Congenital CMV

Education, Screening, and Diagnosis in Pregnancy: Gaining the Attention of Pregnancy Providers

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Disclosures

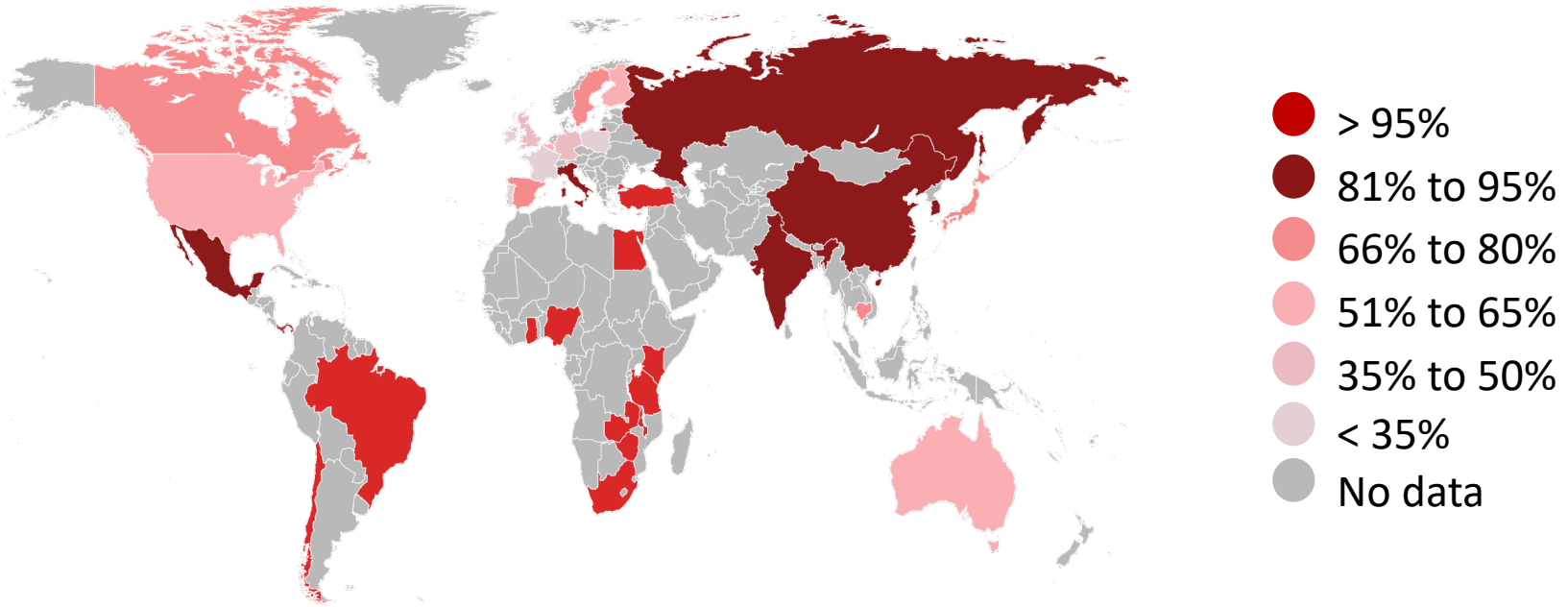
- I have no industry affiliations or financial disclosures.

Overview

- Epidemiology
- Impact on infant/child health
- Transmission and clinical manifestations
- Screening and Diagnosis in Pregnancy
- Findings and Diagnosis in Fetus
- Infant screening
- Prevention
- Antiviral therapy
- Vaccination

Epidemiology

Worldwide CMV Seroprevalence in Individuals Aged 16 to 50 Years



- Seroprevalence approaches 100% for adults in Sub-Saharan Africa, Brazil, India
- In US, 50-80% prevalence by 40 yo

Adland E, et al. Front Microbiol. 2015;6:1016.

Epidemiology: Women and Pregnancy

- Seroprevalence in 14-44 yo women in US– 58%

- Seroprevalence among pregnant women
  - Seropositive: 50-80%
  - 70-85% low-income vs. 50-60% mid/high-income
  - Primary infection (seroconversion): 0.7-4%
  - Non-primary (recurrent or secondary) infection: 13.5%
    - REINFECTION or REACTIVATION

Staras 2006, Cannon 2009, Mustakangas 2000, Fowler 1993

Epidemiology: Women and Pregnancy

- Reinfection in seropositive women
  - ~1/3 (59/205) seropositive women had CMV reinfection over 52 month follow-up
  - New antibody against polymorphic epitopes detected

- 94% of 113 CMV seropositive women with > 1 strain

- Viral DNA detection in seropositive women
  - 205 healthy CMV-seropositive postpartum women
  - Baseline: 39% viruria and 24% viremia
  - Intermittent viruria and viremia throughout study
  - CMV detected at least once 83% urine and 52% blood over 3 year follow-up

Ross 2010, Arora 2010, Novak 2008

Epidemiology

- Most common congenitally acquired infection and leading cause of infectious congenital disabilities in developed nations
  - World-wide incidence of ~ 1 to 24 per 1000 livebirths in high-income countries
  - 2,500 babies in the world each day
  - 1 in 200 (0.5%, [0.2-2%])children are born with CMV in US
  - ~20,000 infants infected annually in US
  - ~4,000 children (1 in 5 infected) with long-term disabilities in US

- Leading cause congenital hearing loss in US and worldwide
  - **4.8% to 12.5% of all cases** in developed countries
- Other impairments: vision, seizures, cerebral palsy, neurodevelopmental
- Miscarriage, preterm birth, stillbirth, postnatal/infant/child death
  - In the **United States**, **CMV** accounts for about **8% of intrauterine fetal demise** due to infectious etiologies
- Annual cost for treatment of CMV complications → ~$2 billion

Watts 1999, Stagno 1986, Stagno 1982, Griffiths 1980, Fowler 1993, Yamamota 2010, Dar 2008, Shi 2018, Page 2019, Satterfield-Nash 2020

Risk Factors

- **Factors that contribute to CMV exposure, infection, and transmission**
  - Lifestyle
  - Population density
  - Crowded households
  - Child-rearing practices
  - Work environments
  - Number of sexual partners

Risk Factors

- Risk factors
  - Work at day care or with young children
  - Contact with children
  - Blood transfusion
  - Multiple sexual partners
  - Unprotected intercourse
  - Parity
  - Child <3 years old
  - Abnormal cervical cytology
  - Infection with STI
  - Lower SES
  - Underdeveloped nations
  - Born outside US
  - First pregnancy at young age (<15 years old)

OTHER Predictors

- **Secondary analysis randomized** placebo-controlled trial (2012 to 2018)
- Women with primary CMV infection (plasma CMV-specific IgM and IgG with avidity < 50% before 24 weeks of gestation or IgG seroconversion before 28 weeks) who were carrying a singleton fetus without ultrasound findings suggestive of CMV infection
- **344** of 399 **(86%)** had informative data for the noninvasive model for **prediction** of **congenital CMV infection**
- The **best performing model** included
  - **Government-assisted insurance**
  - **IgM index ≥ 4.5**
  - **IgG avidity < 32%**
  - **Detectable CMV PCR** in maternal plasma at time of randomization

- Rouse DJ, et al. Obstet Gynecol. 2022;139:400-406.

