Vertical Transmission of Primary Cytomegalovirus Virus (CMV) – Recommendations for Prevention and Improved Fetal Outcomes

By

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Abstract

Cytomegalovirus (CMV) is the most common congenital viral infection in the United States, causing more long-term developmental problems and early childhood deaths than Downs Syndrome, fetal alcohol syndrome, anencephaly, HIV/AIDS, haemophilus influenzae, and congenital rubella. CMV transmission to the fetus can result in numerous developmental and central nervous system morbidities. The direct annual cost of congenital CMV is estimated at approximately $1-$2 billion per year. Despite the fact that almost all adults will contract CMV at some point, infection with the virus is preventable with simple hygiene techniques. While many national organizations have publicized recommendations regarding the impact and prevention of congenital CMV, the disease remains a persistent problem leading to the conclusion that the message is not being heard and acted upon. Additionally, current recommendations may not be sufficient to address this issue. For example proactive screening for the identification of high risk pregnancies is not currently recommended.

Based on a literature review of the natural history and pathogenesis of CMV, its prevailing disease burden, and the prevention of congenital CMV, the following programmatic recommendations seem feasible:

- Develop programs for educating the affected population as well as ancillary populations
- Develop more comprehensive campaigns designed to better promote congenital CMV-preventative behaviors
• Develop selective screening programs for the early identification of at-risk individuals or those infected with a high risk of fetal transmission.

It is anticipated that an efficacious vaccine will not be developed for some time despite ongoing efforts. As such, these recommendations represent more immediate preventative steps that can be adopted in lieu of an approved vaccine and can be used with continued vigilance once a vaccine has been made available to further strengthen ones protection against viral infection.
Introduction

The objective of this paper is to present current information regarding cytomegalovirus (CMV), the impact of vertical transmission of CMV to the fetus during pregnancy, as well as the ways in which this transmission could be prevented.

As part of the process in producing this paper and recommendations made therein, multiple peer-reviewed research articles and abstracts were reviewed and information derived from these sources is provided in the following pages. These articles address the history and epidemiology of CMV, the prevalence of CMV infection in pregnant women, the occurrence of vertical CMV transmission, the health effects of CMV on the developing fetus, the types of preventative programs and recommendations currently in place, potential treatment modalities, the evidence of effectiveness of preventative recommendations, and the implications for future research.

Recommendations regarding future preventative guidelines have been developed based on this literature review and are provided as a conclusion to this document.

Background and Epidemiology

Overview of Cytomegalovirus
Cytomegalovirus (CMV) is a double-stranded DNA virus of the herpesviridae family which includes herpes simplex virus types 1 and 2, varicella-zoster virus, β herpesviruses, cytomegalovirus, human herpesviruses 6 - 8, γ herpesviruses, and Epstein-Barr virus. CMV is transmitted during contact with individuals actively excreting virus via infected blood, saliva, urine, breast milk and other bodily secretions, organ transplantation, and transplacentally. The incubation period for CMV infection is approximately 28-60 days. Upon infection, the virus triggers an antibody response marked by increased Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies followed by residual IgG. While mononucleosis-type symptoms are sometimes seen in primary infections, asymptomatic responses are usual. After recovery from initial infection, CMV remains latent in host cells with recurrent infection possible after viral reactivation.\(^\text{1,2}\) It is estimated that approximately 50-80% of all adults in the United States are infected with CMV by age 40.\(^\text{3}\) Differences between developing and western countries in prevailing age of infection have been noted. For example, most infections are acquired in childhood in developing countries while initial infections are more common in adulthood in western countries. In the United States the prevalence of CMV increases along with the age of the population. Various, genetically different, strains of CMV are known to exist and exhibit differences in virulence.\(^\text{4}\) Though rare, re-infection with a new strain of the virus is possible resulting in CMV that is novel to the host’s immune system.

