Screening and treating for primary cytomegalovirus infection in pregnancy: where do we stand? A decision-analytic and economic analysis

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OBJECTIVE: To estimate which 1 of 3 screening strategies for primary maternal cytomegalovirus infection, with intention to treat with hyper-immune globulin, is most cost-effective.

STUDY DESIGN: A decision-analytic and cost-effectiveness model was constructed for pregnant women, comparing 3 strategies screening for primary maternal cytomegalovirus infection with intention to treat with cytomegalovirus-intravenous immune globulin: (1) serum screen all pregnant women, (2) serum screen women with risk factors for primary cytomegalovirus, (3) serum screen women with suspicious sonographic findings. Probability, use (or value), and cost estimates were derived from published literature.

RESULTS: Universal screening for primary maternal cytomegalovirus was the preferred and most cost-effective strategy. However, if treatment with cytomegalovirus-intravenous immune globulin achieved less than a 47% reduction (relative risk, 0.53) in clinical disease, universal screening would no longer be cost-effective.

CONCLUSION: Universal screening for primary maternal cytomegalovirus infection is cost-effective based on available evidence, highlighting the urgent need for additional study evaluating the efficacy of cytomegalovirus-intravenous immune globulin to prevent congenital cytomegalovirus.

Key words: congenital CMV, cytomegalovirus, pregnancy, primary CMV

The neonatal disease burden of primary cytomegalovirus (CMV) during pregnancy has not been diminished. Despite the fact that CMV affects 1% of all infants born annually in the United States, making it the most prevalent congenital infection, available strategies for prevention of fetal infection have not been successfully developed. The reason for this has been dominated by 2 key issues. The first has been that, at times, it has been difficult to distinguish between primary and recurrent maternal CMV infection, making screening for primary infection inefficient and ineffective. The second has been the lack of evidence for treatment efficacy to prevent congenital infection. Identification of primary CMV exposure has left practitioners with only the ability to counsel patients regarding the potentially devastating outcomes, given that up to 50% of these fetuses will become infected, and 10% will exhibit congenital CMV syndrome at birth, either resulting in death or severe disability.

Recently published data have introduced the possibility of screening for maternal primary CMV by using avidity testing and treating to prevent congenital infection. Nigro et al published a study suggesting that maternal treatment with CMV-intravenous immune globulin (CMV-IVIG) after primary CMV infection might reduce vertical transmission, and resultant neonatal morbidity and mortality. The publication of this study in a high-profile journal with remarkably promising results contrasted by the complex design and many limitations have left many practitioners questioning if this should change clinical practice.

We sought to explore whether universal maternal serum screening for primary CMV infection and subsequent treatment with CMV-IVIG could reduce the neonatal burden of CMV disease, as well as to detect what magnitude of effect CMV-IVIG seen in future research would support using this treatment. We developed a decision analytic and cost-effectiveness model to compare 3 screening strategies for primary CMV with intention to treat.

MATERIALS AND METHODS

We developed a decision-analytic model to compare 3 strategies for maternal screening for primary CMV infection with intention to treat with CMV-IVIG: screen all women, screen all at-risk women, or screen women with abnormal sonographic findings consistent with CMV infection. By using this base model, a fourth strategy of no screening or treating was added to represent a baseline reference, and a cost-effectiveness

For Editors’ Commentary, see Table of Contents
analysis was performed. The analysis was performed from the societal perspective, using relevant costs and outcomes to determine which strategy was most cost-effective. The primary goal of the model was to estimate reduction in the burden of congenital CMV infection by using various clinical strategies, and to identify the most cost-effective way to do so.

