Tobacco and nicotine exposure prevention in pregnancy: a priority to improve perinatal and maternal outcomes

Jorge E. Tolosa, MD, MSCE; Ashley Scherman, PhD, RN; David M. Stamilio, MD, MSCE; Cindy T. McEvoy, MD, MCR

Tobacco smoking is the most important and prevalent modifiable risk factor for adverse pregnancy outcomes. Smoking is a major public health burden because it is associated with multiple adverse health outcomes including both maternal and perinatal morbidity and mortality.

Smoking-related maternal lung diseases such as chronic obstructive pulmonary disease and cancer are well characterized, but other less known smoking risks include hypothyroidism, ectopic pregnancy, and complications associated with surgery or anesthesia. Pregnancies exposed to tobacco smoking are at increased risk for fetal growth restriction, preterm birth and low birthweight, congenital anomalies such as cleft lip and palate, placental abruption, placenta previa, and perinatal mortality.

It is estimated that up to 8% of preterm births, nearly 20% of term low-birthweight neonates, up to 34% of sudden infant death syndrome cases, and up to 7% of preterm infant deaths can be attributed to maternal smoking.[1] In addition, maternal prenatal smoking increases risk for long-term childhood morbidity including asthma, obesity, and other cardiometabolic risk states.[1,2]

In a recent prospective longitudinal study of 587 preterm infants, maternal smoking prior to preterm birth increased the odds of having an infant with bronchopulmonary dysplasia by 2-fold.[3] Women are more likely to quit smoking while they are pregnant,[4] making pregnancy a teachable moment for smoking cessation, which can be extended to partners and family members who use tobacco. Furthermore, prenatal smoking cessation interventions have been shown to reduce the risk for low birthweight, neonatal intensive care unit admission, and possibly preterm birth.[5,6]

Prenatal smoking-cessation interventions represent a significant opportunity to substantially reduce lifetime health risk for the mother and newborn. Notably, maternal prenatal smoking cessation is an important public health benefit, even in the presence of postnatal smoking recidivism beasuse the short-term removal of fetal exposure to tobacco smoking appears to have preventive effects for fetal origins of disease such as obesity and asthma.[7,8]

The study by Oncken et al[9] is of great public health importance, given the recent trends in preterm birth and current tobacco smoking rates. Although the preterm birth rate in the United States declined between 2007 and 2014, the rate has significantly increased annually since 2014, and the most recent estimate is approximately 10%.[10] The preterm birth rate is now nearly 14% among non-Hispanic black American women.[10,11]

While smoking rates in the United States have decreased in recent years, tobacco smoking remains a public health crisis in the United States and worldwide, with increasing smoking rates globally.[12] Although the overall rate of smoking during pregnancy is estimated to be reduced to 7.2% in the United States,[13] this average can be misleading because certain subgroups already at higher risk for adverse perinatal and maternal outcomes have disproportionately higher rates of prenatal smoking, and the rate of smoking prevalence declination is worse among rural communities.[13]

Cigarette smoking differs markedly by maternal age, with the highest rate among women aged 20–24 years (10.7%), by race and Hispanic origin, and by education. Non-Hispanic American Indian or Alaska Native women had the highest prevalence of smoking during pregnancy at 16.7% and non-Hispanic Asian women the lowest at 0.6%. The prevalence of smoking in pregnancy was highest for women with only a high school diploma or general education diploma (12.2%).

Geographically in the United States, the rate was highest in West Virginia (25.1%) and Missouri (15.3%) and lowest in Arizona and California among other states, with a prevalence of less than 5%.[13] In women with high-risk pregnancies, the

From the Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, St. Luke's University Health Network, Bethlehem, PA (Dr Tolosa); Department of Obstetrics & Gynecology, Division of Maternal Fetal Medicine, Oregon Health & Science University, Portland, OR (Dr Tolosa); Global Network for Perinatal & Reproductive Health, FUNDARED-MATERNA, Bogotá, Colombia (Dr Tolosa); Departamento de Obstetricia y Ginecología, NACER Salud Sexual y Reproductiva, Universidad de Antioquia, Medellín, Colombia (Dr Tolosa); Oregon Health & Science University, Pediatrics, Portland, OR (Dr Sherman); Department of Obstetrics & Gynecology, Division of Maternal Fetal Medicine, University of North Carolina, Chapel Hill, NC (Dr Stamilio); and Department of Pediatrics, Division of Neonatology, Oregon Health & Science University, Portland, OR (Dr McEvoy).