Clinical Manifestations of Infection

- Primary infection
  - Usually asymptomatic (90%) versus mild flu-like/other symptoms (10%)

- Mononucleosis syndrome
  - Fever/chills, malaise, myalgia
  - **Mild hepatitis (elevated LFT's)**
  - Leukocytosis, atypical lymphocytes in blood x 6 weeks
  - Less hepatomegaly, splenomegaly, pharyngitis than EBV
  - Older patients, longer fever duration, less cervical LAN
  - Negative Monospot or heterophile-agglutinin tests
  - **Maculopapular rash (1/3)**
  - **Thrombocytopenia**, hemolytic anemia

- Meningoencephalitis, pericarditis, myocarditis
- GI ulcers, PNA less common

Transmission

- Viral presence in most bodily fluids **(ubiquitous virus)**
  - Urine, saliva, blood, throat, cervix, semen, stool, tears, breastmilk

- Transmission routes
  - Sexual, close contact, blood/tissue, occupational
  - Perinatal
  - Transplanted organ, breastmilk, urine, saliva, stool, sexual contact/genital tract, blood, transplacental

Watts, 1999; Stagno, 1986; Stagno, 1982; Griffiths, 1980; Yamamota 2010; Dar 2008

Transmission: Infection states

- **Primary Infection (seroconversion)**
  - Initial infection in someone with no immunity to CMV (seronegative)
  - Presence of anti-CMV IgM and IgG antibodies in a previously IgM- and IgG-negative individual defines seroconversion
  - **30% to 40% risk of vertical transmission**
- **Nonprimary Infection**
  - **Reactivation**
    - Reemergence of latent CMV in someone who is seropositive due to earlier CMV infection
  - **Reinfection**
    - Seropositive person acquires a new CMV strain from someone else (superinfection)
  - **1% to 3% risk of vertical transmission**
- Following seroconversion or reactivation, the pathway leading to CMV excretion in the fetal urine takes ~ 6 to 8 weeks

Maternal Diagnosis

- Presence of **IgM → acute infection**
  - High false-positive in CMV IgM assays; IgM can be produced by nonprimary infections and other virus such as EBV
  - IgM can also persist for months and possibly years
- IgG Avidity
  - More accurate to detect primary infection than IgM alone
  - At time of primary infection, antibodies have a lower antigen avidity than those of recurrent infection or later in primary infection
  - Over time → antibody maturation → higher antigen avidity
  - Low to moderate avidity → 16 to 18 weeks following infection

Maternal Diagnosis

CMV Antibodies	IgG Avidity	Interpretation	Implications
IgM^- and IgG^-[a]	Not applicable	Uninfected or early infection	Counsel about behavioral measures to reduce risk of acquiring infection
IgM^+ and IgG^-[a]	Not applicable	May be false positive because of other viral infections	Repeat tests in 2 to 4 weeks[a,d]
IgM^+ and IgG^+[a]	Low	Recent infection	Counsel about likelihood of fetal infection, possible sequelae, and options for prenatal diagnosis (amniocentesis[e,f]); Monthly ultrasound starting at 18 to 20 weeks of pregnancy (eg, FGR may occur at 26 to 30 weeks); monitor fetal cardiac activity and movement[d]
IgM^+ and IgG^+[a]	High	Past or recurrent infection	Counsel about low risk of fetal infection, possible sequelae if fetus is infected*
IgM^- and IgG^+[a]	High	Past infection	Counsel about low risk of fetal infection and possible sequelae**
IgM^- and IgG^+[b-c]	Low	Further expert opinion needed	

Pathogenicity of Congenital Infection

- CMV causes direct and indirect injury to the fetus
  - Immune-mediated process
- Indirect injury may be caused by modification of inflammatory processes through 2 potential mechanisms:
  - Induction of cytokines results in neurotoxic byproducts
  - Induction of cytokines results in altered neural stem cell migration and differentiation
- This can result in injury to the fetal brain and long-term neurodevelopmental complications

Fetal Ultrasound Findings

Fetal ultrasound abnormalities

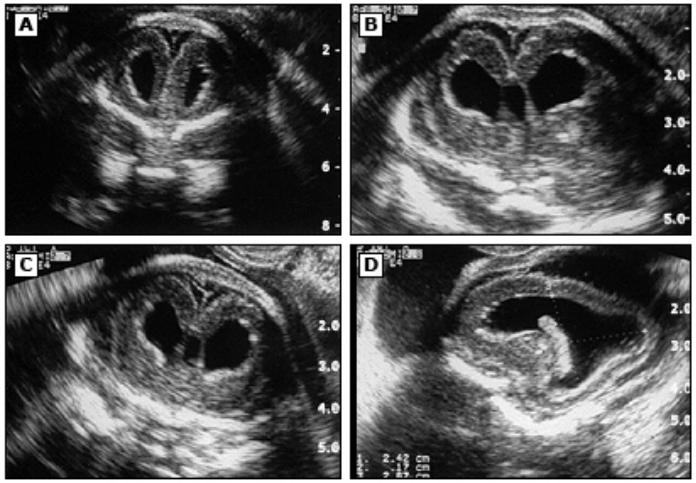
- Ventriculomegaly, periventricular hyperechogenicity (calcifications)
- Microcephaly
- Bowel hyperechogenicity
- Ascites, pleural effusion, hydrops
- Hepatosplenomegaly

Other ultrasound findings

- Amniotic fluid abnormalities (oligohydramnios, polyhydramnios)
- Placentomegaly

Fetal Ultrasound Findings

In utero cytomegalovirus infection at 23 postmenstrual weeks



(A-C) Serial coronal sections from anterior to posterior showing dilation of the lateral ventricles and periventricular calcifications.

(D) An oblique section showing the dilation of the lateral ventricles, the dysmorphic choroid plexus, and periventricular calcifications.

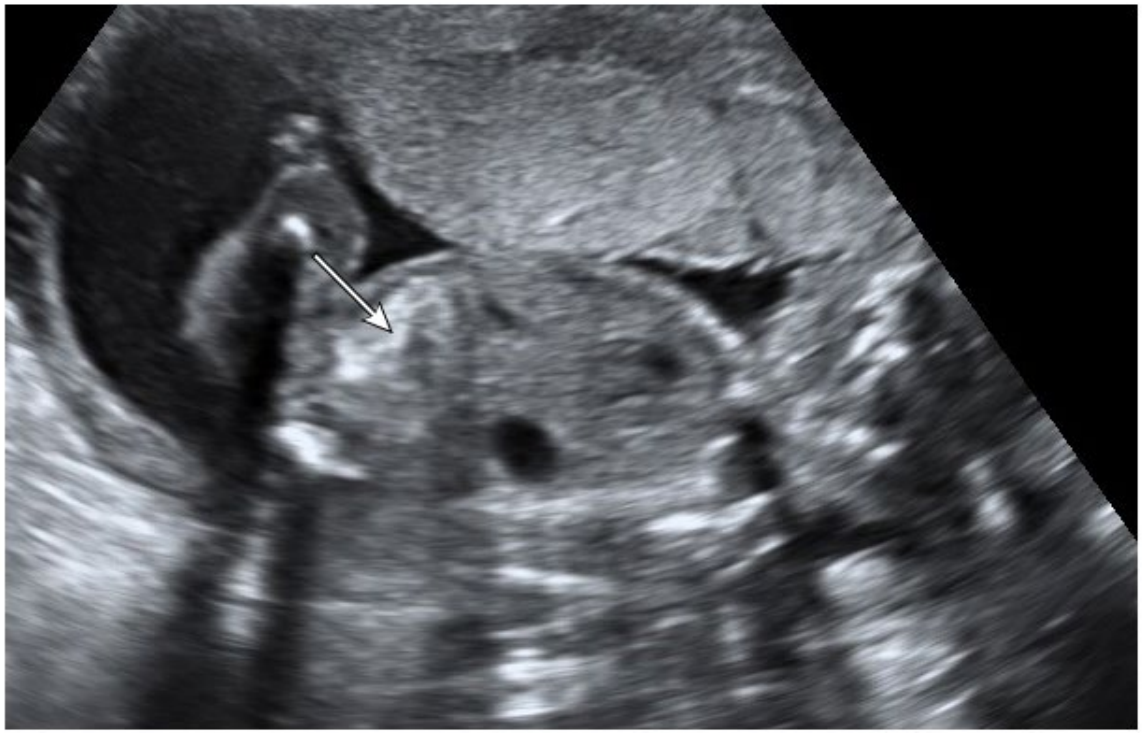
This fetus has a markedly abnormal gyral pattern with more gyri and sulci than normal for this gestational age. This is the early finding that will develop into polymicrogyria.