The decision model was constructed for pregnant women in the United States, who were having a singleton intrauterine pregnancy, at or beyond 20 weeks' gestation. We designed the model based on the sensitivity and specificity of each of the 3 screening strategies to effectively capture the true- and false-positive results, as well as the true- and false-negative results. The first strategy used maternal serum screening for primary CMV infection in all women, referred to as the “universal screening” strategy. The second strategy applied maternal serum screening for primary CMV infection to at-risk women, defined as those in a household with a child <4 years of age, or used in a childcare setting, referred to as “risk factor-based” screening. The third strategy, designed to most closely mimic current obstetric practice if treatment were used, applied maternal serum screening to women with ultrasound findings on routine anomaly survey that were suspicious for congenital CMV infection, including midtrimester growth restriction, echogenic bowel, ventriculomegaly, microcephaly, or intracranial or visceral calcifications. This later strategy is referred to as “ultrasound-based” screening.

In any of the 3 strategies, women with serum screening indicative of primary CMV infection were offered confirmatory amniocentesis for CMV polymerase chain reaction (PCR). Whether amniocentesis was accepted or declined, patients were offered treatment. We accounted for the possibility that patients may elect to terminate their pregnancy at the time of either positive serum screen or after positive confirmatory amniocentesis. We also accounted for the possibility of spontaneous pregnancy loss after amniocentesis in those who elected the procedure. Women who received IVIG had a risk of a severe adverse reaction to the medication. In each strategy, 4 neonatal outcomes were modeled: neonatal death caused by congenital CMV, severe morbidity caused by congenital CMV, mild disability caused by congenital CMV diagnosed by age 2 years, and unaffected child.

Several assumptions were made in the construction of the model. All women sought prenatal care by 20 weeks' gestation, and underwent 1 standard-of-care sonographic anomaly survey at 20 weeks. We assumed screening for primary CMV would occur once, at 20 weeks' gestation, and that all maternal serum screening would be accomplished by testing for presence of CMV immunoglobulin M (IgM) and IgG. In the event that both were positive, IgG avidity testing would be performed. Primary CMV infection was defined as presence of CMV IgM without IgG, or presence of both CMV IgM and IgG with IgG avidity ≤25%. The diagnostic test for vertical transmission of CMV was presence of CMV DNA detected in amniotic fluid by PCR. Treatment was a 1-time intravenous dose of CMV immunoglobulin at a dose of 200 U/kg of maternal weight.

We modeled a strategy of 1-time serum screening for each pregnant woman at 20 weeks' gestation. In doing so, we accepted the possibility that this strategy would be imperfect in that it would miss a small number of cases in which maternal exposure had occurred, but seroconversion had not. However, we chose this approach for several reasons. First, it would capture virtually all of the cases of infection exposure in the first trimester, which is most devastating and accounts for the majority of morbidity. It is a simple approach, and the most inexpensive, both of which are important for any universal screening program. And finally, screening at 20 weeks’ gestation allows for a confirmatory diagnostic test, in this case PCR on amniotic fluid, which has been shown to have a 100% specificity at 21 weeks’ gestation or beyond, at a time when all conceivable options are still available to the patient.

We chose to model a 1-time, high-dose CMV-IVIG treatment (200 U/kg) from the study by Nigro et al14 for a few reasons. First, of the 2 treatment strategies in that study (the other being monthly CMV-IVIG at 100 U/kg, given to women with confirmed vertical transmission), the higher dose achieved higher efficacy. This allowed us to explore lower efficacy rates in sensitivity analyses. For patients with ultrasonographic evidence of congenital CMV, which did not improve after treatment, they received up to 2 additional dosages. This was reflected in the model by tripling the cost of therapy in the sensitivity analysis to achieve a desired efficacy.

Base-case probability point estimates and confidence intervals for event probabilities and plausible outcomes were obtained from a quantitative literature review, using the search terms “cytomegalovirus,” “cytomegalovirus and pregnancy,” “CMV and pregnancy,” “cytomegalovirus and vertical transmission,” and “cytomegalovirus and neonate.” The search was limited to studies involving humans and manuscripts written in the English language. We excluded any studies that were unpublished, published only in abstract form, were case reports or case series, or review articles. We also excluded studies without control groups, except for the purposes of establishing prevalence estimates of rare outcomes. The remaining studies were incorporated into the model (Table 1).