\(^\text{1,2}\)
Based on a 2007 study conducted by Colugnati et al to determine the incidence of CMV among populations, the incidence of infection among the United States population (ages 12-49) was 1.6 infections per 100 susceptible persons per year. When this statistic was combined with the basic reproductive rate, the authors found that the average infected person transmits CMV to nearly two susceptible persons in his/her lifetime. Additionally, the authors noted that the incidence of infection was significantly higher among non-Hispanic blacks and Mexican Americans (than among non-Hispanic whites) and lower income households.5,6

**CMV Risk Factors**

While almost all adults will be infected with CMV at some point in their lives, certain subgroups are more susceptible to the disease. For example, those who are immunocompromised due to an active disease state (AIDS, autoimmune disease, etc.) or due to iatrogenic causes (receiving large doses of glucocorticosteroids, those undergoing chemotherapy or radiotherapy, etc.) are at greater risk. Additionally, higher risk is associated with those having multiple sex partners and individuals who attend or work at daycare centers or otherwise have frequent close contact with children.4

**Current Trends in CMV Detection and Treatment**

As with most viral infection, CMV can be identified in the human body by the presence of viral-specific antibodies termed Immunoglobulin G (IgG) and Immunoglobulin M (IgM). The presence of IgM antibodies is generally a marker
of acute infection. These antibodies are detectable for approximately 3–4 months, and may persist for up to a year or longer in certain situations. IgG is produced later (though early on) in infection and CMV-specific IgG remains detectable throughout life after primary infection. IgG is considered useful as a biological determinant of past or present CMV virus in infected individuals.\(^5\) In addition, determination of IgG avidity can help the clinician ascertain whether the infection is primary, recurrent, or re-infection. Low avidity antibodies typically become apparent within one month of infection, gradually increasing in avidity as time goes on. In general terms, low avidity antibodies are an indicator of primary/new infection whereas detection of high avidity antibodies indicates either reactivation or distant infection.\(^7,8\)

Historically, and in the adult patient with primary CMV infection, treatment is unnecessary because the virus has a minimal impact on daily life. In fact, most adults, unless immunocompromised in some way, experience little to no direct reaction as a result of the infection. When symptomatic cases are identified and action is needed to prevent more serious consequences, antiviral medications are used for the treatment and management of CMV, with ganciclovir widely considered the drug of choice.\(^5\)

Though researchers are actively pursuing effective and safe vaccines for the prevention of CMV, there currently is no licensed product available. It is thought that an efficacious vaccine will eventually be available, but that the necessary developmental process will take several years. With this thought in mind, non-
pharmacologic interventions for the prevention of CMV/congenital CMV will be presented later in this paper.

**Congenital CMV**

**Epidemiology of Congenital CMV**

While CMV infection in healthy adults is rarely symptomatic, it can be devastating to an unborn fetus if passed vertically from the infected mother.

CMV is the most common congenital viral infection in the United States, causing more long-term developmental problems and early childhood deaths than Down Syndrome, fetal alcohol syndrome, anencephaly, HIV/AIDS, haemophilus influenzae, and congenital rubella. It is estimated that congenital CMV affects approximately 1 child in 150 births in the United States and approximately 1 in 750 births result in a child that is born with or develops significant problems due to infection.\(^9\)\(^{10}\) CMV transmission to the fetus can result in significant morbidities including jaundice, thrombocytopenia, petechiae, hepatosplenomegaly, growth restriction, non-immune hydrops, hearing and/or vision loss, and long-term mental disability, among others.\(^1\)\(^{10}\) Many developmental deficiencies have been thought to be attributable to the viral affect on the placenta itself resulting in placental insufficiency as opposed to direct fetal infection.\(^11\) Approximately 30-50% of women of childbearing age in the United States are susceptible to primary CMV infection and between 1-4% of uninfected women will be infected during pregnancy. Of the 1-4% of women who experience primary infection during
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pregnancy, approximately 33% transmit CMV to their developing fetus. Vertical transmission is not specific to primary infection. A study conducted by Kenneson and Cannon of reported results of systematic fetal screening for CMV found that while the transmission rate for women who experienced primary infection was approximately 32%, a transmission rate of 1.4% was also noted for mothers with recurrent infection during pregnancy. These findings seem to indicate that, while somewhat rare, vertical transmission stemming from recurrent maternal infection could also lead to significant morbidity for the unborn fetus.

