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Prenatal Stress, Prematurity, and Asthma

Brock Medsker, MD, MS,* Erick Forno, MD, MPH,†
Hyagriv Simhan, MD, MSc,‡ and Juan C. Celedón, MD, DrPH§

*Fellow, Division of Newborn Medicine, and †Assistant Professor of Pediatrics, Division of Pulmonary Medicine, Allergy and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC; ‡Associate Professor of Obstetrics, Gynecology and Reproductive Sciences, and Chief, Division of Maternal-Fetal Medicine, Magee Women's Hospital, Department of Obstetrics, Gynecology and Reproductive Sciences, Pittsburgh, PA; and §Niels K. Jerne Professor of Pediatrics and Chief, Division of Pulmonary Medicine, Allergy, and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA

Asthma is the most common chronic disease of childhood, affecting millions of children in the United States and worldwide. Prematurity is a risk factor for asthma, and certain ethnic or racial minorities such as Puerto Ricans and non-Hispanic blacks are disproportionately affected by both prematurity and asthma. In this review, we examine current evidence to support maternal psychosocial stress as a putative link between prematurity and asthma, while also focusing on disruption of the hypothalamic-pituitary-adrenal (HPA) axis and immune responses as potential underlying mechanisms for stress-induced "premature asthma." Prenatal stress may cause not only abnormalities in the HPA axis but also epigenetic changes in the fetal glucocorticoid receptor gene (*NR3C1*), leading to impaired glucocorticoid metabolism. Moreover, maternal stress can alter fetal cytokine balance, favoring T_H2 (allergic) immune responses characteristic of atopic asthma: interleukin 6 (IL-6), which has been associated with premature labor, can promote T_H2 responses by stimulating production of IL-4 and IL-13. Given a link among stress, prematurity, and asthma, future research should include birth cohorts aimed at confirming and better characterizing "premature asthma." If confirmed, clinical trials of prenatal maternal stress reduction would be warranted to reduce the burden of these common comorbidities. While awaiting the results of such studies, sound policies to prevent domestic and community violence (eg, from firearms) are justified, not only by public safety but also by growing evidence of detrimental effects of violence-induced stress on psychiatric and somatic health.

Target Audience: Obstetricians and gynecologists, family physicians.

Learning Objectives: After completing this activity, the learner will be better able to understand the quality and limitation of the current evidence for a link between prenatal stress and prematurity or asthma, compare and contrast the feedback mechanisms for cortisol regulation at the brain and placenta in response to stress, demonstrate an understanding of racial differences in hormonal and cytokine response and how this may apply to increased risk of preterm birth among certain groups, and examine potential mechanisms by which alterations in the HPA axis and immune responses can contribute to preterm birth and asthma.

Asthma is a major public health problem and the most common chronic disease of childhood.¹ In the United States, the burden of asthma is unevenly distributed

among racial/ethnic groups, with Puerto Ricans and non-Hispanic blacks being more heavily affected than non-Hispanic whites or Mexican Americans.²

All authors and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations pertaining to this educational activity.

Correspondence requests to: Juan C. Celedón, MD, DrPH, Division of Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Pittsburgh, PA 15224. E-mail: juan.celedon@chp.edu.

Preterm birth is frequent in the United States, and prematurity-related complications may explain approximately 15% of the global mortality in children younger than 5 years.³ Prematurity is also a risk factor for childhood asthma. In a meta-analysis of 19 studies published over a 40-year period, premature children of all ages had 37% greater odds of asthma than children born at term (95% confidence interval [CI] for adjusted odds

ratio, 1.30–1.43).⁴ Prematurity may partly explain racial or ethnic disparities in asthma, as preterm birth is more common in Puerto Ricans (13.7%) or non-Hispanic blacks (17.1%) than in non-Hispanic whites (10.8%) or Mexican Americans (11.3%).⁵

A potential explanation for the high prevalence of both prematurity and asthma in certain minority groups is maternal psychosocial stress. Maternal stress or anxiety during pregnancy has been associated with prematurity⁶ and asthma or morbidity from asthma.⁷ To date, no study has directly examined whether the link between maternal stress and childhood asthma is mediated by the effect of stress on prematurity rather than being independent of such effects (Fig. 1).

Maternal stress leads to excess glucocorticoid production, which can impair the development of the hypothalamic-pituitary-adrenal (HPA) axis and fetal growth, while also causing heritable epigenetic changes.⁸ Moreover, glucocorticoid-regulated genes are key to fetal lung development, especially during the first and second trimesters of pregnancy.⁹ In this hypothesis-generating review, we will discuss some potential mechanisms of stress-related asthma in premature children.