Courtesy of Ana Monteagudo, MD.

UpToDate®

Fetal Ultrasound Findings

Echogenic fetal bowel



In this longitudinal image, arrow points to a very echogenic portion of fetal bowel that is as echodense as fetal bone.

Courtesy of Beryl R Benacerraf, MD.

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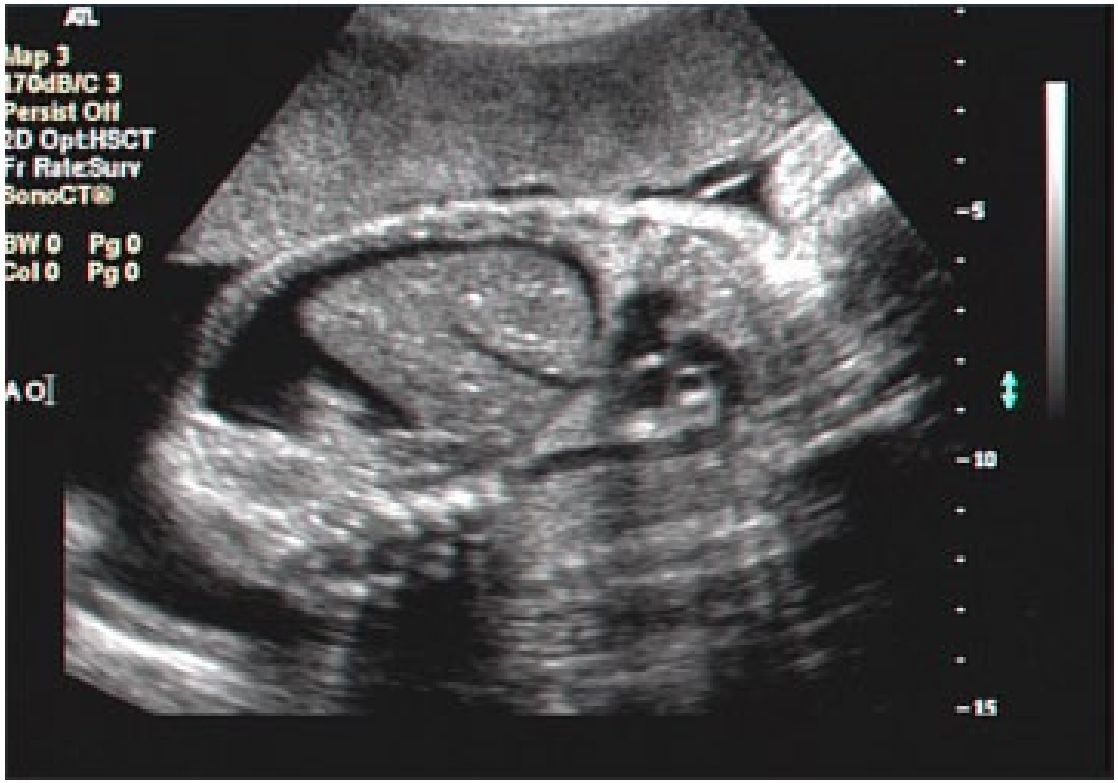
Fetal Ultrasound Findings

Fetal ascites longitudinal view



Courtesy of Svena Julien, MD and Charles Lockwood, MD.

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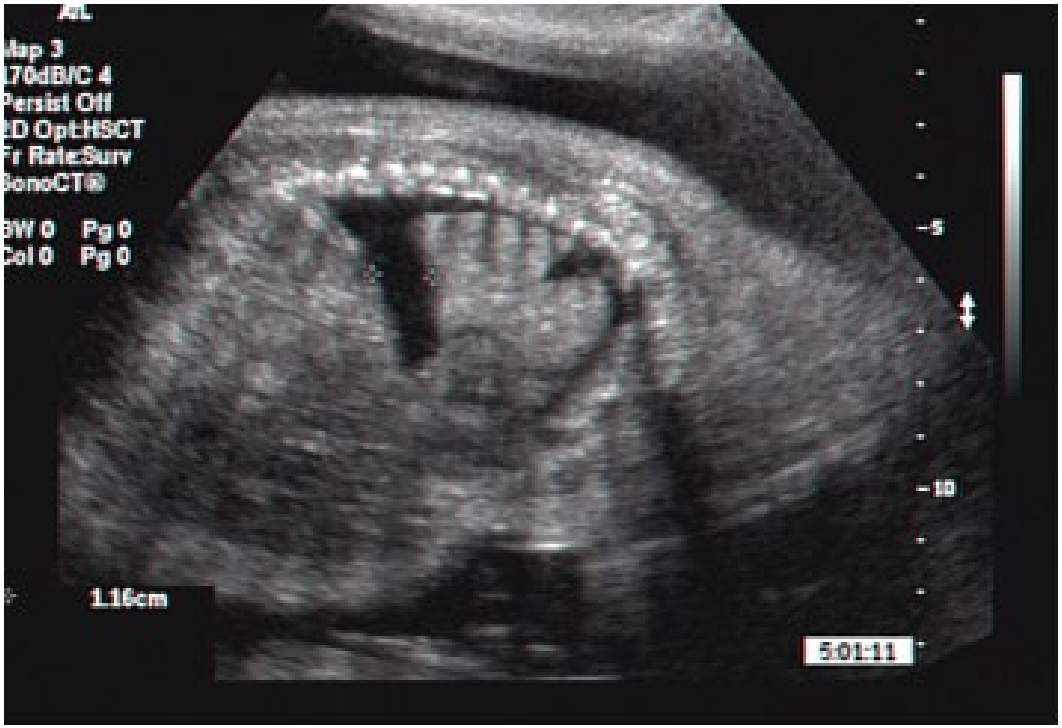
Fetal Ultrasound Findings

Longitudinal view of a unilateral pleural effusion in a fetus with hydrops



Courtesy of Svena Julien, MD and Charles Lockwood, MD.

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FETAL BRAIN MRI

- **Objective:** Role of fetal brain MRI in detecting associated anomalies in fetuses (n = 95) with congenital CMV infection when patient had a normal fetal brain ultrasound
- **Study design**: Multicenter retrospective cohort in Italy (2012 to 2021)
- **Results:**
  - 10.5% (10/95) of structural anomalies were detected exclusively by MRI
  - Type of anomalies detected on MRI only:
    - Malformations of cortical development in 40.0% (4/10) of fetuses
    - Destructive encephalopathy in 20.0% (2/10)
    - Intracranial calcifications in the germinal matrix in 10.0% (1/10)
    - Complex CNS anomalies in 30.0% (3/10)
- **Conclusions: Fetal brain MRI can detect additional anomalies in a proportion of fetuses with congenital CMV infection who have normal fetal brain ultrasound**

Fetal Diagnosis

- Amniocentesis
  - Performed > 21 weeks of gestation and > 6 weeks from maternal infection[a,b]
  - Best option for prenatal diagnosis of fetal congenital CMV infection (specificity > 97%)[a,c]
- Chorionic villous sampling (CVS) [d]

a. SMFM; Hughes BL, et al. Am J Obstet Gynecol. 2016;214:B5-B11; b. Rawlinson WD, et al. Lancet Infect Dis. 2017;17:e177-e188; c. Lazzarotto T, et al. Front Pediatr. 2020;8:13. d. Faure-Bardon V 2021.