Point estimates were calculated as the mean of the estimates in the published literature, weighted by the number of study subjects. Confidence intervals (CIs) were the range of the estimates in the literature. If a point estimate came from a single source, the CI was calculated using an exact 95% CI of binomial proportions. Lastly, sensitivity and specificity estimates for screening based on risk factors and sonographic findings were calculated from published population data. These estimates varied widely in sensitivity analysis to account for potential imprecision. Use, or value, estimates and their ranges were also derived from quantitative literature review. Possible values ranged from 1 (perfect health) to 0 (death). The long-term outcome uses included in the model were neonatal mortality and severe neonatal compromise or handicap. One short-
term outcome, severe adverse reaction to IVIG, was modeled by using the use estimates from the general medical literature. It was incorporated into the model as a disuse, calculated as 1 minus the use value, divided by 365, to account for the fact that this event was short-lived, finite, and recoverable after the event occurring in a single day out of an entire year. For all usages, we used the “decomposed” approach of combining them, because patients could experience multiple events, and it would be difficult to combine them in a single value that would be required for the “holistic” approach (Table 2).

Cost estimates were derived from the literature in the same fashion as the probability and use estimates. However, for many costs there were no available data in the published literature, so we used reimbursement information from our institution to estimate cost (Table 2). The final cost of a particular strategy was the sum of all components of that pathway. Effectiveness was expressed as quality-adjusted life years (QALYs), calculated by the product of use value and life expectancy (in years). In accordance with standard assumptions in economic analysis, we discounted annual costs and QALYs at a rate of 3%. We assumed life expectancy was 75 years.

In the baseline analysis, the 3 screening strategies were compared by use value, derived from the probability of each event in a path multiplied by the use values of the events in that pathway. A theoretic cohort of 4 million women was considered to compare each strategy by number of outcomes generated by each approach. Base-case cost-effectiveness analysis was performed, comparing all the strategies with each other and with a “no screening or treating strategy.” Then 1-, 2-, and 3-way sensitivity analyses were performed by varying 1, 2, or 3 variable estimates, respectively, across the entire plausible range of probability, use, and cost, to determine whether the model was sensitive to 1 or more of the variables. In other words, to determine whether, given a different value or set of value estimates, the preferred strategy would change. Monte Carlo simulation was used as a form of multivariable analysis, simultaneously varying all values
across their plausible ranges at random to estimate the number of times the conclusion of the model (the preferred strategy) would be chosen again. The analytic model was constructed and analyzed by using TreeAge Pro 2006 Suite (TreeAge Software, Inc, Williamstown, MA). The study did not involve human subjects and was exempt from institutional review board approval.

**RESULTS**

Universal screening was the preferred strategy in the base-case analysis, compared with risk factor-based screening and sonographic finding-based screening. Considering a theoretical cohort of 4 million neonates, based on the average annual birth rate in the United States, universal serum screening and treating for primary maternal CMV would significantly reduce the number of severely affected children born annually by 7638 when compared with risk factor-based screening, and by 7712 when compared with sonographic-based screening (Table 3).

In the decision analysis of clinical outcomes, 1-way and 2-way sensitivity analysis revealed the model to be sensitive to the test characteristics (ie, sensitivity and specificity) of risk factor-based screening at the highest values. If risk factor-based screening had a sensitivity of at least 80% and a specificity of at least 70.1%, then risk factor-based screening would be preferred over universal screening. Sonographic-based screening remained the inferior strategy. Additional 1-, 2-, and 3-way sensitivity analyses of all probability and use estimates across their ranges did not yield any additional variables to which the model was sensitive.

In the cost-effectiveness analysis, universal serum screening was also the most cost-effective strategy (Table 4). When compared with risk factor-based screening and sonographic-based screening, as well as a reference strategy with no screening or treatment, universal screening represented the greatest cost savings per QALY ($5243). In 1- and 2-way sensitivity analyses, varying probabilities, uses, and costs across their ranges by 1 and 2 variables at a time, the model was robust.

