



Improving fetal lung development with vitamin C and reducing asthma in children

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Harm reduction (HR) is a public health strategy developed initially in adults with substance-abuse problems when abstinence was not feasible. HR approaches have been effective in reducing morbidity and mortality in these adult populations, and in recent years has been applied to sexual health education to reduce both teen pregnancies and sexually transmitted disease, alcohol consumption and other risky behaviors. HR emphasizes the measurement of health, social, and economic outcomes, as opposed to the measurement of drug (or other substances) consumption.

HR efforts for fetuses exposed to maternal smoking would, ideally, be maternal tobacco smoking cessation and stopping all forms of nicotine. Some programs to reduce smoking during pregnancy have shown some success, but the goal of a tobacco free pregnancy is difficult to achieve [1]. While pregnancy appears to motivate 46% of pregnant women to quit smoking before or during pregnancy [2], cessation focused therapies including motivational interviewing, cognitive behavioral therapies, text messaging, and nicotine replacement therapies have been ineffective in persuading all pregnant women to quit [3–5]. An estimated 13 to 25% of American women continue to smoke tobacco during pregnancy. This is despite the known dose-dependent negative effects of smoking during pregnancy on infant birth weight and its contribution to preterm birth [6].

Use of alternative forms of nicotine delivery, such as electronic cigarettes and vaping, have increased substantially in recent years; however, minimal evidence demonstrates that these alternative nicotine delivery systems alter the detrimental health effects of nicotine exposure compared to traditional cigarettes. The promotion of

electronic cigarettes as a method of HR has been falsely championed as a method to reduce cigarette smoking, when in fact, many pregnant women choose to combine both cigarette smoking and e-cigarette use rather than participate in cessation programs [7]. The U.S. Preventive Services Task Force has concluded that current evidence is insufficient to assess the balance of benefits and harms of nicotine replacement products or other pharmaceuticals for smoking cessation during pregnancy [8]. Further, conflicting evidence exists regarding whether nicotine replacement therapy increases abstinence rates of smoking during pregnancy, and it does not appear to increase the odds of permanent smoking cessation during the postpartum period or during breastfeeding [9].

Several authors have reported reduced pulmonary function among preterm and term infants whose mothers smoked during pregnancy [10–13]. Recent evidence supports that much of the adverse effects of tobacco smoking during pregnancy on neonatal lung function is mediated by nicotine. Therefore, electronic cigarette use (or “vaping” nicotine) during pregnancy is likely also to have harmful effects on newborn lung function. For instance, McGrath–Morrow and colleagues demonstrated convincingly that exposure of neonatal mice to electronic cigarette vapor impaired lung growth and decreased body weight compared to vehicle (propylene glycol) [14].

Nicotine is a primary modulator of fetal lung development. Fetuses of mothers who smoke are exposed to nicotine in utero and multiple studies in animal models, including primates, clearly document that nicotine stunts fetal lung growth (alveolar and pulmonary vasculature development, airway growth, and reduces total lung weight). Various mechanisms have been proposed. Several years ago, McEvoy, et al. showed that a daily supplement of 500 mg vitamin C during pregnancy reduced abnormalities in neonatal pulmonary function and was associated with reduced relative risk of wheezing at 1 year of age by 56% [15]. Pharmacokinetic data suggest that 500 mg of vitamin C daily saturates vitamin C receptors and maximizes plasma

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concentrations [16]. McEvoy, et al. demonstrated that pregnant smokers randomized to 500 g of vitamin C had significantly increased levels of ascorbic acid compared to pregnant smokers randomized to placebo, and their vitamin C levels were to comparable to pregnant non-smokers in the trial.

Based on the McEvoy, et al. [15] data (and three other prospective birth cohorts that demonstrated longitudinal effects of fetal and infant smoking exposure through adolescence) in this issue of *J Perinatology* Yieh, et al. [17] develop an intriguing decision-analytic model to estimate the effect of maternal vitamin C administration on costs and outcomes specifically related to the burden of pregnancy-induced asthma in the United States. They considered primarily the extrapolated effect of additional maternal vitamin C supplementation to pregnant women who smoke during pregnancy on quality adjusted life years and asthma associated economic costs through adolescence for the US population. The economic impact was huge as was the improvement in quality adjusted life years. The author's carefully describe limitations of their model and predictions, leading to new questions and where to next focus our efforts for HR.

In this issue, Yieh, et al. [17] estimate economic benefit of vitamin C supplementation, along with the usual prenatal vitamins, exceeds \$30,000,000 over 18 years and increases quality adjusted life years by 19,200 for the >400,000 infants annually exposed to maternal smoking. This economic benefit whether measured in dollars saved or quality adjusted life years improved is "small change" considering the impact of asthma on childhood activities such as healthy exercise, sports participation, better school attendance, and improved self-esteem among these children. The reduction in cost burden to parents in terms of loss of work, trips to the emergency department, or for medications is also a major economic benefit. The analysis also predicted fewer deaths from asthma with this simple intervention, but childhood death secondary to asthma is a rare event.

How can the impact of this novel HR approach be proven to reduce asthma in childhood on a national or global scale? A large multicenter trial (with high power and with stringent *p*-values) could be undertaken to demonstrate vitamin C in addition to prenatal vitamins normalizes pulmonary function in newborns compared in a prenatal multi-vitamin alone. Such cohorts would require follow-up through at least 6 years to determine differences in asthma prevalence, needed medical services including hospitalization, and prescriptions to treat asthma. Alternatively, adopting the strategy that vitamin C supplementation for all pregnant women who smoke or use e-cigarettes could be compared with historical non-supplementation data.

All providers of maternity care should stress effective HR strategies by encouraging tobacco (and nicotine vaping) cessation when possible, recommending a healthy diet rich in ascorbic acid, and by prescribing supplemental vitamin C to mitigate the harm of nicotine to their fetuses, babies, and children.

Let us not delay.

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