Fetal Diagnosis: Amniocentesis

- **Secondary analysis of a randomized** placebo-controlled trial (2012 to 2018)
- **397 pregnant women** diagnosed with **primary CMV infection** before 24 weeks of gestation
- **55 (14%)** underwent **amniocentesis**
- 53 fetuses and neonates had CMV results available, of which **14 (25%) amniocenteses tested positive for CMV**

- CMV infection was confirmed at delivery in:
  - **26% (14/53) of neonates** born to mothers with a **positive amniocentesis**
  - **5% (2/41) of neonates** born to mothers with a **negative amniocentesis**
  - Sensitivity 86% (57-98); Specificity 100% (91,100)
  - PPV 100% (74,100); NPV 95% (83,99)

- Dinsmoor MJ, et al. Am J Obstet Gynecol MFM. 2022;4:100641.

Fetal Diagnosis: Amniocentesis Predictor of Anomalies

- 104 fetuses with congenital CMV (PCR confirmed)

- **18.3%** of cases **(19/104)** had **anomalies** detected at **follow-up ultrasound** or **fetal MRI**
  - A high **CMV viral load** in AF **(≥ 100,000 copies/mL)** was the only independent **predictor** for **anomalies** occurrence, **OR: 3.12** (95% CI: 1.0, 9.4) [a]

- Mean **AF CMV viral load** was significantly **higher in fetuses with additional anomalies** (3,346,634) vs to those without (761,934) (*P* < .001)[b]
  - **CMV viral load** independent predictor of **additional anomalies → OR: 1.07** (95% CI: 1.01, 1.11)[b]
  - **Optimal cut-off of CMV viral load in AF > 1,310,520 copies/mL**
  - **Sensitivity 67% , Specificity 84.3%, positive likelihood ratio 4.2**

- a. Mappa I, et al. J Perinat Med. 2022;51:102-110; b. Mappa I, et al. Fetal Diagn Ther. 2023;50:1-7.

Fetal Diagnosis: CVS

- Chorionic villous sampling (CVS)
  - Positive in 3 and negative in 34 cases
  - CMV-PCR following amniocentesis, performed at a median (range) gestational age of 17.6 (16.7-29.9) weeks, was positive for the 3 which were positive following CVS
  - **In 34 patients with a negative finding following CVS, amniocentesis was negative in 31 and positive in 3**
  - Sensitivity was 50% (95% CI, 19-81%)
  - Specificity was 100% (95% CI, 89-100%)
  - Positive predictive value was 100% (95% CI, 44-100%)
  - Negative predictive value was 91% (95% CI, 77-97%).

Faure-Bardon V 2021

Neonatal Findings

- Jaundice
- Thrombocytopenia
- Petechiae
- Hepatosplenomegaly
- Growth restriction
- Hemolytic anemia
- Mental and motor deficits
- Sensorineural deficits
- Myocarditis
- Hydrops

Screening in Pregnancy: United States

ACOG, SMFM, and CDC → Do not support screening

- Routine serologic screening (universal or targeted) not recommended
- No delineation of special cases that should get testing
- Tests: IgG, IgM, and IgG avidity
- Interpretation of IgG, IgM, and IgG avidity results is challenging in the absence of symptoms
- Laboratory tests cannot predict which developing babies will become infected with CMV or have long-term health problems
- Lack of proven treatment to prevent congenital transmission

- ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention; SMFM, Society for Maternal-Fetal Medicine. a. Committee on Practice Bulletins--Obstetrics. Correction in: Obstet Gynecol. 2016;127:405. Obstet Gynecol. 2015;125:1510-1525; b. Society for Maternal-Fetal Medicine (SMFM). June 2016. Accessed April 12, 2023. https://www.smfm.org/publications/227-diagnosis-and-antenatal-management-of-congenital-cytomegalovirus-infection; c. CDC. September 2018. Accessed April 12, 2023. https://www.cdc.gov/cmv/fact-sheets/parents-pregnant-women.html;

Screening in Pregnancy: Canada

Canadian guidelines→ support screening

- Society of Obstetricians and Gynaecologists of Canada
- Pregnant patients with mononucleosis-like illness, undifferentiated hepatitis
- May OFFER first trimester universal screening in provinces where IgG avidity is available
- Tests: IgG, IgM, and IgG avidity

Boucoiran I, et al. J Obstet Gynaecol Can. 2021;43:893-908

Screening in Pregnancy: International

Universal CMV serological screening is offered

- In some locations in France and Italy
- In some countries like Belgium and Israel
  - Note: Between 2010 and 2020, 95% of pregnant women from Jerusalem were tested even though Israeli guidelines recommend against routine CMV serology testing*

*Unless a CMV infection is suspected.

a. Beaudoin ML, et al. Eur J Obstet Gynecol Reprod Biol. 2021;258:409-413; b. Ben Shoham A, et al. Isr J Health Policy Res. 202325;12:16; c. Ministry of Health. Testing for detection of CMV infection in pregnant women; 2011. Available at: https://www.gov.il/he/Departments/policies/mk25-2011. Accessed May 18, 2023.

Screening in Pregnancy: Targeted

- Ultrasound abnormalities of the fetus
  - Echogenic bowel, fetal growth restriction, microcephaly, ventriculomegaly
- Influenza-like illness in patient
  - Fever, lymphadenopathy
- Mononucleosis-like syndrome
  - Rule out EBV
- Unexplained transaminitis, thrombocytopenia, rash, etc.
- CMV exposure
  - Pregnant woman having an exposure to a child who is going to daycare or school, occupational exposures in daycare or healthcare workers

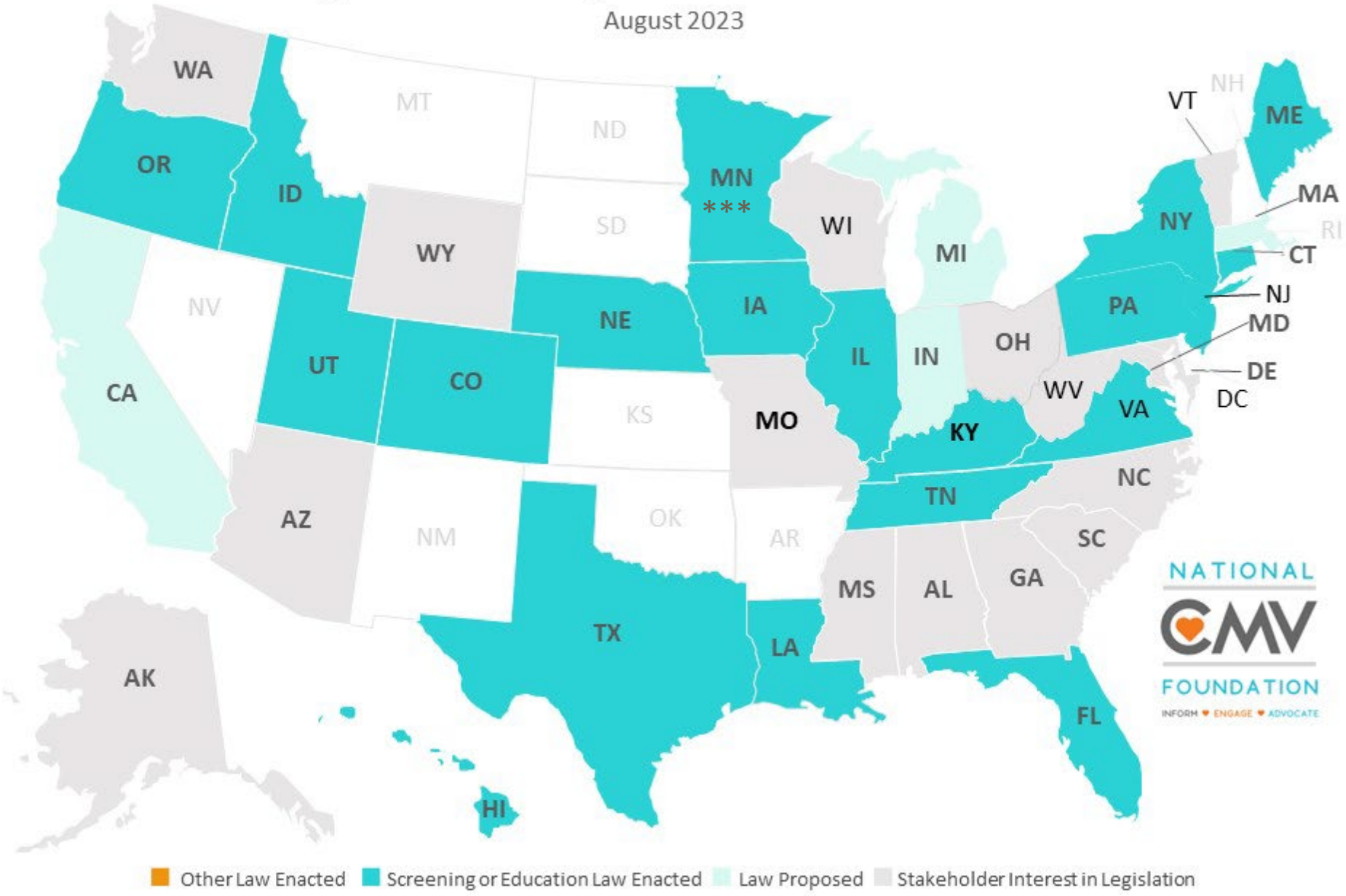
a. Expert opinion; b. Rodrigues S, et al. Rev Bras Ginecol Obstet. 2016;38:196-200; c. Cavoretto PI, et al. Diagnostics (Basel). 2020;10:542; d. Imafuku H, et al. Sci Rep. 2020;10:19706; e. Geraili Z, et al. Caspian J Intern Med. 2018;9:211-219; f. Boucoiran I, et al. J Obstet Gynaecol Can. 2021;43:893-908; g. Jhaveri TA, et al. Open Forum Infect Dis. 2022;9:ofac316; h. Gupta P, et al. Am J Case Rep. 2014;15:447-449

