

## Discussion: 'Predicting congenital cytomegalovirus infection' by Guerra et al

In the roundtable that follows, clinicians discuss a study published in this issue of the Journal in light of its methodology, relevance to practice, and implications for future research. Article discussed:

Guerra B, Simonazzi G, Puccetti C, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. *Am J Obstet Gynecol* 2008;198:380.e1-380.e7.

### DISCUSSION QUESTIONS

- How important is the subject?
- Was the study objective clearly stated?
- Was the study design appropriate for the question?
- What were the outcome measures?
- Were outcome measures determined in a dependable manner?
- How reliable are outcome data obtained from questionnaires and telephone calls?
- Was the length of follow-up adequate to detect serious sequelae?

- Were appropriate statistical methods used?

### INTRODUCTION

According to the Centers for Disease Control and Prevention, roughly 1-4% of women have a primary cytomegalovirus (CMV) infection during pregnancy.<sup>1</sup> Annually, CMV-related disabilities are noted in an estimated 1 in 750 children, whether documented in a newborn or a child whose disability emerges later. A new study by Guerra et al weighs the value of ultrasound findings in predicting symptomatic CMV disease in infants. Their results underscore the difficult questions this situation generates for patients and their physicians. Journal Club members talked over the study design, the data, and the practical value of the results.

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### BACKGROUND

**Odibo:** Welcome to another session of the *American Journal of Obstetrics and Gynecology* Journal Club. CMV infection is the most prevalent infection in the prenatal period. Once a patient is confirmed to have a CMV infection, ultrasound surveillance and secondary prevention through pregnancy termination are still the only reliable interventions available.

**Odibo:** *How important is the subject?*

**Stout:** Given the potentially devastating outcome of fetal or neonatal CMV infection, it is important to maximize diagnostic modalities for evaluating possible organ involvement. Patients expect physicians to help them understand abnormal findings on ultrasound, and this study could help interpret abnormal

clinical markers—or lack thereof—on ultrasound in the context of maternal primary CMV infections.

**Odibo:** *Did the authors justify the need for the current study? Do previous studies address the same subject?*

**Hoff:** Whereas multiple studies have evaluated the utility of prenatal ultrasound markers in the diagnosis of a CMV-affected fetus, a positive diagnosis does not indicate the severity of fetal injury or postnatal sequelae. Some minor ultrasound findings might identify infants at increased risk for symptomatic disease, but no studies have been devised to specifically look at ultrasound parameters in fetuses at risk of postnatal effects of CMV. This makes counseling patients rather difficult. Studying ultrasound markers that not only identify infected fetuses but also delineate risk for symptomatic disease would be very helpful when counseling patients. It would also provide important information for families weighing the possibility of pregnancy termination.

### STUDY DESIGN

**Odibo:** *Was the study objective clearly stated?*

**Krings:** Yes. The stated study objective was to assess the ability of ultrasound to antenatally predict symptomatic congenital CMV infection in cases of serologically-proven primary maternal infection.

**Odibo:** *Was the study design appropriate for the question?*

**DeFranco:** Yes. This was a retrospective cohort study of women with primary CMV infection in pregnancy. The authors compared congenital infection rates in 2 groups: those with abnormal antepartum ultrasound findings (the

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case group) and those with normal antepartum ultrasound findings (the control group). From this information, they calculated sensitivities, specificities, positive predictive values (PPVs), and negative predictive values (NPVs) of abnormal ultrasound findings for the prediction of congenital CMV infection.

**Odibo:** I agree that the retrospective study design was appropriate for the study's aim. However, it has the disadvantage of certain unforeseen biases, including recall bias and other potential confounders that might limit the conclusions. Obviously, a prospective study design would avoid these, but given the low incidence of CMV infection, such a design would take a long time to complete and would be associated with increased cost!

**Odibo:** What outcome measures were studied and were they reliably ascertained?

**Stout:** Outcome measures were reliably ascertained. These included:

1. Neonatal infection status. The presence of neonatal infection was based on viral isolation from newborns or by the detection of CMV inclusions, antigen, or both in multiple organs during macroscopic and histologic tissue examination of products of conception.
2. Symptomatic vs asymptomatic neonatal infections. Infants were deemed to be symptomatic when signs and symptoms of systemic involvement were identified in the neonatal period. These included intrauterine growth retardation (IUGR), hepatosplenomegaly, skin petechiae, thrombocytopenia, jaundice with elevated direct bilirubin, elevated alanine aminotransferase, pneumonia, neurologic involvement, sensorineural defects (eg, chorioretinitis, deafness), and CMV-specific neurological imaging findings.
3. Presence of antenatally diagnosed ultrasound abnormalities in fetuses with neonatal infection and the PPV of these ultrasound abnormalities in fetuses with symptomatic congenital infection.