Pathophysiology and Vertical Transmission of CMV

The vertical transmission of CMV to the fetus or placental insufficiency due to maternal infection is the most common intrauterine infection associated with congenital defect and is known to be based upon the uterine-placental interface. During the early stages of pregnancy, in anticipation of fetal development, the placenta begins to form a bridge to facilitate fetal support. The result is often referred to as the uterine-placental interface which allows for the more rapid movement of nutrient-rich maternal blood necessary for proper fetal development and also forms the foundation for the early development of fetal passive immunity through the transportation of maternal antibodies. Ironically, this same interface along with the umbilical vein allows cells infected with CMV to enter fetal circulation. In addition, CMV-infected cells can also be shed into amniotic cells and fluid via the placenta and then ingested by the fetus allowing for infection of the developing fetus. In contrast to other commonly transmitted maternal
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disease, CMV viral shedding is measured in months or years, making it possible for infection to be transmitted to the fetus for some time after maternal acquisition. Transmission of the virus can occur at any gestational stage and women with primary infection during later stages may have a higher risk of fetal infection. However, it is speculated that infection during late gestation results in less severe fetal symptoms due to the timing of infection relative to fetal neuronal development. In addition, vertical transmission has been shown to occur due to reactivation of latent infection or maternal re-infection with a viral strain different from primary infection in cases of known positive serology. However, pre-existing maternal antibody protection seems to positively affect fetal outcomes and reduce damage to the fetus. Fowler et al conducted a study of 197 children with congenital CMV infection in which maternal infection was either primary or recurrent. Their findings indicated that antibodies to CMV due to existing latent infection extends at least some protection to the fetus and lessens severity of sequelae of the virus.

Vertical transmission of CMV infection is well documented, though we are still learning about how it affects fetal development and many of the recorded fetal morbidities could be the result of the virus on the development and sustainment of the placenta itself. Infection of placental cells in the early stages of pregnancy could result in improper implantation of the placenta contributing to spontaneous abortion. Placental effects later in gestation could result in the restriction of fetal growth and development. Furthermore, many of the poor mental outcomes of
CMV-infected fetuses may be attributable to fetal hypoxia resulting from this placental pathology.

**Psychosocial and Financial Impacts of Congenital CMV**

While the psychosocial impact of congenital CMV cannot be quantified, it seems clear that this disease has a significant impact on the families of those it affects. Proof of this are the many published stories submitted by the parents of CMV-infected children which are available through organizations like The CMV Action Network and other groups like the Parent to Parent CMV support group sponsored by CMVKids. These first-hand accounts provide a glimpse into the pain and suffering these children and their families endure as well as the frustration of feeling uninformed regarding the existence and risk factors of CMV that often accompanies the pain.

In terms of the financial impact, the direct annual cost of congenital CMV is estimated at approximately $1-$2 billion per year.\(^{19}\) Additionally, given an effective preventative measure for congenital CMV, some studies have estimated a $50,000 per quality adjusted life-year savings.\(^{20}\) Outside of the United States, the financial burden brought about by this disease is just as problematic. For example, Seale et al reported that the cost estimate of 104 congenital CMV single admissions was approximate $294,736 in their study of hospitalization trends for CMV-infected infants and children in Australia.\(^{21}\) Though these estimates were based upon general costs adjusted for relative complexity of patient disease, they
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seem to support the idea that congenital CMV infection is a significant drain of public health resources.

Current Congenital CMV Avoidance Recommendations and Screening

Many organizations have documented recommendations for the prevention of congenital CMV. For example, the CDC recommends that pregnant women avoid contact with the virus found in urine and saliva of young children by following these guidelines:

- Wash your hands often with soap and water for 15-20 seconds, especially after
  - changing diapers
  - feeding a young child
  - wiping a young child’s nose or drool
  - handling children’s toys
- Do not share food, drinks, or eating utensils used by young children
- Do not put a child’s pacifier in your mouth
- Do not share a toothbrush with a young child
- Avoid contact with saliva when kissing a child
- Clean toys, countertops, and other surfaces that come into contact with children’s urine or saliva

The American Congress of Obstetricians and Gynecologists (ACOG) promotes similar steps recommending frequent hand washing, especially after contact with a child who is in day care.
Baylor College of Medicine, via their National Congenital CMV Registry has developed a guide for distribution entitled ‘What Everyone Should Know About CMV’. In this guide, the CDC steps above are advocated for and reinforced. Clearly, these guidelines focus on limiting exposure to CMV via interactions with young children which is a known risk factor for the acquisition of CMV.