Infant Screening

- Minnesota is FIRST state to enact universal newborn CMV screening (June 2021)
- Connecticut is set to become SECOND state to enact universal screening (2025)
- 8 states require both education of pregnant women and targeted newborn screening
  - Illinois, Iowa, Kentucky, Maine, New York, Pennsylvania, Texas, and Utah
  - Illinois requires that a CMV test be offered to the parents of every child who fails the newborn hearing screening
- 9 states have legislation requiring CMV screening of babies who do not pass their newborn hearing screening
  - Connecticut, Florida, Iowa, Kentucky, Louisiana, New York, Texas, Utah, and Virginia
- New Jersey law requires CMV newborn screening to be implemented when approved for inclusion in the RUSP (Recommended Uniform Screening Panel)
- Total of 20 states have passed CMV legislation

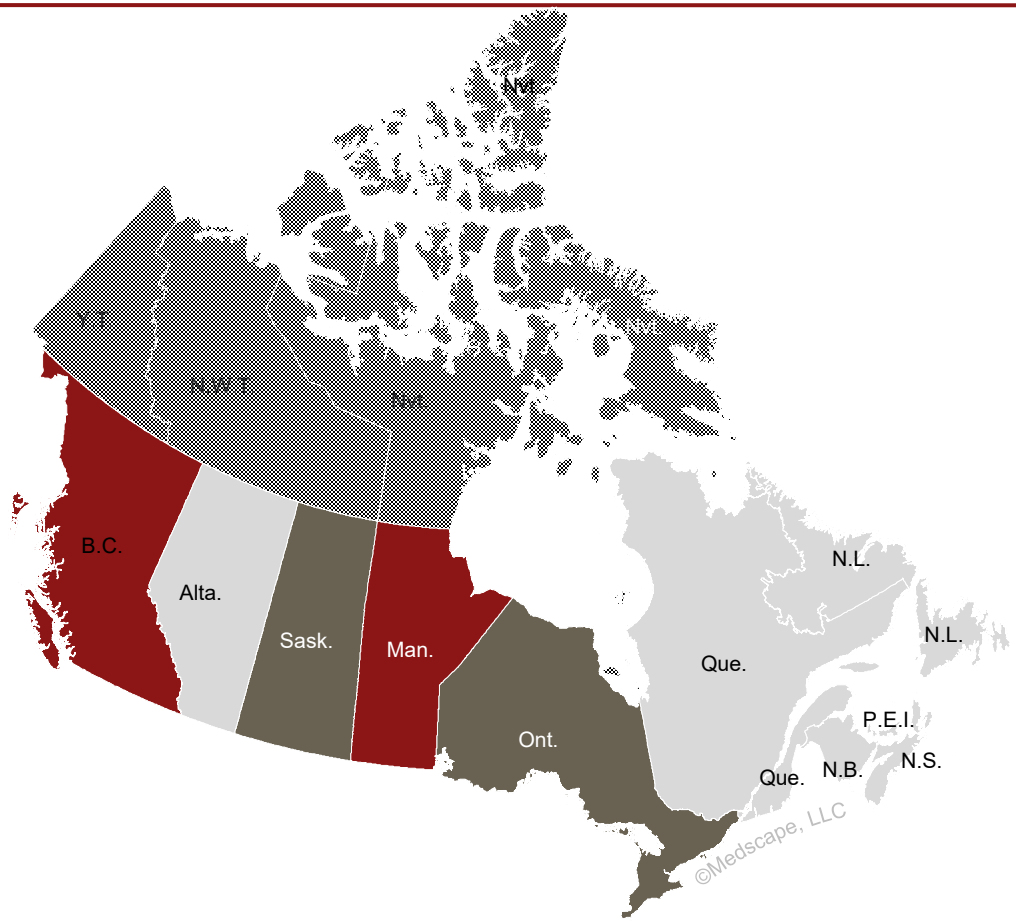
Congenital CMV Legislation in the United States

August 2023



Other Law Enacted | Screening or Education Law Enacted | Law Proposed | Stakeholder Interest in Legislation

Congenital CMV Policies in Canada



No province-wide screening

Targeted screening

Universal screening

No data

CMV Canada. Accessed April 12, 2023. https://cmvcanada.com/get-involved/

Infant Screening: Targeted versus Universal

- **7 Medical Centers in US, from 2007-2012**
- **99,945 infants** screened for hearing impairment and congenital CMV (hearing-targeted approach)
  - Only identified 57% of infected infants
- **Newborn hearing screen missed 43% of the infants with CMV-related SNHL** in the neonatal period and **CMV-infected infants who are at risk for late-onset SNHL**

Fowler KB, et al. Pediatrics. 2017;139:e20162128.

Infant Screening: Targeted versus Universal

- **Management of Existing Sequelae**
  - Hearing loss
  - Epilepsy
  - Cerebral palsy
  - Feeding issues
  - Antiviral
- **Monitoring for New Sequelae**
  - Hearing loss
  - Developmental delays
  - Feeding issues
  - Autism
  - Retinal scarring
- **Early Intervention**
  - Hearing aids/ cochlear implants
  - PT/OT/Speech
  - ASL
  - Bracing
  - Vestibular PT

Infant Screening: Targeted versus Universal

- **Targeted**
  - Detects **7% of all babies with CMV**[a] , **some** never develop long term complications
  - Detects **57% of babies with CMV-related hearing loss** in infancy[a]
    - **Misses 43%** babies with symptomatic CMV
  - **Lower cost** compared with searching for all etiologies[b,c]
    - Easier testing burden hospitals/labs (more feasible)
- **Universal**
  - Detects **all babies with congenital CMV**[e],most will never develop long-term complications (80%)
  - Detects **all babies with CMV-related hearing loss** in infancy[a,e]
  - **More costly** than targeted screening[b]; large number of test handling and higher cost
  - Unknown long-term cost effectiveness[d]

- a. Fowler KB, et al. Pediatrics. 2017;139:e20162128; b. Gantt S, et al. JAMA Pediatr. 2016;170:1173-1180; c. Expert opinion, Mark Schleiss, MD; d. Grosse SD, et al. Semin Perinatol. 2021;45:151393; e. Chiereghin A, et al. Front Pediatr. 2022;10:909646.