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Corresponding author: Jorge E. Tolosa MD, MSCE. Jorge.Tolosa@sluhn.org

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TABLE 1
Biomarkers of tobacco smoke exposure for clinical use[a,b]

Biomarker	Sensitivity/specificity	Sample collection	Other considerations
Urinary cotinine[c]	↑ Sensitivity (100.0%) ↑ Specificity (95.0%)	■ Simple collection process ■ Cold storage required prior to shipping	■ Noninvasive ■ Cotinine levels are 4 times that of serum ■ Identify active from passive smoke exposure ■ Cost effective and simple point-of-care testing available ■ Appropriate for combustible and noncombustible nicotine exposure
Salivary cotinine[c]	↑ Sensitivity (100.0%) ↑ Specificity (96.0%)	■ Similar to urine	■ Similar to urine
Serum nicotine[d]	↑ Sensitivity (88%) ↑ Specificity (99%)	■ Blood draw by trained personnel required ■ Cold storage required prior to shipping	■ Invasive ■ Off-site analysis required, with costs varying widely among laboratories ■ Appropriate for combustible and noncombustible nicotine exposure
Exhaled carbon monoxide (CO)[e]	Sensitivity (23.1–92%) ↑ Specificity (88–100%)	■ Results may be influenced by the time of last cigarette smoked ■ Minimal training required	■ Noninvasive ■ Immediate results ■ Cost effective ■ Sensitivity dependent on device, parts per million cutoff, and patient factors such as exposure to air pollution and ability to exhale ■ Inappropriate for noncombustible nicotine exposure

Sensitivity is percentage of smokers detected accurately; specificity is percentage of nonsmokers detected accurately; cotinine is nicotine metabolite; half-life is 7–40 hours compared with a 1–4 hour nicotine half-life. *PPM*, unit of measurement of CO concentration in exhaled breath.

[a] Data from Chang et al. Biomarkers of tobacco exposure: summary of an FDA-sponsored public workshop. Cancer Epidemiol Biomarkers Prev 2017;26:291-302; [b] The gold standard for nicotine exposure is total nicotine equivalents or the molar sum of urinary nicotine, cotinine, and the metabolites of nicotine trans-3'-hydroxycotinine and their respective glucuronides. This test is likely impractical for routine clinical use and is not included here; [c] Stragierowicz et al. Estimation of cutoff values of cotinine in urine and saliva for pregnant women in Poland. BioMed Res Int 2013;2013; [d] Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. Am J Public Health 1987;77:1435-8; [e] Christenhusz L, De Jongh F, Van Der Valk P, Pieterse M, Seydel E, Van Der Palen J. Comparison of three carbon monoxide monitors for determination of smoking status in smokers and nonsmokers with and without COPD. J Aerosol Med 2007;20:475-83.

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rate of smoking reported in published data from the Maternal-Fetal Medicine Units Network of the National Institutes of Health—*Eunice Kennedy Shriver* National Institute of Child Health and Human Development can be as high as 16%.[14] Furthermore, prenatal smoking is determined by self-report with the risk of nondisclosure of smoking between 15% and 20%.[15]

Identifying pregnant women who are smoking is a critical first step to cessation. Biochemical markers of tobacco exposure are used in clinical studies and would likely improve the smoking detection rate if implemented universally in the clinical setting. Some of the screening methods available today may not be practical for the prenatal clinical setting (Table 1). However, the simple and cost-effective measurement of exhaled carbon monoxide (CO) is routinely used in the United Kingdom by the National Health Service. The introduction of routine CO monitoring increased the number of pregnant women referred to stop smoking services by more than 6% and doubled the number of pregnant women who were smoke free at 4 weeks after their quit date.[16]

Screening methods with urine or salivary cotinine appear promising for clinical use, given the favorable test characteristics (high sensitivity and specificity), relatively low cost, and ease of performing as a point-of-care test in the office.