GLUCOCORTICOIDS AND THE HPA AXIS

In humans, the HPA axis is regulated through negative feedback mechanisms. After being released from the periventricular nucleus of the hypothalamus, corticotropin-releasing hormone (CRH) binds to CRH receptors in the anterior pituitary gland to stimulate the synthesis of pro-opiomelanocortin, which is then cleaved to produce adrenocorticotrophic hormone. Adrenocorticotrophic hormone is next released from the pituitary gland into the bloodstream, where it travels to the adrenal glands and triggers the synthesis of cortisol.

Cortisol can then down-regulate the HPA axis by binding to glucocorticoid receptors (GRs) and mineralocorticoid receptors in the hippocampus, periventricular hypothalamus, and the pituitary gland.

The role of glucocorticoids in fetal programming has been recently reviewed.^{10,11} During pregnancy, the fetus is exposed to endogenous glucocorticoids from the maternal circulation and, potentially, to exogenous glucocorticoids used to treat relatively common (eg, preterm labor, maternal asthma, or autoimmune disorders) or uncommon (eg, congenital adrenal hyperplasia) conditions. This is important, as prenatal exposure to increased levels of endogenous (eg, due to increased stress) or exogenous glucocorticoids can cause lasting alterations in the fetal and neonatal HPA axis.¹⁰

THE PLACENTA AND THE HPA AXIS

The placenta influences the maternal-fetal HPA axis in two ways. First, the placenta is a second source of CRH production. Corticotropin-releasing hormone is produced and released from the placenta through positive feedback in response to both maternal and fetal cortisol levels.^{12,13} This differs from the negative feedback effect of cortisol on the maternal-fetal HPA axis. The overall result is an exponential increase in CRH levels in late gestation, which has been postulated to trigger parturition.¹⁴ Second, the placenta serves as a buffer for glucocorticoids passing from mother to fetus because of the presence of 11 β -hydroxysteroid dehydrogenase type 2 (HSD11B2), an enzyme that converts cortisol into less active forms. HSD11B2 levels can in turn be up- or down-regulated by environmental cues or maternal stress.¹⁵

Acute and chronic stress has been shown to differentially affect expression of the gene for HSD11B2 (*HSD11B2*) in murine models and in humans. In

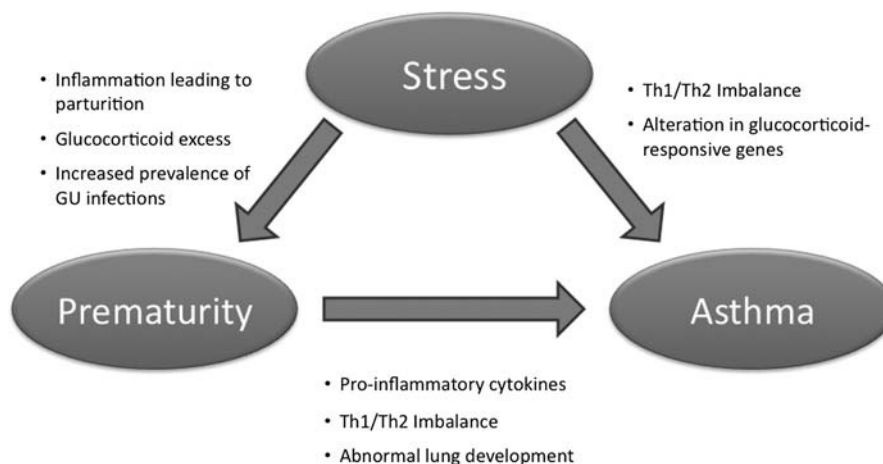


FIG. 1. Potential mechanisms for the links among prenatal stress, prematurity and asthma.

pregnant women, increased levels of HSD11B2 have been found in the placenta in response to acute stress,¹⁶ and chronic stress (assessed by questionnaires¹⁷) is associated with down-regulation of *HSD11B2*, which can lead to excess cortisol and lower neonatal birth weight.¹⁵ Stress could alter regulation of HSD11B2 through increased methylation of the gene promoter¹⁸ or through inflammatory mediators.¹⁹