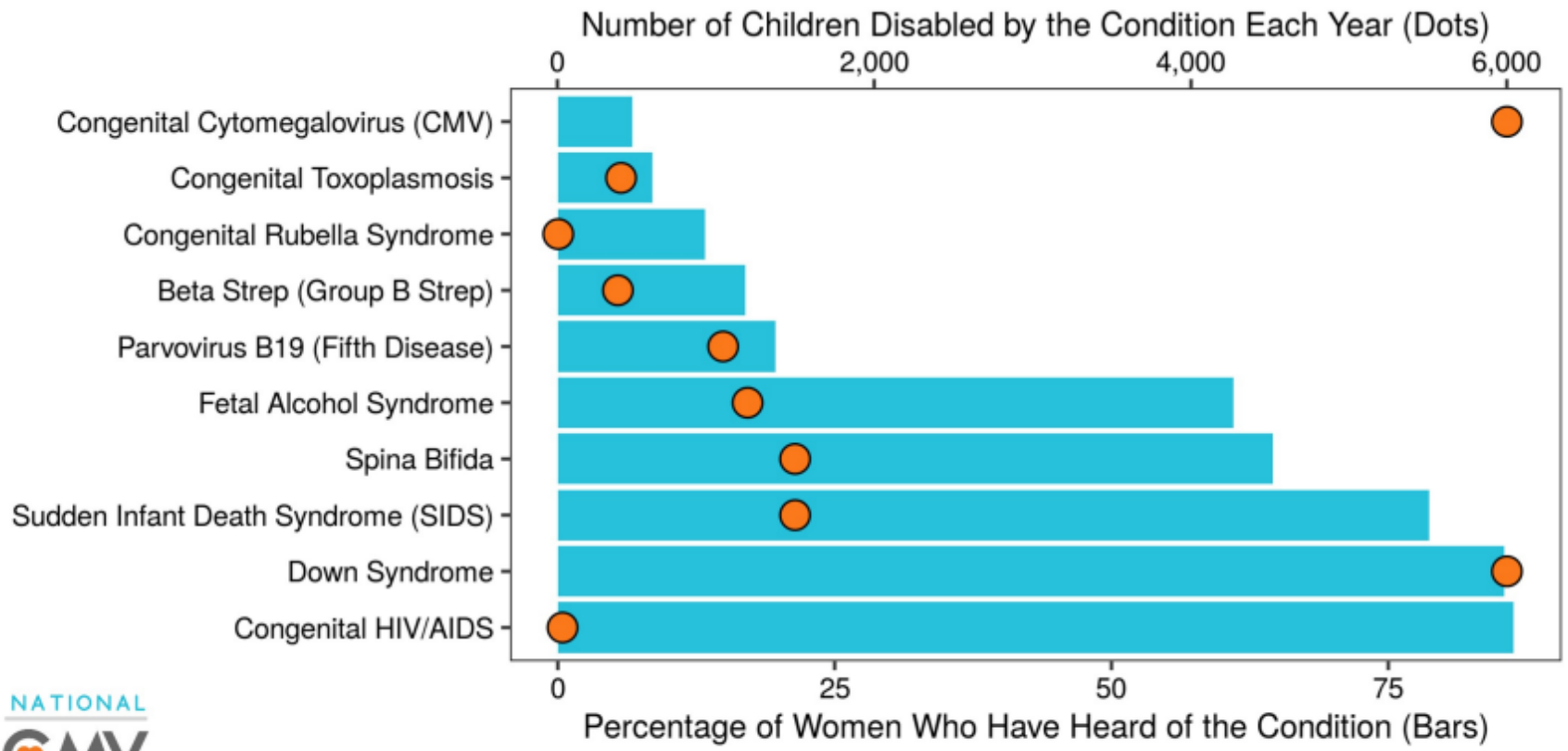
Public Knowledge

- Only 9% of women are aware of CMV
  - 15% to > 20% in some specific groups of women

- 91% of women DO NOT know about CMV
  - <9% know about the steps to take to reduce the chance of acquiring a CMV infection during pregnancy and passing it on to their unborn baby

Doutre SM, et al. J Early Hear Detect Interv. 2016;1:39-48; Tastad KJ, et al. PLoS One. 2019;14:e0221725.