In the sensitivity analysis of the cost-effectiveness model, we explored the effect of optimizing the sensitivity and specificity of risk factor-based screening...
that was influential in the clinical outcomes decision model. However, even at the extreme values of risk factor-based sensitivity and specificity, modeling a theoretically optimized risk factor-based screening system, the risk factor-based screening strategy became less expensive than universal screening, but universal screening remained the most cost-effective. For example, if risk factor-based screening was optimized with a sensitivity of 90% and a specificity of 85%, risk factor-based screening is more cost-effective than sonographic-based screening and no screening or treating ($383 vs $2643 vs $5334 per QALY, respectively), but universal screening remains the most cost-effective strategy ($89/QALY).

Because the efficacy data for CMV-IVIG is based on a single, observational treatment study with a relatively high rate of reported efficacy (relative risk [RR], 0.1 with treatment compared with no treatment), we explored a wide range of treatment efficacy and specifically the threshold at which universal screening would no longer remain cost-effective. If treatment with CMV-IVIG achieved a 47% disease reduction (RR, 0.53) or less, universal screening would no longer be cost-effective. In addition, given that CMV-IVIG availability is fairly limited and the medication is fairly expensive, we explored threshold cost of CMV-IVIG. If treatment cost was $30,158 or more, universal screening and treating would no longer be cost-effective.

Finally, we performed a multivariable analysis, simultaneously varying probabilities, uses, and costs across their probable ranges using Monte Carlo simulation of 100,000 trials with a willingness-to-pay threshold of $50,000. Universal screening was found to be the superior strategy 99.2% of the time.

**COMMENT**

The significant health burden of congenital CMV after primary maternal infection has not been reduced by current available interventions. Our results suggest that advances in the ability to use maternal serology to identify primary CMV infection, and the ability to potentially treat fetuses exposed to CMV to reduce neonatal morbidity and mortality, could make universal screening and treating to prevent congenital CMV cost-effective. However, these results must be tempered. Our findings are reliant on the reported efficacy of CMV-IVIG by Nigro et al, which is not a study of sufficient rigor to support change in practice or universal screening for primary CMV. Additional trials are desperately needed. Our results show that a trial that demonstrates CMV-IVIG efficacy as at least a 47% reduction in congenital CMV would make universal screening and treating for primary CMV in pregnancy cost-effective.

Maternal screening for infectious diseases that can transmit significant morbidity and mortality to infants is not foreign to obstetrics. Universal screening for group B streptococci (GBS) has significantly reduced the burden of neonatal disease caused by this organism. Interestingly, GBS caused about 1 case of perinatal sepsis in 1000 births when universal screening was recommended, a fraction of the estimated neonatal morbidity attributed to CMV. Yet until now, we have had no plausible, cost-effective strategy to screen and treat for the prevention of congenital CMV. This has primarily been driven by the inability to identify maternal primary infection, and the subsequent inability to treat the infection. However, several investigators have provided evidence to the contrary. Lazzarotto et al performed maternal serum antibody testing in women undergoing prenatal diagnosis for CMV by amniocentesis. They found that the addition of IgG avidity testing, with a cutoff of <25%, was 100% sensitive for fetal CMV infection. Others have reported similar findings, supporting the notion that screening for primary CMV infection can be effectively performed.

But the ability to screen for primary CMV infection in pregnant women is futile with no medical treatment to offer other than termination of pregnancy. Nigro et al published a recent study that offered evidence for the ability to prevent and treat congenital CMV with maternal CMV-IVIG. After confirmation of primary maternal CMV infection, patients were offered confirmatory amniocentesis. Both those with confirmed infection and those who declined amniocenteses were offered treatment. The authors found the greatest reduction (90%) in neonatal morbidity, and no mortality, in the group who received CMV-IVIG. Although the study design had several limitations, including the

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**TABLE 4**

Cost-effectiveness analysis of strategies for screening and treating primary maternal CMV to prevent neonatal morbidity and mortality, under base-case assumptions