If screening methods for assessment of tobacco exposure are available and were to be introduced into clinical practice, are there effective interventions to achieve the expected goals for improvement of perinatal and maternal outcomes? (Table 2) The clinical use of nicotine replacement therapy (NRT) in pregnancy remains controversial because of its questionable efficacy in prenatal smoking cessation and limited data on prenatal safety.[6,17]

We applaud Oncken et al[9] for performing this critically needed NRT intervention trial and in a population with a high rate of history of substance abuse. As the authors mention, most of the existing data are based on other NRT delivery methods such as patches, and it is quite possible that efficacy varies based on the drug vehicle used.[1,6,9]

While existing studies are heterogeneous with regard to design and quality, there may be a 40% improvement in smoking cessation with NRT.[6] The data on the effect of NRT on neonatal and longer-term childhood outcomes are remarkably sparse; the large majority of studies were not

TABLE 2
Clinical care interventions for smoking in pregnancy adapted from Scherman et al[a]

Maternal level interventions	Effectiveness	Implementation
Behavioral counseling	Highest effectiveness Interventions varying from self-help[c] to general health education increased prenatal smoking cessation by 44% compared with usual care (n = 30 studies; RR, 1.44; 95% CI, 1.19–1.73)[b]	■ Strong dose relationship ■ Time constraints in clinical setting common barrier ■ Screening every woman for tobacco exposure is critical first step
Pharmacotherapy		
Nicotine replacement therapy	Low effectiveness Placebo-controlled trials among pregnant women (RR, 1.28, 95% CI, 0.99 to 1.66, n = 5 studies. No difference in birth outcomes.[d]	■ FDA pregnancy categories C (gum) and D (all other formulations) ■ Cessation rates vary by NRT formulation ■ No prescription required ■ Costs range from $10 to >$100. depending on formulation and insurance coverage
Bupropion HCL (Zyban, Wellbutrin) or Varenicline (Chantix)	Effectiveness in pregnancy unclear[d]	■ FDA pregnancy category C ■ No rigorous RCTs in pregnant women ■ Adverse side effects similar for both including insomnia and dry mouth and increased risk of seizures ■ Costs dependent on insurance coverage
Contingency management	Trending toward effective Financial incentives and deposit return interventions improved smoking cessation across early and late pregnancy (n = 6 studies; ORs range 2.86 to 3.96; $P < .01$)[e]	■ Concern for cost and public opinion ■ Lacks standardized protocol for implementation; requires more RCTs ■ Incentives-based and deposit-based methods
Fetal-level intervention		
Vitamin C supplementation	Effective Prenatal 500 mg/daily of vitamin C significantly ↑ pulmonary function at birth with 50% ↓ wheezing at 1 year vs placebo[f]	■ Must be combined with maternal level cessation interventions ■ Simple: can be ingested in diet or as a supplement, well tolerated ■ Vitamin C may have adverse effects at high doses; 500 mg/day normalized vitamin C blood levels to those of pregnant nonsmokers[f] ■ Cost effective[g]

Bupropion is from Glaxo Smith Kline, England; Varenicline is from Pfizer, United States.

CI, confidence interval; *FDA*, US Food and Drug Administration; *NRT*, nicotine replacement therapy; *OR*, odds ratio; *RCT*, randomized clinical trial; *RR*, relative risk; *SGA*, small for gestational age.

[a] Scherman A, Tolosa JE, McEvoy C. Smoking cessation in pregnancy: a continuing challenge in the United States. Ther Adv Drug Saf 2018;9:457-74; [b] Chamberlain C, O'Mara-Eves A, Porter J, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev 2017:CD001055; [c] https://women.smokefree.gov/; [d] Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev 2015:CD010078; [e] Wilson Smet al. Contingency management versus psychotherapy for prenatal smoking cessation: a meta-analysis of randomized controlled trials. Womens Health Issues 2018;28:514-23; [f] McEvoy CT, Schilling D, Clay N, et al. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. JAMA 2014;311:2074-82; [g] Yieh L, McEvoy CT, Hoffman SW, Caughey AB, MacDonald KD, Dukhovny D. Cost effectiveness of vitamin c supplementation for pregnant smokers to improve offspring lung function at birth and reduce childhood wheeze/asthma. J Perinatol 2018;38:820-7.