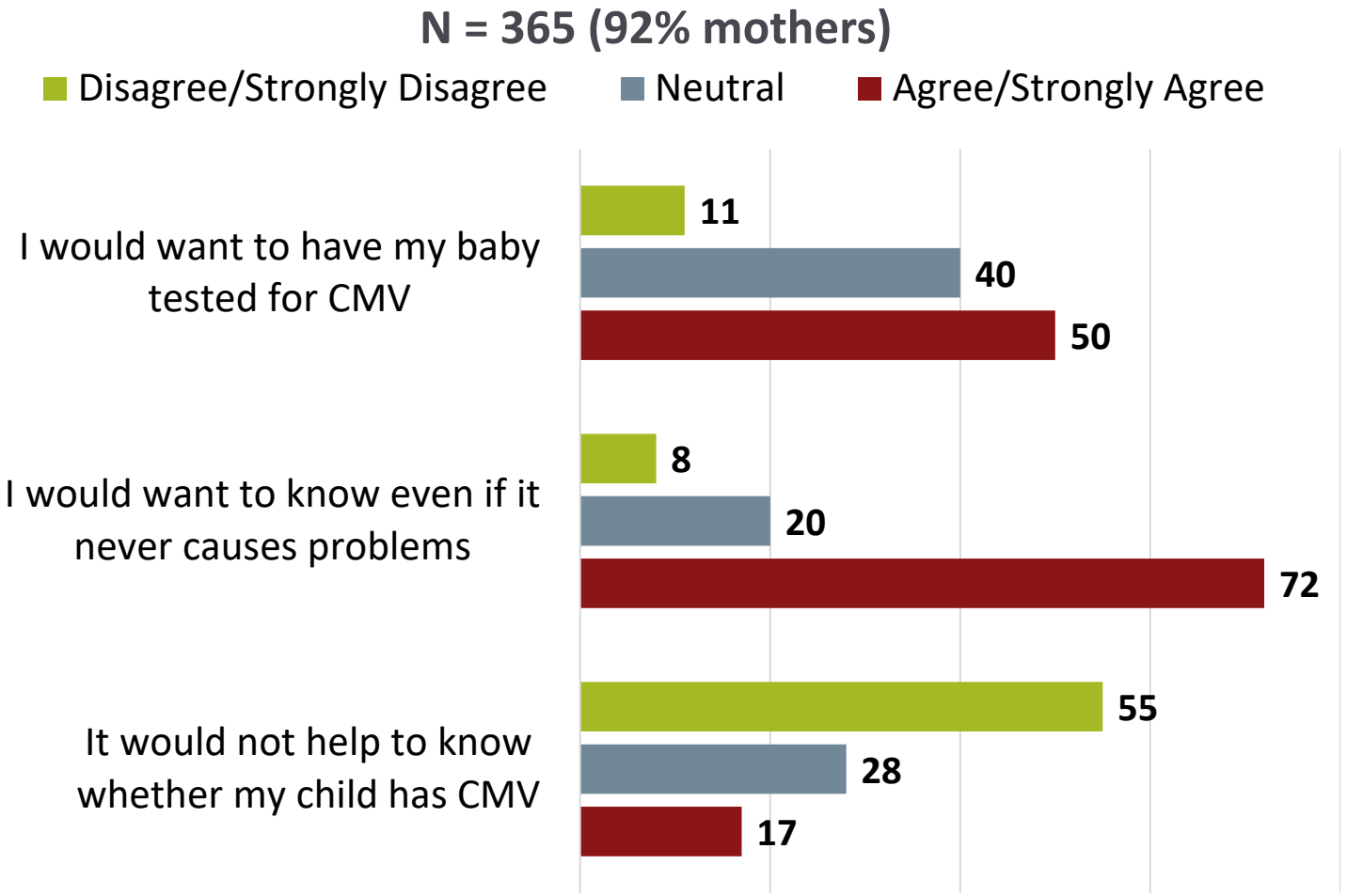
Public Knowledge



NATIONAL CMV FOUNDATION
INFORM ♥ ENGAGE ♥ ADVOCATE

Based on US data from Doutré SM *et al.* (2016) Losing Ground: Awareness of Congenital Cytomegalovirus in the United States. *Journal of Early Hearing Detection and Intervention* 1:39-48. Chart by Artful Analytics, LLC (@_sethdobson). For more information, visit nationalcmv.org.

Knowledge: Parents/Caregivers Would Want to Know if Their Child Had Congenital CMV



Diener ML, et al. J Pediatr. 2020;218:151-156.e2; b. Cannon MJ, et al. Int J Neonatal Screen. 2021;7:80

Prevention/Education Strategies

- **Prevention**
  - Avoid sharing food, drinks, utensils, straws, or toothbrushes
  - Washing your hands frequently, especially after changing a diaper or wiping a child's nasal secretions or saliva
  - Avoiding contact with saliva when kissing children
  - Avoid placing children items (pacifiers, toys) in mouth

- **Education**
  - Medical professionals
  - Obstetric (OBGYN, FP, Midwives, NP), preconception, REI (infertility) health care settings
    - Similar to STI, toxoplasma, listeria counseling, etc.
  - National level
  - Public health forefront

Prevention Strategy Studies

- Mixed interventional and observational controlled study (N=646)
- Seronegative patients at 11 to 12 weeks of gestation (at risk for CMV)
  - Intervention group- educated about hand hygiene and prospectively tested for until delivery (N=331)
  - Control group- not tested for and not informed about CMV during pregnancy (N=315)
    - Serum sample stored at time of fetal aneuploidy screening
- Primary outcome was CMV seroconversion

- Seroconversion in 1.2% of those who received hygiene information
- Seroconversion occurred in 7.6% of patients enrolled at delivery
  - $P < 0.001$ (delta = 6.4%; 95% CI 3.2-9.6)

- 3/331 newborns with congenital CMV in intervention group
- 8/315 newborns with congenital CMV in comparison group
  - 1 with cerebral ultrasound abnormalities at birth

Revello MG 2015

Prevention Strategies: Systematic Review

- Evaluated 7 studies pertaining to preventative hygiene-based interventions in pregnancy for their impact on knowledge about CMV prevention, the uptake of preventative behaviors or the acquisition of CMV in pregnancy

- Demonstrated preventative measures are acceptable to pregnant women
- Measures impact their behavior
- Strategies have the potential to reduce CMV in pregnancy

- Limitations: sample size, nonrandomized trial design and interventions that are beyond routine clinical practice

Barber V 2020

CMV Management in Pregnancy: United States

- ACOG
  - No therapies are recommended to prevent CMV transmission from mother to fetus
- SMFM
  - Antenatal treatment with ganciclovir or valacyclovir not recommended
  - Any antenatal therapy, either with antivirals or CMV hyperimmune globulin, should only be offered as part of a research protocol

Committee on Practice Bulletins--Obstetrics. Correction in: Obstet Gynecol. 2016;127:405. Obstet Gynecol. 2015;125:1510-1525; Society for Maternal-Fetal Medicine (SMFM). June 2016. Accessed April 12, 2023. https://www.smfm.org/publications/227-diagnosis-and-antenatal-management-of-congenital-cytomegalovirus-infection

CMV Management in Pregnancy: Canada

- SOGC
  - In the case of documented primary CMV infection in the first trimester, early treatment with valacyclovir can be considered
  - CMV hyperimmune globulin should not be used to prevent congenital CMV if a primary CMV infection is diagnosed during pregnancy
  - For established congenital CMV infections during pregnancy, decisions concerning treatment options should be made in a shared process involving patients and experienced teams

Boucoiran I, et al. J Obstet Gynaecol Can. 2021;43:893-908

Antiviral Therapy for Primary Maternal CMV Infection: Prevention of Fetal Infection

Study	Study Design	Treatment/Analysis	Results
Shahar-Nissan, 2020[a]	▪ Randomized, double-blind, placebo-controlled trial ▪ Pregnant women with primary CMV infection	▪ Valacyclovir 4 g twice daily (total 8 g per day) or placebo in the first trimester until amniocentesis (21 to 22 weeks)	▪ 5 of 45 (11%) amniocenteses in valacyclovir group were CMV positive vs 14 of 47 (30%) in placebo ▪ **OR: 0.29** (95% CI: 0.09, 0.90); ***P* = .027**
Faure-Bardon, 2021[b]	▪ Case-control longitudinal cohort ▪ Women screened between 11 and 14 weeks of pregnancy for primary maternal infection	▪ Valacyclovir 4 g twice daily (total 8 g per day) or untreated women ▪ Initiated at a median of 12.7 weeks; duration: median of 35 weeks	▪ Fetal infection lower in treated group (N = 65) vs controls (N = 65) ▪ **OR: 0.318** (95% CI: 0.12, 0.84); ***P* = .021**
Egloff, 2023[c]	▪ Retrospective, multicenter study ▪ Pregnant women with primary CMV infection	▪ Valacyclovir (total 8 g per day) or untreated women	▪ Valacyclovir reduced the rate of maternal-fetal CMV transmission ▪ **OR: 0.40** (95% CI: 0.18, 0.90); ***P* = .029**
D'Antonio, 2023[d]	▪ Systematic review and meta-analysis of prenatal valacyclovir therapy data in pregnancies with maternal CMV infection	▪ Three studies (325 fetuses) assessed pregnancies treated with valacyclovir vs not treated	▪ Lower risk of vertical transmission after valacyclovir (**OR: 0.37** [95% CI: 0.21, 0.64]; ***P* < .001**) especially following first trimester maternal infection (3 studies; 184 fetuses; **OR: 0.34** [95% CI: 0.15, 0.74]; ***P* = .001)**

Antiviral Therapy for Primary Maternal CMV Infection: IPD Meta-Analysis

- 3 studies (n=527 women)
- 8 grams/day of oral valacyclovir
- Valacyclovir reduced the vertical transmission rate of CMV (aOR, 0.34; 95% confidence interval, 0.18-0.61) for both periconceptional period and first-trimester infections
  - Periconceptional period (aOR, 0.34; 95% confidence interval, 0.12-0.96)
  - First-trimester (aOR, 0.35; 95% confidence interval, 0.16-0.76) infections
- Valacyclovir reduced the rate of neonatal infection (aOR, 0.30; 95% confidence interval, 0.19-0.47), in both periconceptional period and first-trimester infections

Chatzakis 2023

Cost Efficacy of Antiviral Treatment: Maternal Primary Infection in Pregnancy

- **Population-based screening with serologic testing at 7 weeks and 12 weeks of gestation**
  - IgG, IgM, and IgG avidity (for cases of IgG and IgM positivity)
- **Treatment with or without valacyclovir**
- **Secondary prevention with valacyclovir had significant effect on maternal-fetal CMV transmission and clinical outcomes in newborns, with a 58% decrease of severely infected newborns for a 3.5% additional total costs**

Seror V, et al. BJOG. 2022;129:301-312.