4. Long-term sequelae. Postnatal clinical appraisal, neurodevelopmental assessment, and psychointellectual assessments included cranial ultrasound, computed tomography, and magnetic resonance imaging; fundoscopic examinations; and audiologic exams. Visits were scheduled at 1, 3, 6, 12, and 18 months and then annually to school age.

**Odibo:** *For mothers who delivered at outside hospitals, questionnaires and telephone interviews were used to obtain outcomes. How reliable are such outcome data?*

**Hoff:** Both questionnaires and telephone interviews can be good for gathering information, but they are subject to recall bias. Respondents can find it hard to accurately recall past events, possibly because of motivation, attitude, cognitive issues, or mood. The outcome, symptomatic CMV infection, is being studied postnatally. By the study's definition, symptomatic infection is based on physical, instrumental, and laboratory findings. Newborns were considered symptomatic when they presented any sign or symptom of systemic involvement. You can see the numerous ways in which bias could be introduced. Considering the potential for multiple insults over the course of pregnancy and the postnatal findings used to determine symptomatic CMV infection, I would like to see the responses to questionnaires and interviews compared with clinical records. I suspect that the reliability of such questionnaires and telephone interviews would be biased toward the diagnosis of symptomatic CMV in children.

**Odibo:** *Was the length of follow-up adequate to detect serious sequelae of CMV infection?*

**Krings:** Yes. The length of time for follow-up was adequate to detect serious sequelae of CMV infection. As noted, follow-up visits and examinations were scheduled at 1, 3, 6, 12, and 18 months of life and then annually up to school age. The median age of follow-up for infected neonates was 42 months with a range of 6-72 months.

## STATISTICAL ANALYSES

**Odibo:** *Did researchers use appropriate statistical methods to analyze their data? How precise were the estimates of ultrasound performance in detecting CMV effects?*

**DeFranco:** The authors calculated sensitivity, specificity, PPV, and NPV to describe the validity of ultrasound as a screening test. The methods in which cases—fetal ultrasound abnormalities in this instance—are identified can have an impact on the accuracy or validity of those measures. For example, if only 1 ultrasound was performed in pregnancy at a relatively early gestational age, the identification of sonographic abnormalities (cases) would be lower than the 15% identified in this study. For example, that limitation in case-identification methodology could produce an artificially low NPV by classifying as negative cases that would have developed abnormal ultrasound findings at a later gestational age. The authors in this study reported results based on a practice that included serial ultrasound screening for abnormalities at 21, 28, and 33 weeks of gestation, although they did not report what percentage of cases actually received screening at those times. Assuming that compliance with serial ultrasound screening was optimal and that the sonograms were of good quality and interpreted by experienced specialists, the estimates of performance for these measures can be assumed to be relatively accurate and precise.

**Odibo:** In addition, calculation of the 95% confidence interval around their estimates of sensitivity and specificity would have been informative regarding the precision of their calculations.

**Odibo:** *In addition to sensitivity, specificity, and the other measures used, what other assessment of the effect size of CMV manifestation might have been included?*

**Krings:** Another measure of effect size that could have been included is the odds ratio comparing ultrasound abnormalities among those with a symptomatic infection and among those who are asymptomatic.

## CONCLUSIONS

**Odibo:** *Let us now look at the results. What do the data in Table 1 tell us of the efficiency of ultrasound in screening for congenital CMV?*

**Stout:** The data in Table 1 report that abnormal ultrasound findings have a sensitivity of 15% and specificity of 94% in predicting congenital CMV infection. This indicates that many congenital CMV infections were undiagnosed based on the finding of ultrasound abnormalities alone. In addition, a relatively low PPV of 45% indicates that abnormal ultrasound findings could be attributed to congenital CMV in less than half of cases. Based on these data, ultrasound evaluation is not especially efficient as a screening tool for congenital CMV infection.