PRENATAL STRESS AND PREMATUREITY

The relation between prenatal stress and prematurity is complex and likely influenced by timing and degree of maternal perceived stress, type of stressor^{20,21} and maternal coping mechanisms, and maternal race or ethnicity. For example, exposure to an earthquake (a traumatic event) has been associated with preterm birth only when such exposure occurred during the first trimester of pregnancy.²² Similarly, a mother's previous history of stressful events and development of successful mechanisms to cope with stress may be more important to the pathogenesis of preterm birth than the number of stressful events per se.²³ Moreover, race or ethnicity may modify the effect of stress on immune responses relevant to preterm birth. In a study of 78 pregnant and nonpregnant women, serum interleukin 6 (IL-6) levels measured 2 hours after exposure to an acute stressor were 46% higher in African Americans than in whites (95% CI, 8%–81%).²⁴

Maternal stress may directly lead to prematurity through effects on the maternal-fetal HPA axis and immune responses or indirectly by promoting unhealthy behaviors that increase the risk of preterm delivery (eg, smoking, substance abuse, or poor dietary habits).¹⁴ Maternal stress leads to increased cortisol levels, which can in turn lead to increased placental CRH and prostaglandin (PG) production, signaling the start of labor. Increased serum CRH at 33 weeks of pregnancy has been associated with a 3-fold increased risk of spontaneous preterm birth (95% CI for adjusted relative risk, 1.2–9.4).¹³ Of interest, CRH levels were highest in African American women who reported higher levels of cumulative stress, racial discrimination, and community violence.²⁵

Alternatively, stress can lead to impaired cellular immune responses and impaired suppression of proinflammatory cytokines.²⁶ For example, maternal stress could enhance susceptibility to genitourinary infections such as bacterial vaginosis, ultimately leading to increased risk of premature delivery.²⁷ Prevalence of bacterial vaginosis among pregnant women is estimated at 16% to 49%, with 2 to 3.3 times higher prevalence in African Americans than in whites.²⁷ Racial disparities also exist in the cytokine response to genitourinary

infections, with African Americans having increased IL-1 β and tumor necrosis factor α (TNF- α) and decreased soluble TNF receptor responses resulting in an imbalance of proinflammatory cytokines.²⁸ Moreover, racial disparities could be amplified when the cytokine milieu associated with underrecognized infections such as subclinical microbial invasion of the amniotic cavity (MIAC) is considered. In a previous study, amniotic fluid cultures showed MIAC in 12.8% of women in preterm labor with intact membranes and in 32.4% of women with preterm prelabor rupture of membranes.²⁹ Of note, a separate study showed that cases of *Ureaplasma* infection detected by polymerase chain reaction alone demonstrated increased IL-6 in amniotic fluid, as well as histologically graded chorioamnionitis and funisitis equal to culture-positive cases.³⁰ As a corollary, amniotic fluid IL-6 is utilized as a bedside test for detection of MIAC, achieving a positive predictive value of 82%.³¹

Whether due to infection or stress, certain cytokines play an important role in the physiology of preterm labor by triggering PG synthesis. Disruptions in the balance of proinflammatory and anti-inflammatory cytokines can initiate early steps in parturition, including PG production and cervical ripening.¹⁹ This cytokine imbalance may be more pronounced in African American women. Fetal membranes from African American mothers have been shown to produce higher concentrations of IL-1 β , matrix metalloproteinase 9, CRH, and PGE₂,²⁸ suggesting a more intense response to inciting events such as infection or stress.

PRENATAL STRESS AND ASTHMA

Prenatal stress has been associated with asthma or wheeze (a key symptom of asthma) in several studies.^{7,32–38} Similar to prematurity, factors or exposures that may confound or modify the putative effects of prenatal stress on asthma include socioeconomic status and access to health care,³⁹ in utero environmental tobacco smoke,³⁹ intensity of stressful exposures or perceived maternal stress,³⁶ maternal obesity,³³ maternal race or ethnicity,³⁹ air pollution,⁴⁰ and parental history of asthma or allergies.^{32,41}

There is conflicting or insufficient evidence of a critical “time window” for detrimental effects of maternal stress during pregnancy,^{33,35,37} an interaction between prenatal stress and the neonate's sex,³⁶ or the relative independent contributions of prenatal and postnatal stress^{32,33,35} to the pathogenesis of childhood asthma. Because a significant proportion of children who experience wheeze before age 4 years have transient wheeze but no asthma, a key limitation of most (but not all³⁴)

published studies is the relatively short duration of follow-up after birth, which precludes a confident diagnosis of asthma.

