytomegalovirus-infected fetuses

Shahar-Nissan, 2020

- Prospective, randomized, double blinded trial
  - 90 patients with primary maternal infection
  - Amnio done for both groups
- Lower transmission & neonatal infection in the treatment group
- “Valaciclovir is effective in reducing the rate of fetal CMV infection after maternal primary infection acquired early in pregnancy”
- “Early treatment of pregnant women with primary infection might prevent termination of pregnancies or delivery of infants with congenital CMV”

Faure Bardon, 2021

- Case control study
- Clinic screening prior to 14 weeks
- 310 patients with primary infection
  - 269 had amniocentesis for PCR
  - 65 treated with valaciclovir 8 grams/day for 35 days
    - Average gestational age treatment onset 12.71 weeks
  - 65 untreated patients as controls
- Lower infection rate in treated patients
- One mother had acute renal failure, resolved after treatment stopped

Monitoring therapy – Nigro & Adler

- Maternal CMV DNAemia independently predicts infant outcomes
- This may help patient counseling

Outcomes – prognosis after treatment

- Depends upon:
  - Timing of seroconversion & fetal infection
  - Antenatal ultrasound findings
  - Possibly some relationship to maternal viremia & response to treatment
  - Newborn findings

Pregnancy termination – decision making

- Timing of diagnosis
- Avidity
- Evidence of fetal disease
  - Mild?
  - Severe
- Amnio results

Novel treatments (Acosta)

Novel treatments on the horizon (Acosta)

- Other viral targeted therapies
- Transplant and immunosuppressed patient experience
- Monoclonal antibodies
- Vaccination

Monoclonal antibodies

- Tabata, Pereira & others
  - mAbs decreased CMV attachment/entry in placental explants
- Vlahava
  - Used Cytotect (clinical grade donor pooled HIG)
  - Examined NK cell activation in CMV infected target cells
    - Activated cellular immunity, as opposed to viral neutralization per se
- Note: mAbs being investigated in newborns and non-pregnant settings
  - Stem cell transplant in immunocompromised patients

CMV vaccine

- Moderna
  - mRNA
  - Phase 3
  - Estimated completion April 2026
  - University of Alabama and multiple other sites
- Merck, Sharp & Dohme
  - Estimated completion December 2025?
  - Not sure what type of vaccine this is
  - University of Alabama

Summary

- Prevention is effective
- Serum diagnosis is not necessarily complex, it just takes suspicion and learning
- There is effective sonographic and invasive diagnosis
- Treatment, though not the “standard of care”, is reasonable and quite plausibly effective
- There is hope on the horizon for an mRNA vaccine, as well as other novel therapies

Thank you

Stephen L Pedron, MD, MBA

Perinatal Medicine

Pathophysiology

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- Auriti, Pregnancy and viral infections, BBA – *Molecular Basis of Disease*, 2021
- Zhuang, MCMV triggers ROS/NLRP3-associated inflammasome activation, *International Journal of Molecular Medicine*, 2018
- Bradford, Murine CMV-Induced hearing loss, *PLOS Pathogens*, 2015

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- Pesch, Improving obstetric provider CMV knowledge, *Infectious Diseases in Obstetrics and Gynecology,* 2020
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Treatment

- Leruez-Ville, In utero treatment of CCMV with valacycolivir, *AJOG*, 2016
- Shahar Nissan, Valaciclovir to prevent vertical transmission of CMV, *Lancet*, 2020
- Faure Bardon, Secondary prevention of CCMV with valacyclovir, *Ultrasound in Obstetrics & Gynecology,* 2021
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- Tabata, Neutralizing MABs reduce CMV spread in placentas, *Vaccines*, 2019
- Vlahava, MABs targeting nonstructural viral antigens can activate ADCC against CMV, *Journal of Clinical Investigation*, 2021

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- Vlahava, MABs targeting nonstructural viral antigens can activate ADCC against CMV, *Journal of Clinical Investigation*, 2021

Current patient

- 29 yo G2P1 @ 8 weeks gestation
- 1.5-year-old toddler
- Bronchitis/pneumonia about 4 weeks ago
- Positive CMV IgM, negative IgG 2 weeks ago
- Actions
  - Repeat titers 2 weeks from first set
  - Avidity
  - Begin valaciclovir