**Odibo:** *What do Table 2 and Table 3 tell us about the sonographic markers of congenital CMV infections?*

**Hoff:** Tables 2 and 3 report ultrasound abnormalities among infants. In 28 of 51 cases, anomalous ultrasound findings were not attributable to intrauterine CMV infection; these are described in Table 2. Follow-up information on 600 fetuses carried by mothers with primary CMV infection identified 154 with CMV infection, as diagnosed by postnatal urine testing or autopsy. Only 23 of these newborns or fetuses had abnormal ultrasound findings, which are detailed in Table 3.

What is interesting about these 2 tables is the overlap of abnormal ultrasound findings among infected and uninfected fetuses. We can see the difficulty in identifying specific ultrasound markers associated with CMV infection; ventriculomegaly, IUGR, and hyperechogenic bowel were found among both infected and uninfected fetuses. A closer look at Table 3 reveals that of the 23 fetuses with known CMV infection and abnormal ultrasound findings, 18 had symptomatic infection. In addition, ventriculomegaly,

IUGR, and hyperechogenic bowel were found in symptomatic infants as well as 4 asymptomatic infants with CMV infection: 1 had ventriculomegaly; 2 had IUGR; and 1 had hyperechogenic bowel. In all, abnormal ultrasound findings were predictive for only 15% of fetuses at risk for symptomatic CMV infection.

**Odibo:** *Can you explain the results in Tables 4 and 5?*

**Krings:** Table 4 describes the screening efficiency of ultrasound examination in predicting symptomatic CMV infection in all fetuses with an in utero exposure. Of the 600 fetuses exposed, 51 had an abnormal ultrasound finding. Of those 51, 18 had a symptomatic CMV infection. This provided a PPV of 35.3%.

Table 5 describes the screening efficiency of ultrasound examination in predicting symptomatic CMV infection in the congenitally infected fetuses and newborns. Of the 154 infected fetuses, 23 had an abnormal ultrasound finding. Of those 23, 18 were symptomatic. This produced a PPV of 78.3%.

**Odibo:** *When considering the subject being studied, is a higher sensitivity or specificity more important?*

**DeFranco:** In screening for congenital CMV infection, early identification of injured fetuses is of significant importance because patients might choose to terminate these pregnancies. With congenital CMV, we would prefer our screening test to have a very high specificity (correct identification of true positives), even at the expense of sensitivity which is the ability of the screening test to identify those without the disease. The cost of incorrectly identifying a case as abnormal would be very high earlier in pregnancy if the mother chose to terminate the pregnancy based on the abnormal ultrasound finding. Therefore, in that scenario, we would prefer a high specificity.

Alternatively, when ultrasound is used for screening later in pregnancy, after termination is not an option, reassur-

ance with accurate identification of a healthy fetus would be preferred at that point. If a test is extremely sensitive, it can reliably detect "true positives" or patients who actually have the disorder of interest. A negative result from a particularly sensitive test can be encouraging to patients

**Odibo:** *What does the PPV tell us, and how is this influenced by the prevalence of CMV?*

**Krings:** The PPV is the probability that, among all patients who test positive for a disease, a single patient with a positive test actually has the disease. The PPV is not intrinsic to the test but is influenced by prevalence. If the prevalence of the disease is higher, then the PPV, which is calculated with the numbers of true positives and false positives, would also come out higher. This effect is seen in the 2 PPVs presented in Tables 4 and 5. The prevalence of symptomatic CMV infection in the study sample in Table 4 was 14.3% with a PPV of 35.3%, whereas the prevalence of symptomatic CMV infection in the study sample in Table 5 was 55.8%, yielding a PPV of 78.3%.

**Odibo:** *Will the findings help you in caring for your patients?*

**DeFranco:** Yes, knowing that symptomatic cases of congenital CMV infection will be detected only 35% of the time by screening for abnormalities with ultrasound is useful in counseling women about how ultrasound findings should be interpreted and in considering invasive diagnostic testing with amniocentesis.

**Odibo:** Thank you all for participating in this Journal Club. I hope you will join us again for future meetings. ■

## REFERENCE

- Centers for Disease Control and Prevention, Division of Viral and Rickettsial Diseases. Cytomegalovirus: Pregnancy. Centers for Disease Control and Prevention website. 2006. Available at: <http://www.cdc.gov/cmvpregnancy.htm>. Accessed Feb. 11, 2008.