We greatly disagree with Drs Janssen and Oudijk who stated that NRT should not be a valid option to stop smoking during pregnancy on the basis that it might increase the risk of chronic obstructive pulmonary disease in animals. Of note, chronic obstructive pulmonary disease is a condition that is diagnosed at 40 years of age on average and where smoking/second-hand smoking are the main risk factors.[7] This is in direct contradiction with what Janssen and Oudijk are putting forward based on animal studies. Finally, psychologic interventions to stop smoking during pregnancy have shown very modest success rates,[6] which again is in contradiction with Janssen and Oudijk. ■

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Primary maternal cytomegalovirus infections: accuracy of fetal ultrasound to predict sequelae in offspring

TO THE EDITORS: We thank Leyder et al[1] for their contribution that addresses the important and challenging issue of predicting outcome when cytomegalovirus infection is diagnosed prenatally. Their group in Brussels has a long-standing experience in this field. The study confirms findings by us[2] and others that the time of maternal infection is a prognostic factor, because all cases with a poor outcome had an infection before 15 weeks of gestation (2 cases with unknown timing). The other major factor to be associated with poor outcome is the presence of ultrasound abnormalities.

Leyder et al conclude that, of 38 fetuses with normal ultrasound results, more than one- of them half had cytomegalovirus-related anomalies at clinical follow up or at autopsy in case of pregnancy termination, which led them to state that prenatal ultrasound findings are correlated poorly with postnatal outcomes.

This conclusion may be overstated for several reasons, in addition to the number lost to follow up. First, the paper fails to mention when the ultrasound examinations were performed. This is important because it has been shown that ultrasound signs may take several weeks or months to appear.[3] Second, the autopsy findings must be interpreted with caution. It is impossible to determine whether microscopic lesions would have resulted in neurologic impairment had the child lived, but the presence of cytomegalovirus inclusions in the placenta, lungs, or abdomen does not lead necessarily to neurologic impairment. Furthermore, since microscopic lesions may precede visible abnormalities by many weeks, ongoing surveillance with serial ultrasound examinations would have been likely to detect the most severe evolving lesions, microcephaly for instance. Third, regarding the liveborn children, of 23 children with normal prenatal ultrasound scans, 1 child had had mild developmental delay, and 1 child had mild neurologic sequelae, thus a negative predictive value of 91% to exclude neurologic problems. Of course, ultrasound scans cannot detect hearing loss, which much be discussed with the couple.

Thus, the negative predictive value is underestimated in this article. Furthermore, more complete evaluation may be considered with fetal blood sampling for platelet count and magnetic resonance imaging. This is important with regards to the high proportion of pregnancies that were terminated, despite normal ultrasound findings. Lack of confidence in favorable prognostic elements and serial follow-up evaluations can lead to distress leading to termination of pregnancy.

Thanks to the better knowledge of the natural history of the disease, we now can establish with good reliability which

fetuses will go on to be asymptomatic neonates with a low risk of neurologic sequelae.[2,4] Of course, the prediction is not perfect, and we cannot exclude the occurrence of hearing loss. We strongly agree with Leyder et al that further longitudinal studies are required. Management of these cases must be performed with experts on fetal ultrasound scanning and cytomegalovirus disease. ■

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REPLY

We thank Picone and Mandelbrot for their interesting comments. In Belgium, 3 prenatal ultrasound scans are refunded by the Federal Institute for Health Insurance (1st, 2nd, and 3rd trimester ultrasound examinations). As mentioned in our article, pregnant patients with primary cytomegalovirus infections were invited for targeted additional ultrasound scans to be performed every 4 weeks until delivery. Dates of the ultrasound scans and gestational ages for every included patient were registered (data not shown) as well as fetal and placental findings. We share the same opinion about correlations between autopsy findings and clinical postnatal cytomegalovirus impairments. Histopathologic observations should be interpretated with caution to avoid overestimation of adverse outcomes. On the other hand, underestimation of adverse outcomes should not be neglicted. A few patients in this study declined autopsy or were lost for follow-up. For several cases of pregnancy terminations, neuropathological examinations failed because of fetal brain tissue autolyse. Underestimation of adverse outcomes or missed falsely negative ultrasound assessments are therefore not excluded and could have led to overrated negative predictive values for fetal ultrasound. This study was initiated 20 years ago, the knowledge about cytomegalovirus infection, its natural history during pregnancy, and available tools for prenatal risk stratification were limited, compared with actual management options. In 1996, patients with first-trimester primary cytomegalovirus infection and proven fetal infection based on amniotic fluid analysis were considered to be at high risk for severe neurologic postnatal impairments. Therefore, management options that included pregnancy termination, even for cases with negative fetal ultrasound results, were discussed with patients. Important progress has been made. Risk for fetal neurologic impairments can be stratified with the use of noninvasive techniques like magnetic resonance imaging analysis with improved sensitivity and sensibility when compared with fetal ultrasound scanning.[1] This was implemented in our clinical practice with fewer indications for terminations. Nevertheless, discussions about prognosis and cytomegalovirus-related postnatal sequelae remain difficult. Counseling should include a broader clinical approach with a more extended screening for adverse outcomes. Ophthalmologic cytomegalovirus complications are clearly underestimated[2] as is long-term progressive hearing deterioration that has been noted in 18−62% of all children with sensorineural hearing loss at birth.[3] Both could lead to cytomegalovirus-related neurodevelopmental impairments without adequate identification and management. ■

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