study also showed a reduction in premature birth rates and small for gestational age. However, so far, evidence from trials of pharmacologic interventions failed to show a positive impact on neonatal outcomes.[2] We agree with the authors that smoking cessation is of utmost importance in improving neonatal outcomes. However, the intervention that was offered should have been unambiguously proven to be both effective and safe for short- and long-term endpoints. We disagree with Bérard et al that NRT is a good option for helping pregnant women quit smoking. Our concerns (based on animal studies) focus on its potential long-term pulmonary consequences.

Elastin is an extremely long-living protein that plays a crucial role in the lungs. Elastin's precursor tropoelastin is mainly synthesized perinatally after which the production is suppressed. Once tropoelastin has been produced, it is secreted into the extracellular matrix and aligned with other tropoelastin proteins into elastin fibers. Subsequently, elastin fibers have to be crosslinked with each other by the enzyme lysyl oxidase (LO). LO crosslinking is a crucial step in elastogenesis. Whereas crosslinked elastin is relatively resistant to degradation by elastases, uncrosslinked elastin is extremely vulnerable to these destructive enzymes. Furthermore, elastin only acquires its full elastic properties after proper LO-crosslinking.

Nicotine inhibits LO activity thereby interfering with elastin crosslinking.[3] Although nicotine during pregnancy has been shown not to have a significant effect on fetal growth, it does have an unfavorable effect on lung development.[3] The age of pulmonary elastin corresponds with the age of a subject and there is usually no substantial elastogenesis in the lungs after the perinatal period.[4] It is therefore likely that subjects who produce inadequate amounts of crosslinked elastin in utero have an increased likelihood of the development of chronic obstructive pulmonary disease (a respiratory disease characterized by loss of elasticity) as adults.

We propose a large intervention trial to be undertaken in order to assess the short- and long-term effects of NRT compared to placebo or against psychosocial interventions. In our opinion, pregnant women should not be advised to use NRT until it has been proved unequivocally that this intervention does not lead to adverse long-term pulmonary effects in their children. ■

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REPLY

We thank Drs Janssen and Oudijk for their comment on our article on the use of smoking cessation interventions during gestation among pregnant smokers.[1] However, their comments are based on animal studies and have limited clinical implications; furthermore, they do not provide comparative data with the effect of smoking itself. Furthermore, Janssen and Oudijk falsely interpret a non−statistically significant increased risk as "no positive effect" in the only human data that they gave as supporting documentation.[2] In Coleman et al's[2] meta-analysis, nicotine replacement therapy (NRT) use during gestation increased smoking cessation (which confirms our finding[1]); Coleman et al also showed that NRT use during pregnancy decreased the risk of adverse pregnancy outcomes, although the estimates were non−statistically significant. Coleman et al further revealed that NRT regimens were associated with higher rates of "survival without developmental impairment" in children, which is a benefit. In another study, Vaz et al[3] described that greater adherence was seen with NRT patches, which is what we are looking for in clinical practice.

With regards to smoking and second-hand smoking risks, human scientific peer-reviewed literature has shown that maternal smoking during pregnancy leads to adverse pregnancy outcomes such as major malformations, low birthweight, and chronic comorbidities in children such as asthma, which is a baseline risk.[1,4-6] Hence, our study[1] has attempted to determine the best option available to stop smoking during and after pregnancy to decrease the likelihood of 2 specific outcomes: low birthweight and prematurity. To do that, we have selected a study group of pregnant smokers within a predefined prospective pregnancy cohort; all our study subjects were smokers at the beginning of pregnancy. Hence, our findings reflect the clinical pathway by which a pregnant smoker would decide whether to stop or continue smoking once pregnancy is diagnosed. Our findings give the risk of adverse pregnancy outcomes above and beyond the risk that is associated with smoking.[1]

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