

Managing Asthma during Pregnancy What Information Do We Need to Optimize Care?

Eight percent of pregnant women have asthma and are at increased risk for complications including preeclampsia, preterm birth, low infant birth weight, and infant congenital malformations (1–3). In addition studies show strong association between poorly controlled asthma and increased risk of these adverse outcomes, suggesting that good asthma management in the preconception period and during pregnancy benefits both mother and fetus (4, 5). However, optimal asthma management relies primarily on symptomatic treatment of acute exacerbations with bronchodilators and possibly oral corticosteroids and the regular use of inhaled corticosteroids (ICS) to reduce the frequency and severity of exacerbations. Pregnant women have reported concerns regarding the risks of birth defects as reasons to avoid corticosteroid use (6), and in one study there was a 23% decrease in ICS prescriptions during pregnancy compared with the preconception period. Nonadherence to treatment has been associated with significant asthma exacerbations during pregnancy (7, 8) and, in at least one study, poor asthma control in mothers with severe asthma was associated with increased risk of asthma development in the offspring (9). It is clear that treatment strategies which optimize maternal asthma control benefit both mother and child (5, 7–9). However, few studies have addressed the effects of asthma medication use in the pregnant mother and developing fetus. Bronchodilators in pregnant women have been examined (primarily their use as tocolytics rather than for asthma exacerbations). Witter and coworkers (10) have suggested that the use of β_2 -agonists increases the frequency of neurodevelopmental disorders in the offspring, possibly resulting from β_2 -agonist effects on the balance of sympathetic–parasympathetic tone, which may be particularly affected at specific developmental stages (10).

The mainstay of asthma prevention and management is ICS. One study suggested that use of high-dose ICS during pregnancy may increase the risk of congenital malformations (11); however, several studies have not shown similar adverse effects with use of lower-dose therapy ($< 1,000 \mu\text{g/d}$ budesonide equivalent) (12, 13). Studies of any potential adverse effects are, however, largely observational and do not examine different ICS formulations available. Presently budesonide is the only ICS that was well evaluated and has a specific indication for pregnant women. It is not clear whether other ICS with less bioavailability may have reduced impact on the fetal/maternal interface while providing good asthma control.

Systemic corticosteroid treatment in pregnant women have effects on fetal adrenal function (14), autonomic heart rate (15), cerebral vasculature (16), and amniotic fluid protein expression (17). Given the differences in absorption and utilization of inhaled versus systemic corticosteroids, it is reasonable to postulate that the effects seen with oral steroids are not directly translatable to the inhaled medications. However, there is a paucity of investigations on the effects of ICS on the maternal adrenal axis and the developing fetus. One study by Clifton and colleagues (18) showed that inhaled budesonide was associated

with increases in placental 11β -hydroxysteroid dehydrogenase type 2 activity from subjects with asthma compared with control subjects without asthma, while other ICS, such as fluticasone, had no effect. 11β -hydroxysteroid dehydrogenase type 2 activity has been associated with fetal growth, but in this study changes in activity were not associated with significant differences in growth parameters at birth. To determine optimal asthma management during pregnancy, studying the potential effects of inhaled corticosteroid on both maternal and fetal physiology is essential.

In the study by Hodyl and colleagues (19) in this issue of the *Journal* (pp. 716–722), the investigators have prospectively studied women during all stages of pregnancy and compared subjects with asthma versus control subjects without asthma with respect to asthma severity, ICS use, effects on maternal HPA axis, and fetal growth parameters to determine the effects of ICS use and dose regimens for the management of asthma. Specifically, they studied maternal serum levels of hormones associated with fetal adrenal activity (estriol), placental activity (CRH), maternal HPA axis, and glucocorticoid-regulated pathways (cortisol and osteocalcin). They show that fetal-related adrenal activity is unaffected by ICS treatment. Fetal growth was also unaffected. There were, however, changes in maternal glucocorticoid dependent pathways which varied depending upon the hormone assessed, the trimester of pregnancy, and sex of the fetus in a dose-dependent manner. These very interesting data show effects of ICS on maternal pathways, but no effects on fetal HPA axis as determined by maternal estriol levels, demonstrating that the use of ICS in pregnancy does not significantly impact fetal HPA function.