Serologic screening for CMV in pregnant women is not currently recommended in the absence of clinical presentation in the mother or suspicious ultrasound findings in the fetus. While CMV screenings are increasingly being performed in some areas with the hope of proactively identifying infection, the difficulty in determining fetal prognosis and the lack of proven treatment induces a sense of hesitation to issue clear guidelines among the various organizations that are known to exert influence among practitioners.

Problems with Recommendations and Reasons for Change

Preventative behavior, as recommended by the CDC and ACOG, revolve around common safe hygiene practices which are relatively simple and easy to adhere to. However, although these recommendation are available to the public via various resources and practitioners are encouraged to provide counseling to expectant mothers regarding infection control, it is clear that this message is either not being heard or is misunderstood. For example, Jeon et al reported that of 643 women surveyed at seven pediatric outpatient facilities located in large US cities, only 22% reported any knowledge of congenital CMV. Additionally, knowledge of CMV ranked last among other birth defects and childhood illnesses included in
the survey. Further, among the 142 women who reported some knowledge of congenital CMV, there was alarming number who recorded inaccurate information regarding the disease as part of their survey response. While the message was clearly not getting out, the saving grace was that of those who reported some knowledge of congenital CMV, 78% correctly indicated that pregnant women could transmit the disease to her developing fetus and 57% correctly reported that this transmission could possibly be avoiding by simple hand washing techniques.25

One possible conclusion that can be drawn from the study above regarding the inadequacies of the education and information received by expectant mothers regarding congenital CMV is that those in the best position to educate them are unaware or misinformed as well. This conclusion is supported by a survey conducted by ACOG among members of its Collaborative Ambulatory Research Network (CARN) which is a nationally representative group of practicing Obstetricians and Gynecologists. This study showed that only 44% of caregivers surveyed provided any form of counseling to their patients regarding CMV preventative measures. Additionally, while approximately 90% of those surveyed reported knowing that hand washing reduces risk of CMV infection, a smaller proportion (57%) were aware that sharing utensils with young children and avoiding children’s salvia (55%) were effective countermeasures as well.26 These statistics seem to support the need for the promotion of simple, non invasive, strategies for the prevention of CMV acquisition and transmission – especially among high risk populations (e.g. those exposed to pre-school aged children). In
addition, it is quite possible that although many people might be exposed to the concepts of good hygiene and the positive effects they may have in terms of viral avoidance, this behavior is not being put into practice. Past research has shown that knowledge is necessary, but not sufficient to foster behavior change. This phenomenon is not unique to health care and some guidance can be drawn from the business literature. For example, it is similar to the concept known as the ‘The Knowing-Doing Gap’ referred to in the implementation of innovations in business settings. The ‘Knowing-Doing Gap’ points to complexity and reinforcement as prime considerations when disseminating information with the expectation of action.\(^2\) With this in mind, any interventions designed to elicit better hygiene among the targeted population must maintain a simple message that is easily understood and maintained by the audience and reinforcement techniques should be included to maximize adherence to the expected behavior change. These range from proven public health techniques, to more formal behavior modification techniques, such as social marketing, which have proven to be effective in public health and medical care.

As noted in the previous section, no current recommendations for CMV screening in pregnant women exist. CMV status, positive or negative, is a prime indicator of the potential for vertical transmission; however, status is often determined by the simple presence or absence of CMV-specific antibodies and, while helpful, this does not provide a timeline for infection. Though the presence of CMV antibodies is a good indicator of CMV infection in the maternal host, it can be misinterpreted in the presence of re infection or viral recurrence. On the other
hand, antibody avidity has been shown to be reliable in identifying primary
infection in pregnant women. The problems with utilizing simple CMV-specific
antibody presence alone as a marker for primary CMV infection in the maternal
host and the value of confirmatory antibody avidity can also be seen in the study
presented by Cavlek et al which lends credence to the use of CMV-specific
antibody avidity as a marker for new onset CMV infection.

