In Utero Smoke and Gene Interactions: Long-Term Consequences on Respiratory Health

There are convincing data from longitudinal birth cohorts demonstrating how an individual's pulmonary function tracks over time and is established very early (1). This trajectory can be affected by both prenatal and early postnatal insults, as well as by genetic factors. These variables can have long-term effects on lung function and lung heath, and also may affect risk for chronic obstructive pulmonary disease in adulthood (2). *In utero* tobacco smoke exposure has consistently been associated with reduced pulmonary function test (PFT) values in infancy and childhood, and recent studies have shown that this effect on PFTs extends into early adulthood. Despite campaigns to decrease *in utero* smoke exposure, 50% of pregnant smokers continue to smoke (3). In addition, 40% do not realize that e-cigarettes contain nicotine, which is believed to be one of the primary mediators of *in utero* tobacco insults on the fetal lung (4). As a consequence, ascertaining new ways to mitigate the effects of *in utero* smoke exposure on lung function is of substantial importance.

Longitudinal birth cohort studies are difficult, but are critical to our understanding of factors affecting PFT trajectories. In this issue of the *Journal*, Owens and colleagues (pp. 462–470) report the continued follow-up of the Perth Infant Asthma Follow-up study, a longitudinal nonselected birth cohort of 253 term subjects recruited antenatally (5). These subjects have had regular respiratory assessments from infancy up to age 24 years, including PFTs at 6, 11, 18, and 24 years. Prenatal and postnatal tobacco exposures were documented for the mother, the father, or both parents. In the current publication, the authors report the longitudinal assessment of PFTs from 6 to 24 years in 199 of the subjects. They document a lower FEV_1 and FVC from ages 6 to 24 years after *in utero* smoke exposure (mean difference, −3.87% predicted [$P = 0.021$] and −3.35% predicted [$P = 0.035$], respectively). Although these differences are modest, they are likely clinically important and are similar to differences reported in other longitudinal studies (6).

The authors also evaluated the effect of GST (glutathione *S*-transferase) genotypes on PFT outcomes after *in utero* smoke exposure. GST can affect xenobiotic metabolism, antioxidant defenses, and nitrogen oxide metabolism (7–9). Variants in GST genes are known to increase both the sensitivity of the fetus to maternal smoking and the risk for asthma, likely in association with loss of lung function (8, 9). Conversely, the presence of normal GST genes may have protective effects against the negative effects of *in utero* smoke. Here, the authors have confirmed the relevance of GST gene variants. They have also shown that subjects who had a genotype associated with the more "active" GST isoform M1 are somewhat protected after infancy from lower FEV_1 associated with smoke exposure *in utero*. The largest deficit in FEV_1 after *in utero* smoke exposure in the GSTM1 null genotype subjects was at 6 years of age; FVC was decreased at 6, 11, and 24, but not 18, years of age.

Note that the data from Owens and colleagues (5) support the potential for prevention of both obstruction and restriction by targeting fetal antioxidant pathways in infants of smokers. For example, two randomized controlled trials of vitamin C supplementation (500 mg/d) to pregnant smokers (10, 11) reveal that infants born after vitamin C supplementation had both improved newborn PFTs and decreased wheeze through 12 months of age (10) and significantly improved/increased forced expiratory flows at 3 months of age (11). Although the mechanism of action of vitamin C is still under investigation, antioxidant effects and beneficial effects on collagen synthesis seem likely. A key unanswered question concerns the relative role of nicotine alone versus other toxins in tobacco smoke. This question has increasing importance with the rising use of e-cigarettes.

Physiologically, it is curious that the prenatal lung is highly affected by circulating maternal toxins resulting from smoking. Fetal blood in contact with toxins from the placenta largely bypasses the lung on its first pass through the fetal circulation. Indeed, GST isoforms are not prominently expressed in pulmonary vessels. Why should the lung periphery and lung volume be selectively affected? One possible explanation is that the toxins may be excreted into the amniotic fluid through fetal urine, and inspired into the distal airway during fetal respiration. Another reason may be the high expression of nicotinic receptors in developing lung (12). Future studies could compare amniotic with placental and with umbilical toxin profiles. The effects that amniotic nicotine, nitrogen oxides, oxidants, and other toxins have on airway and acinar prenatal growth could be studied in animal models.

The study by Owens and colleagues (5) does have limitations. First, it was an observational study, and causation cannot be evaluated. Second, only 46% of the initial cohort had PFTs done at 24 years of age, and only 179 subjects had genotypes done. These factors limit power, particularly given that multiple comparisons were performed. For example, the GSTT1 null genotype is rare, and only six subjects had both the GSTT1 null genotype and maternal *in utero* smoke exposure. Third, the smoking history was by maternal report: only a subset of subjects had urine cotinine assayed. Fourth, up to 20% of pregnant smokers lie about their smoking (13), and there was likely some misclassification. Fifth, children of smokers often smoke (14), but information on personal smoking by the offspring was not collected. Sixth, direct measurements with techniques, such as plethysmography or gas dilution, were not made to confirm loss of lung volume, and other investigators suggest that *in utero* smoke exposure primarily causes obstruction (15). Finally, GST deletions were not analyzed by gene copy number, and dose response from single allele deletion may have been missed. Despite these limitations, the work represents an important contribution.

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In summary, Owens and coworkers (5) have shown that *in utero* smoke exposure is associated with PFT deficits later in life. They argue that *in utero* smoke affects lung size, and that this effect is modulated by antioxidant genotype. Although more studies are needed, this article confirms the value of primary prevention to mitigate the adverse effects of *in utero* smoke exposure on the sensitive fetal lung. ■

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Fail-Fast in Respiratory Syncytial Virus Vaccine Development

Despite of progress made for the past decades in the field of respiratory syncytial virus (RSV), we are still lacking a safe and effective RSV vaccine. In the absence of a correlate of protection to RSV, vaccine developers are working in the dark, and therefore often find out that their product is insufficiently effective (1). For example, Novavax developed a nanoparticle-based RSV vaccine for older adults and went through a large phase 2b trial, only to find out it was not effective in a large phase 3 trial (2). Novavax got back on its feet and is currently unblinding their next phase 3 trial, now in pregnant women (3). To accelerate RSV vaccine development, developers adopted the fail-fast approach.

Fail-fast systems were designed to immediate report failure to stop product development, rather than continue developing a product that likely will never be good enough. The fail-fast approach has been adopted by the pharmaceutical industry and became the mantra of many start-up companies not only to prevent wasting efforts, but also to create a healthy society in which entrepreneurs can fail, learn and improve (4). However, the fail-fast strategy has its own challenges, which are illustrated in this issue of the *Journal* by Ascough and colleagues (pp. 481–492) (5). In their article, they describe the results of a phase 1 study of a novel needle-free RSV vaccine: SynGEM. The vaccine is based on a stable prefusion F antigen of the virus and uses a bacterial-like particle as an

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