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<tr>
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</thead>
<tbody>
<tr>
<td>Screen all with intention to treat</td>
<td>$6311.10</td>
<td>70.7</td>
<td>$89</td>
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</tr>
<tr>
<td>Risk factor based screening</td>
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<tr>
<td>Sonographic based screening</td>
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<td>$97</td>
<td>Dominated</td>
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<tr>
<td>No screening or treating</td>
<td>$6630.50</td>
<td>66.4</td>
<td>$100</td>
<td>Dominated</td>
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</tbody>
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CMV, cytomegalovirus; QALY, quality-adjusted life year.
Dominant = least costly and most effective.

lack of randomization or blinding, the reported findings were provocative both in direction and magnitude of effect of CMV-IVIG on reduction in congenital CMV. Because of the many limitations of the study by Nigro et al., a paucity of external validation studies, and the significant cost and limited availability of CMV-IVIG, interpretation of these results and use of this treatment in practice have been broadly inconsistent.

Our study showed that universal screening with the intention to treat with CMV-IVIG is cost-effective, based on the available screening evidence and the efficacy of the study by Nigro et al.14 study. As some have suggested, one could hypothesize that the ability to screen the portion of the population with the highest prevalence of primary CMV would be ideal, and this was revealed in our sensitivity analysis. In other words, if the sensitivity and specificity of maternal serum screening based on risk factors were optimized, then that strategy would become the most preferred in the decision analysis. But the cost-effectiveness analysis revealed that even at optimized values of the sensitivity and specificity of risk factor-based screening, universal screening remained the most cost-effective. In addition, with our current ability (or inability) to effectively identify that subpopulation that is most at-risk, universal screening would be a more efficient strategy for reduction of congenital CMV morbidity and mortality if the efficacy data on CMV-IVIG from Nigro et al.14 are validated. Lastly, despite the fact that current estimates of sensitivity and specificity of risk-factor based screening are far from the threshold at which this strategy would be cost-effective, it is an important strategy to continue to consider in future research.

This analysis has several strengths. Our model was robust to all cost, probability, and use variables, with the exception being the optimized sensitivity and specificity of risk factor-based serum screening. However, because published literature does not reflect an ability to identify those women at risk with a sensitivity that would approach the upper range considered in our model,24-26 we would conclude that our analysis can be considered robust. We believe decision-analytic and cost-effective models are important tools for complex questions such as congenital CMV prevention, in which existing evidence is disbursed across disciplines, the evidence available is not of the level of evidence that the compulsion to change practice is abundantly clear, and the trade-offs between risk or cost and benefit seem unclear or subjectively unfavorable.

It is very important to keep in mind that treatment efficacy was based on the results of a single study,14 because that is all that is currently available in the literature. Although one could argue that this is a potential weakness of this analysis, we would argue that it makes 1 of the most important points for the importance of this analysis. That is, there are no other treatment trials for maternal primary CMV infection for the prevention of congenital CMV currently ongoing to our knowledge.27 Neither treatment nor screening is currently used in general practice in the United States, and yet CMV is the most common and 1 of the most devastating congenital infections. When we explored this in our sensitivity analysis, we demonstrated that even if efficacy of CMV-IVIG was at least 50% of that reported by Nigro et al.,14 universal screening and treatment would still be cost-effective.

Our model brings to light the potential for dramatic impact on the significant health burden of congenital CMV, at the same time simultaneously highlighting areas of research in critical need. Although international studies have demonstrated that serum maternal screening and the use of avidity testing can distinguish between primary and recurrent CMV infection, there is a need for confirmatory studies in the United States and a subsequent need to improve regional availability. These data indicate that further trials on the efficacy of CMV-IVIG, and other potential treatments, for prevention and treatment of congenital CMV are urgently needed to further inform our clinical decision and policy making. Adopting a strategy of national universal screening would be an enormous undertaking, but one worth pursuing to reduce the health burden of congenital CMV if additional evidence could confirm the efficacy of CMV-IVIG.

REFERENCES