Antiviral Treatment: Maternal Therapy for CMV Infected Fetus In-Utero

- Study Design
  - Multicenter, open-label, phase 2 trial
  - Compared with historical cohort
  - Maternal oral administration of valacyclovir 2 grams every 6 hours
  - MODERATELY CMV-infected fetuses
    - Pregnancies with severe brain anomalies excluded
- Results
  - 43 pregnancies treated from a median of 25.9-week gestation until delivery; total treatment time was median of 89 days
  - Asymptomatic neonates compared with a historical cohort: **82% vs 43%**
  - **34 asymptomatic neonates at 12 months of life**
  - Fetal blood VL decreased ($P = .01$) and platelet counts increased ($P < .001$) between treatment initiation and birth after treatment completion
- Study Limitations
  - Study design is not randomized AND small number of treated women

Leruez-Ville M, et al. Am J Obstet Gynecol. 2016;215:462.e1-462.e10.

Antiviral Treatment: Maternal Tx for CMV Infected Fetus Systematic Review and Meta-Analysis

Outcome	Fetuses Affected VCV vs no VCV (n/N)	Pooled OR (95% CI); *P* value
Symptomatic infection	11/65 vs 20/67	**0.46** (0.18, 1.14); **.092**
Asymptomatic infection	54/65 vs 47/67	**2.98** (1.18, 7.55); **.021**
Perinatal death	1/66 vs 1/71	**1.15** (0.07, 19.60); **.923**
Termination of pregnancy	8/66 vs 18/71	**0.40** (0.14, 1.15); **.089**
Fetal anomaly at follow-up or at birth	11/73 vs 16/91	**1.04** (0.42, 2.58); **.934**
Severe symptoms	0/58 vs 0/57	**0.91** (0.02, 46.91); **.965**
Mild to moderate symptoms	4/58 vs 0/57	**4.62** (0.50, 42.97); **.179**
Neurological symptoms	2/58 vs 0/53	**2.72** (0.27, 27.41); **.395**
Hearing symptoms	4/58 vs 5/53	**0.93** (0.02, 35.14); **.970**
Visual symptoms	0/58 vs 0/53	**0.91** (0.02, 46.91); **.965**
Other symptoms	2/58 vs 1/53	**1.64** (0.13, 21.10); **.706**

D'Antonio F, et al. Ultrasound Obstet Gynecol. 2023;61:436-444

Antiviral Treatment for Symptomatic Infant

Study	Randomized, Controlled Trials	Treatment/Analysis	Results
Kimberlin, 2003	▪ Neonates with symptomatic CMV disease involving CNS	▪ 6 weeks of IV ganciclovir* (6 mg/kg per dose every 12 hours) or no treatment ▪ Follow-up: 6 months ▪ BSER audiometric examination	▪ **21 of 25 (84%) ganciclovir recipients had improved hearing or maintained normal hearing vs 10 of 17 (59%) controls (*P* = .06)** ▪ None (0%) had worsening in hearing vs 7 (41%) (*P* < .01), respectively
Oliver, 2009	▪ Infants with symptomatic congenital CMV involving CNS	▪ 6 weeks of IV ganciclovir (6 mg/kg per dose every 12 hours) or no treatment ▪ Denver Developmental Tests at 6 weeks, 6 months, and 12 months	▪ **Average number of delays in ganciclovir recipients vs "no treatment"** • At 6 months, 4.46 and 7.51 (*P* = .02) • At 12 months, 10.06 and 17.14 (*P* = .007)
Kimberlin, 2015	▪ Neonates with symptomatic congenital CMV disease with or without CNS involvement	▪ 6 months of oral valganciclovir* therapy vs 6 weeks of therapy (16 mg/kg, twice daily) ▪ Follow-up: 6, 12, and 24 months ▪ "Best-ear" and total hearing assessed	▪ **At 6 months: "Best-ear" hearing similar in 6-month vs 6-week group** (improvement: 2 vs 3 participants; no change: 36 vs 37; worsening: 5 vs 3; *P* = 0.41) ▪ At 12 months: Total-ear hearing improved or normal in 6-month vs 6-week group (73% vs 57%, *P* = 0.01) ▪ At 24 months: Benefit in total-hearing maintained in the 6-month group

Vaccines

- **Institute of Medicine**
  - CMV vaccine is the top priority for 21st century in the United States
- CMV vaccine research ongoing since 1970s
  - Many candidates from many NIH- and industry-sponsored trials evaluated
  - None successful thus far
- Many CMV vaccine candidates, including mRNA platforms under evaluation currently
  - Phase 1 and 2 clinical trials with encouraging results; phase 3 trials underway
  - No licensed CMV vaccine available yet

Institute of Medicine (US); Stratton KR, et al. APPENDIX 4: Cytomegalovirus. In: Institute of Medicine (US); Stratton KR, et al, eds. Vaccines for the 21st Century: A Tool for Decisionmaking. National Academies Press (US); 2000; Arvin AM, et al. Clin Infect Dis. 2004;39:233-9; Esposito S, et al. Vaccines (Basel). 2021;9:523; Scarpini S, et al. Vaccines (Basel). 2021;9:551.

Vaccines Trials: Underway in United States

- Phase 2 study of V160 2-dose and 3-dose regimens in healthy CMV seronegative females (V160-002)[a,b]
- Phase 3 study to evaluate the efficacy, safety, and immunogenicity of mRNA-1647 CMV vaccine in women of childbearing age[c,d]
- A phase 1/2, first-time-in-human, dose-escalation study to assess safety, reactogenicity, and immunogenicity of a candidate CMV vaccine comprising recombinant protein and adjuvant in healthy adults[e]

a. ClinicalTrials.gov. Accessed March 31, 2023. https://clinicaltrials.gov/ct2/show/NCT03486834; b. Le-Trilling VTK, et al. NPJ Vaccines. 2023;8:8; c. ClinicalTrials.gov. Accessed March 31, 2023. https://clinicaltrials.gov/ct2/show/NCT05085366; d. Kadambari S, et al. Pediatr Infect Dis J. 2023;42:e45-e47; c. ClinicalTrials.gov. Accessed March 31, 2023. https://clinicaltrials.gov/ct2/show/NCT05089630

Counseling My Patient with Infected Fetus

- Studies show a increased risk of possible preterm delivery, fetal growth restriction, hearing loss, other CNS problems, neurodevelopmental complications, cerebral palsy, seizures, and fetal demise/neonatal death.
- In ultrasound-affected fetuses, we would expect a greater risk for symptomatic infant with long-term sequelae.
- Now that we have ultrasound, MRI, and amniotic fluid viral load information, let's discuss your goals for the pregnancy and for your family.
- Although antiviral therapy is not yet standard of care for management in pregnancy, there are some studies that demonstrate possible benefit of antiviral therapy administered to mother to decrease fetal transmission and to fetus to decrease symptomatic disease, and to infant to decrease disease severity.
- Multidisciplinary team: Pediatric ID, Neonatology, Maternal-Fetal Medicine, OB, in addition to postnatal subspecialty teams.

Summary

- Education and prevention strategies must be increased
- Vaccine development is still underway and in our horizon
- Antiviral therapy during pregnancy and in infants may offer benefit
- Is it time for UNIVERSAL INFANT screening in all states?
- Is it time for more expanded screening of pregnant and preconception patients?

- ***"Together, we can reduce the number of babies born with Congenital CMV," identify those who are at risk for long term complications, and optimally/timely treat those that have symptomatic disease… for our patients and their families! (NCHAM)***

Thank you!

Cell: 209-480-2040

Resources

- CDC
  - https://www.cdc.gov/cmv/index.html
- National CMV Foundation
  - https://www.nationalcmv.org/
- National Center for Hearing Assessment and Management https://www.infanthearing.org/cmv/index.html