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designed to detect differences in clinically relevant neonatal outcomes, and several studies were discontinued early by a Data Safety Monitoring Board (DSMB), further reducing the ability to assess differences in neonatal and smoking cessation outcomes.[1,6]

This lack of NRT perinatal safety data is overlaid on the very well-characterized and formidable risks of continued maternal smoking without a cessation intervention. The clinical trial by Oncken et al[9] is the initial next step toward advancing the great and urgent need for research evidence on the efficacy and safety of NRT and other smoking-cessation prenatal interventions.

These results should pave the way for future placebo controlled randomized controlled trials designed to maximize adherence and to assess the important neonatal and childhood outcomes. While these future studies must be designed to minimize NRT-related fetal risk with DSMB oversight, the rules for safety should bear in mind the high burden of smoking risk as well as the need to simultaneously monitor both maternal and perinatal outcomes.

We believe that this clinical trial will significantly inform future intervention studies aimed at tobacco smoking cessation/mitigating the effects of smoking in pregnancy. The results of this study highlight the importance of defining

neonatal primary outcomes in addition to or in lieu of smoking cessation outcome measures. This study demonstrates the significance of perinatal outcomes such as preterm birth and low birthweight because the risk for these outcomes was reduced, even without an apparent effect on smoking cessation.

The small sample size and low follow-up for planned visits in the trial by Oncken et al[9] limit the interpretation of those results because of the finding of a very low rate of preterm birth in the nicotine group of only 4%.

From the fetal and neonatal perspectives, reducing risks of preterm birth and low birthweight with their accompanying downstream lifelong morbidities is equally (if not more) important as maternal smoking cessation. Perhaps the observed improved neonatal outcomes were mediated by an overall reduction in cigarettes per day and/or by a reduction in nonnicotine cigarette toxin exposure with the use of the nicotine inhaler vs placebo, but this theory is a topic for further research.

Similarly, this study also informs how future DSMB protocols are developed. For example, future studies may consider using rules for stopping a study based on a futility definition that include both smoking-cessation outcomes and neonatal/perinatal outcomes rather than only cessation. This study was discontinued for reasons of futility based on smoking-cessation rates after approximately 50% enrollment. While the study results are informative, its early termination and low rate of treatment completion limits its power in estimating the effects of the change in cigarettes per day, particularly in the more distant follow-up points and limits precision in estimates of adverse neonatal outcome rates.

While smoking cessation should always be the foremost goal, including in the postpartum period and for a lifetime, decreasing the effects of in utero smoke on neonatal/childhood outcomes will likely take a multipronged approach. This may include counseling and other interventions proven safe, effective, and feasible during pregnancy. For example, 2 randomized controlled trials of vitamin C supplementation (500 mg/day) to pregnant smokers revealed that infants born after vitamin C supplementation had improved newborn pulmonary function tests and decreased wheeze through 12 months of age[18] and significantly improved forced expiratory flows/pulmonary function tests at 3 months.[19]

In addition, the relative role of nicotine alone vs other toxins in the tobacco smoke on perinatal outcomes is a critical unanswered question and of mounting importance because the rate of the use of the electronic cigarette (e-cigarette) or the practice of vaping has increased significantly, especially in adolescents.[20,21]

Coinciding with the historic publication of this first issue of the AJOG-MFM, we propose that research and action to prevent exposure to tobacco and nicotine in pregnancy and across the life span of women be moved up in the list of urgent priorities in health care. This strategy will need to be addressed by professional organizations by advocacy and commitment and by the National Institutes of Health with increased funding of research in this field.

In the clinical area, as specialists in maternal-fetal medicine, neonatology, and nursing conducting research on this topic and caring for women and babies every day, we propose a direct, practical, and measurable action to be taken such as screening with the use of biological markers of exposure, to be introduced as a routine into prenatal care and the postpartum period. ■

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