**Recommendations and Future Strategies**

Based on the available literature, it seems clear that congenital CMV is a disease
that can be prevented in many cases. While pharmaceutical or vaccine options
remain somewhat unproven, preventative measures are available that could
provide considerable protection to the developing fetus at relatively low cost.
Given the available data regarding the prevention of congenital CMV, its natural
history and pathogenesis, and prevailing disease burden, the following
programmatic recommendations seem feasible:

- Develop programs for educating the affected population as well as
  ancillary populations
- Develop more comprehensive campaigns designed to better promote
  CMV-preventative behaviors
- Develop selective screening programs for the early identification of at-risk
  individuals or those infected with a high risk of fetal transmission
These recommendations represent more immediate preventative steps that can be adopted in lieu of an approved vaccine and can be used with continued vigilance once a vaccine has been made available to further strengthen one’s protection against viral infection. Each of these recommendations are discussed in greater detail below.

**Developing Education Programs**

As is commonly said, ‘Knowledge is Power’. As discussed previously, the Jeon et al study showed somewhat poor knowledge of congenital CMV among a relatively representative sample of women of child-bearing potential. Equally disturbing is the seeming lack of knowledge among caregivers, as noted in the ACOG study, who historically serve as the primary educators of the targeted population. CMV is a disease without much fanfare and few consequences for most affected populations – thus CMV prevention is often an afterthought if considered at all. Without prior knowledge of this disease, many individuals will unknowingly put their developing fetuses at risk. This is especially true for more at risk populations such as those who are serologically CMV negative but who have frequent contact with young children or bodily secretions.

Developing educational programs is a relatively inexpensive and non invasive means of informing the public of the risk factors involved in congenital CMV infections and the means in which this infection can be transferred to the developing fetus. These educational programs can be marketed to all women of child-bearing potential regardless of known serostatus, to applicable healthcare
providers, as well as to ancillary locations such as daycares and churches. Key to this effort will be the recruitment and development of collaborative partnerships with national stakeholders such as The Centers for Disease Control and Prevention and The American Congress of Obstetricians and Gynecologists as well as private and non profit organizations such as The Congenital CMV Foundation and The CMV Action network. Many of these organizations have similar, existing, programs that can benefit from group synergy – allowing them to collectively affect change among more varied populations. Additionally, these organizations will often have well-established funding mechanisms and sources that can be brought to bear more effectively for common ground goals.

**Developing Campaigns for the Promotion of Preventative Behavior**

As noted in the previous discussion of the proposed educational campaign, informing those potentially affected by congenital CMV as well as those occupying positions that can be leveraged to provide education is a relatively inexpensive means of inspiring behavioral change. Michael Cannon and Katherine Davis detailed the merits of this intervention in their article entitled ‘Washing our hands of the congenital cytomegalovirus disease epidemic’. In this article, the authors acknowledge that data regarding the effectiveness is limited, but also describe congenital CMV as the greatest opportunity for improved outcomes among children among all other causes of birth defects and developmental disabilities. The authors base their argument regarding the effectiveness of the intervention by focusing on the ineffectiveness of methods to
promote it. In fact, they clearly outline the non existent arguments against both the effectiveness and efficacy of hand washing intervention by citing the fact that hands are indisputably important vehicles in the transmission of disease and that the effectiveness of good hygiene techniques have been proven time and again. Further, they stress that individual women have a right to be informed of the potential effectiveness of these methods against the transmission of CMV and that medical professionals have an ethical obligation to inform all women, regardless of serostatus (there is a chance of re-infection even with positive serostatus) of this opportunity just as they do in the case of safe sexual practices in the prevention of HIV transmission. 