Several mechanisms could explain the influence of prenatal stress on the infant's susceptibility to asthma. First, prenatal stress may alter fetal cytokine balance, favoring persistence of enhanced T_H2 immune responses (characterized by increased production of IL-4 and IL-13, and total immunoglobulin E) in early childhood. Following exposure to prenatal stress, cord-blood mononuclear cells produce IL-8 and TNF- α in response to a microbial challenge, as well as IL-13 in response to dust-mite allergen.⁴² Interleukin 6 may further promote T_H2 differentiation by increasing IL-4 production by CD4⁺ T cells, as well as by stimulating production of IL-13.⁴³ Infants born to mothers with high prenatal stress also have higher cord-blood immunoglobulin E than do those born to mothers with lower stress levels, perhaps due to IL-4 promoter isotype switching.³⁸

Second, perinatal stress influences the GR system, which may lead to persistent abnormalities in the HPA axis. Offspring of mothers who experience depression⁴⁴ or are exposed to major stressful events (eg, war⁴⁵ or intimate partner violence⁴⁶) have increased methylation of the gene for the GR (*NR3C1*) in cord blood⁴⁴ or peripheral^{46,47} mononuclear cells. Infants with increased *NR3C1* methylation of cord-blood mononuclear cells have significantly higher cortisol levels after experimental stress at 3 months of life,⁴⁴ as well as decreased sensitivity to dexamethasone suppression.⁴⁵ Findings in rats further suggest that disrupted mother-infant bonding may cause postnatal methylation of *NR3C1* in premature infants, which could persist into adulthood.⁴⁸ This effect has been demonstrated in preterm infants, who have higher methylation rates of *NR3C1* in peripheral blood than term infants.⁴⁹

Third, maternal stress may alter immune responses through effects on the HPA axis. In murine models, maternal stress has been shown to increase eosinophils in bronchoalveolar lavage fluid in the offspring.⁵⁰ In another model, prenatal stress was associated with increased plasma corticosterone (the murine equivalent of cortisol) and IL-13 following aeroallergen challenge.⁵¹ Of interest, both the corticosterone and IL-13 responses were suppressed by inhibition of glucocorticoid synthesis or the GRs.^{50,51}

Postnatal stress may amplify the detrimental effects of prenatal stress on asthma, and separating the relative contribution of such effects to the development of asthma can be very difficult.⁷ For example, children or adolescents exposed to traumatic experiences have increased methylation of *NR3C1*⁵² and are at risk of

posttraumatic stress disorder, a condition associated with increased risk of asthma.⁵³

PREMATURITY AND ASTHMA

Prematurity, which occurs in approximately 11% of births worldwide, has been consistently associated with childhood asthma. In an illustrative study, birth at less than 32 weeks' gestation was associated with 2.8 times increased odds of wheezing.⁵⁴ Other factors correlated with prematurity, such as chronic lung disease, need for mechanical ventilation, and corticosteroid use, have also been linked to asthma.⁵⁵ The link between prematurity and asthma has been shown to decrease after school age,⁴ and thus, "premature asthma" may be an independent phenotype. Moreover, we recently reported that prematurity is associated with 5-fold increased odds of atopic or allergic asthma but is not significantly associated with nonatopic asthma in school-aged children,⁵⁶ suggesting that both structural changes in the lung and abnormal immune responses are required for prematurity-induced asthma in later childhood (the "2-hit hypothesis").

In 1989, Strachan⁵⁷ first hypothesized that the rising prevalence of allergic diseases is due to reduced exposure to microbial infections due to declining family size and improved hygienic conditions (the "hygiene hypothesis"). Since then, a growing body of literature suggests that changes in the neonatal gut flora lead to atopy and atopic diseases such as asthma (a "modified hygiene hypothesis"). Although full characterization or "correction" of gut flora abnormalities leading to atopy remains elusive in humans,^{58,59} it is reasonable to postulate that prematurity leads to persistence of predominantly T_H2 immune responses after birth through changes in the gut flora (broadly characterized by reduction in anaerobes such as *Bifidobacterium* species and increased number of aerobic bacteria such as *Escherichia coli* and *Clostridium difficile*). Such changes can in turn be explained by perinatal factors including cesarean delivery^{60,61} and antibiotic use.^{60,62} Alternatively, birth by cesarean delivery may alter neonatal immune responses in premature infants because of the absence of labor.⁶¹