These investigators limited their study to a surrogate marker of fetal HPA axis function. Direct assessment of fetal and/or newborn HPA activity was not assessed. Comprehensive assessment of infant HPA axis soon after birth using cord blood analysis and infant cortisol levels would provide direct evidence regarding the safety of maternal ICS use. Given the multiple effects of maternal systemic corticosteroid use on fetal end organs such as the heart, lung, and brain, these areas also need to be examined to further support the safety of ICS in pregnancy for fetal outcomes. In addition, studies of glucocorticoid-responsive pathways during postnatal development should also determine long-term effects (if any) of prenatal ICS exposure in infants and children of mothers with asthma.

This study relied on maternal reporting of ICS use, which may have been limited by recall biases and potentially by the reluctance of mothers to use regular ICS during pregnancy. Given these potential limitations, the results showing little or no ICS effects on fetal measurements must be interpreted with caution. However, the authors were able to demonstrate effects on maternal HPA axis, suggesting that most mothers used at least some ICS, although the precise amounts used were not rigorously quantified. The ideal study design would need to objectively monitor maternal ICS use and compare the different ICS such as budesonide versus the newer ICS specifically formulated to have reduced systemic bioavailability, thus providing clinicians with objective evidence for the formulation of optimal asthma management plans for pregnant women.

In conclusion, the potential negative effects of ICS use in the pregnant woman and the developing fetus continue to be of significant concern to both patients and healthcare providers. The study by Hodyl and colleagues (19) is one of only very few studies that specifically assessed physiologic effects of ICS on the fetal/maternal interface. The encouraging results from this paper seem to *a priori* support the concept that ICS may be safe for use during pregnancy, such as to decrease the adverse effects of poor asthma control on both mother and child.

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Regenerative Pathways and Emphysema A New Paradigm?

Chronic obstructive pulmonary disease (COPD) is a major source of healthcare burden around the world with few therapeutic remedies (1). Cigarette smoking is the most important risk factor for COPD, including emphysema, whose pathogenesis centers on the roles of smoking-induced oxidative stress (2), inflammation leading to protease/antiprotease imbalance (3), and alveolar epithelial cell apoptosis (4) in promoting alveolar destruction. In this issue of the *Journal*, Kneidinger and colleagues (pp. 723–733) expand on the paradigm that emphysema follows from an absence of cellular and molecular maintenance and/or repair mechanisms (5, 6). Specifically, their investigations address whether a failure to activate a core developmental pathway after injury causally contributes to disease, and whether its forced activation can boost suboptimal repair processes that restore alveolarization and lung function.

The authors' rationale for choosing to focus on the Wnt/ β -catenin pathway is compelling. Wnts are secreted lipoglycoproteins used reiteratively throughout development and adult tissue homeostasis to instruct cellular identities. Wnt-mediated cell specification is ultimately controlled by a tran-

scription complex that contains a DNA-binding factor from the lymphocyte enhancer factor (LEF) or T cell factor (TCF) families, and the dual signaling/adhesion protein, β -catenin (Figure 1). In this complex, β -catenin serves as an obligate co-activator through its ability to recruit components that promote chromatin remodeling and transcriptional initiation/elongation. In the lung, Wnt/ β -catenin signaling is required throughout development from its earliest stages (7) through distal lung morphogenesis (8). In adult tissues, β -catenin signaling maintains dedicated stem cell fates (9, 10), and in the adult lung may contribute to airway repopulation after injury (11) and alveolar epithelial cell survival (12). Excessive β -catenin signaling is known to drive proliferative diseases like cancer (13) and, more recently, fibrosis (14, 15). Based on these data, Kneidinger and coworkers hypothesized that a reduced capacity to activate Wnt/ β -catenin signaling might contribute to the phenotype of alveolar loss that characterizes emphysema due to improper repair.

Using both elastase- and cigarette smoke-injury models in mice, the authors show substantial down-regulation of Wnt signaling components in treated versus control mice. Reduc-

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