Evidence of successful hand washing campaigns is widely available. For example, in a study of the effects of washing hands with soap on the development of diarrheal diseases, Curtis and Cairncross found up to a 44% risk reduction for diarrhea, a 48% risk reduction in severe intestinal infections and a 59% risk reduction in shigellosis when good hand washing practices were adhered to. While hand washing is perhaps the most productive target among CMV-related prevention measures, other measures as noted in the CDC congenital CMV infection prevention guidelines share the same underlying infection control themes. Any activity in which infected bodily secretion could presumably be transmitted from the initial host to a new host should be avoided or counteracted. For example, the sharing of food/drinks, oral hygiene instruments, kissing, etc. with young children while pregnant should be avoided.
In light of previous sections in which the insufficiency of current attempts to inform both the general public and health care providers have been discussed, I believe it is important to touch upon the concept of social marketing and its potential application in future congenital CMV prevention interventions. Social Marketing uses marketing principles which can be applied in situations where changing human behavior is the intended outcome. For any public health application, it is important to determine if the intervention exhibits specific characteristics including relative change over what currently exists, compatibility with current norms, and non complexity, among others. The use of social marketing techniques as they pertain to our proposed education-based CMV-prevention strategies would help to remove perceived barriers to behavior changes among our targeted audience as well as allow us to set realistic expectations for the initial success of the proposed program.

**Developing Selective Screening Programs**

Probably the most controversial component of this proposed congenital CMV infection prevention strategy is the implementation and use of screening programs. It has been widely argued that the implementation of such programs as they pertain to congenital CMV would suffer from marginal testing specificity/sensitivity, economic constraints, and ethical considerations. One, classic, example of this is Schlesinger’s paper entitled ‘Routine Screening for CMV in Pregnancy: Opening the Pandora Box?’ in which the author applies the Principles of Early Disease Detection as (championed by Wilson and Jungner). In
doing so, the author admits that the severity and prevalence of congenital CMV seemed to meet these principles but that test discrimination, diagnostic timing, possible intervention, and cost-effectiveness preclude formal congenital CMV screening programs. While the author calls into question the sensitivity, specificity and general reliability of single antibody-based CMV screening programs, he acknowledges the potential effectiveness of full panel antibody screening including avidity testing. With this in mind, I would propose a screening program that incorporates all of the current primary antibody-specific assessments in order to not only identify the serologic status of the individual but also to offer some measure of viral aging to differentiate residual maternal CMV infection from primary, potentially problem causing, infection. The combination of these tests should allow the care giver to establish one of three baseline serology statuses and courses of follow-up for the patient:

- **Uninfected/High Risk of New Maternal Infection:** The patient is at high risk of primary infection, the course of action will be dependent upon the results of a serial screening process in which the patient will be monitored every 3 months for new infection as determined by the sudden detection of CMV-specific antibodies.

- **Infected/High Risk of New Maternal Infection:** The subject is positive for CMV antibodies and there is possible risk of infection for the developing fetus(s). In this situation, CMV antibody Avidity testing will be performed to determine the relative age of the infection. The age of the
infection will serve as an indicator of potential risk to the fetus(s) which will be used to drive additional intervention

- Residual Infection: In this scenario, primary maternal infection is remote and the patient will receive continued hygiene education to restrict the possibility of re-infection

Initial screening is conducted to determine the potential for maternal-fetal CMV transmission. Emphasis is placed upon primary maternal infection as this has been shown to result in a far greater number of symptomatic fetal infections.\(^\text{18}\) By establishing a baseline status early in the first trimester of gestation, new infection can be more readily identified in those of highest risk for fetal transmission and appropriate steps can be taken to possibly control infection. Additional details regarding this proposed CMV screening program can be found in Appendix I.