Premature infants have increased salivary levels of proinflammatory cytokines such as IL-6, IL-8, and IL-12,⁶³ which could play a role in neonatal morbidity. Interleukin 6 is used to operationally define fetal inflammatory response syndrome, a condition associated with increased risk of respiratory distress syndrome, sepsis, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis.⁶⁴ Both IL-6 and IL-8 are increased after cesarean delivery of full-term

infants,⁶⁵ which may be relevant because of modestly increased asthma risk among infants delivered by cesarean section.⁶⁶ Interleukin 6 is associated with increased airway resistance⁶⁷ and acts on a subset of effector memory CD8⁺ T cells to enhance production of T_H2 cytokines.⁶⁸ Interleukin 8, a proinflammatory cytokine influenced by ozone and particulate matter, acts as a potent chemoattractant of neutrophils leading to airway inflammation.⁶⁹ Thus, beyond the developmental deficiencies associated with preterm birth, cytokine profile alterations may constitute a risk marker of wheeze or asthma.

DISCUSSION AND FUTURE DIRECTIONS

Prenatal stress has been associated with asthma in children born at term,⁷⁰ and thus, not all cases of “stress-induced asthma” could be explained by prematurity. Similarly, stress may lead to prematurity but no asthma. Although not formally studied, it is also plausible that (1) prematurity is associated with asthma in children exposed to low levels of maternal (prenatal) stress, and (2) stress leads to prematurity-induced asthma (“premature asthma”) (Fig. 1). Given marked detrimental effects of prematurity and asthma on the health of children worldwide, identifying modifiable risk factors for one or both conditions could have major public health implications.

Maternal stress can lead to elevations of cortisol and cytokine imbalance, leading to early parturition signals. The resulting proinflammatory environment can result in intrauterine growth restriction, a condition associated with fetal hypoxemia, hypoglycemia, and increased catecholamine and cortisol concentrations. High cortisol levels may alter the transcription of GR-regulated genes, which—together with intrauterine growth restriction—could affect lung development.^{9,71} Elevated fetal cortisol is also inversely related to surfactant proteins A and B mRNA expression,⁷² potentially leading to structural lung changes that predispose to postnatal asthma, particularly in neonates with an atopic predisposition (either through heredity or an altered HPA axis). Stress-induced changes in the postnatal HPA axis, including increased production of intrinsic glucocorticoids, may lead to alterations in the production of proinflammatory cytokines (eg, IL-1 β , TNF- α , or IL-6),⁴² as well as “classic” T_H2 or T-regulatory cytokines relevant to asthma (eg, IL-4 or IL-13).⁶³ For example, IL-6 not only influences the development of prematurity but also has been shown to promote CD4⁺ T cell-mediated production of IL-4 and IL-13.⁴³

We have presented evidence that perinatal stress may cause changes in glucocorticoid and cytokine production,

leading to preterm labor; in turn, changes in immune responses and lung development due to both stress and prematurity place these children at increased risk of asthma (Fig. 1). Large birth cohorts with adequate data on prenatal stress and prematurity, as well as sufficient duration of follow-up (to assess the development of “true asthma”), are needed to elucidate which proportion of stress-induced asthma is mediated by prematurity. If the presence and importance of stress-induced “premature asthma” are confirmed, clinical trials of prenatal stress reduction to prevent prematurity and asthma would be justifiable.

The United States has the highest rate of firearm-related deaths of all industrialized countries.⁷³ The recent and highly publicized shootings in Newtown (Conn), Aurora (Colo), Oak Creek (Wis), Tucson (Ariz), and Charleston (SC) continue to raise concerns about the harmful effects of firearms. For example, we and others have shown that Puerto Ricans not only are exposed to violence in their communities^{2,74,75} but also may be particularly susceptible to developing psychosocial stress after such exposure.^{76,77} A growing body of evidence suggests that stress resulting from exposure to violence (eg, firearm-related⁷⁸) or heavy trauma (eg, domestic abuse⁷⁹) partly explains the high burden of asthma in Puerto Ricans^{75–79} and other economically disadvantaged groups.^{7,80}

Even though health policies cannot be based solely on existing data on both prematurity and asthma, there is ample justification for policies designed to prevent domestic abuse and firearm violence. Fatal and nonfatal firearm violence not only poses a serious threat to public safety, but also has detrimental effects on psychiatric and somatic health in general and on anxiety disorders (eg, posttraumatic stress disorder) and asthma in particular. The time for sound policies on gun control in the United States is long overdue.

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