**Conclusions**

Congenital CMV is a proven cause of viral-related developmental handicaps and other morbidities among children throughout the world. As such, it is also known to create substantial burden on public health systems. While further research is needed regarding the cost of the suggested screening program and the potential for antiviral intervention, I think it is important to consider this non invasive means of proactively identifying those at highest risk of new maternal infection. Implementing campaigns to inform both those at risk of transmitting this disease to their unborn children as well as those in positions to further educate them
coupled with well planned and implemented screening algorithms should significantly decrease the incidence of this disease and its associated emotional and financial costs.
REFERENCES


**Appendix I: Additional Information Regarding Viral antibodies and Suggested Screening Program**

As with most viral infections, CMV can be identified in the human body by the presence of viral-specific antibodies termed Immunoglobulin G (IgG) and Immunoglobulin M (IgM). Upon infection, the virus triggers an antibody response marked by increased Immunoglobulin M (IgM) antibodies followed by residual Immunoglobulin G (IgG). As you can see in Figure I below, IgM antibodies become detectable early in the primary infection process and may continue to circulate long after primary infection. Low avidity IgG typically becomes apparent within one month of infection, gradually increasing in avidity as time goes on.\(^7,8\)

**Figure I: Relative Levels of IgM and IgG Antibodies and IgG Avidity during CMV infection**

Our proposal includes the active screening of all women as they present for their initial first trimester obstetric/gynecology appointment. This testing would include both IgM and IgG serology assessments as well as IgG avidity testing.
The combination of these tests should allow the care giver to establish one of three baseline serology statuses and courses of follow-up for the patient:

- **IgM-/IgG- (Uninfected/High Risk of New Maternal Infection):** The subject is serologically negative for CMV antibodies. The absence of both IgM and IgG indicates the patient is at high risk of primary infection, the course of action will be dependent upon the results of a serial screening process in which the patient will be monitored every 3 months for seroconversion as determined by the sudden detection of either IgM or IgG antibodies. If the patient seroconverts at anytime during pregnancy, the patient will be counseled regarding potential fetal infection and pharmaceutical treatment may be recommended as prophylaxis. Fetal infection will be monitored via clinical methods (e.g. ultrasound findings, MRI, amniocentesis, etc.).

- **IgM+/IgG+ (Infected/High Risk of New Maternal Infection):** The subject is serologically positive for CMV antibodies and there is possible risk of infection for the developing fetus(s). In this situation, IgG Avidity testing will be performed to determine the relative age of the infection. The age of the infection will serve as an indicator of potential risk to the fetus(s) as low avidity is associated with new/primary infection. If the testing reveals low avidity, the patient will be counseled regarding potential fetal infection and pharmaceutical treatment may be recommended as prophylaxis. Fetal infection will be monitored via clinical methods (e.g.
ultrasound findings, MRI, amniocentesis, etc.). IgG Avidity revealing residual infection will result in no further intervention.

- IgG+/IgM (Residual Infection): In this scenario, primary maternal infection is remote and the patient will receive continued hygiene education to restrict the possibility of re-infection
Figure II: Suggested Congenital CMV Screening Algorithm

Initial screening is conducted to determine the potential of maternal-fetal CMV transmission. Emphasis is placed upon primary maternal infection as this has been shown to result in a far greater number of symptomatic fetal infections. These guidelines allow the caregiver to assign relative risk to individuals based upon IgG status and avidity aging. This, combined with known ancillary risk factors will drive decisions for further intervention. By establishing a baseline status early in the first trimester of gestation, seroconversion can be more readily identified in those of highest risk for fetal transmission and appropriate steps can be taken to possibly control infection. With that said, although pharmacological intervention for congenital CMV is yet to be clinically proven, and further studies are required to establish true efficacy, I feel the use of treatment modalities that
are found to be effective for CMV in other infection scenarios should be applied in the event of positive confirmatory amniocentesis or hallmark imaging findings. Of note, it is important for the caregiver to understand the vital contribution of proper counseling for those who are identified as having passed this disease onto their children. The purpose of proper counseling is to inform the patient of her options with regard to congenital and/or postpartum care. As described by Revello and Gerna, the role of the care giver is to provide unbiased and informative counseling and impart relative knowledge to the patient.\textsuperscript{34} In addition, it is imperative that caregivers remain cognizant of the impact of this screening program as well as the possibility of misuse and misinterpretation of the testing by some physicians which may incite unneeded anxiety among parents. Again, careful planning regarding the dissemination of the screening results and direct counseling will help to alleviate some of this anxiety.