Ann Allergy Asthma Immunol 116 (2016) 306–312

Contents lists available at ScienceDirect

Prenatal and postnatal stress and wheeze in Mexican children
Sex-specific differences

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ARTICLE INFO

Article history:
Received for publication November 11, 2015.
Received in revised form December 18, 2015.
Accepted for publication December 22, 2015.

ABSTRACT

Background: Increasing evidence links early-life exposure to psychosocial stress with adverse childhood respiratory outcomes. The influence of exposure timing has not been completely elucidated.
Objective: To examine the association between prenatal and postnatal maternal stress and wheeze in 417 children enrolled in a prospective birth cohort in Mexico City.
Methods: Maternal negative life event (NLE) scores were ascertained in the second or third trimester of pregnancy and at the 48-month postnatal visit. Children's respiratory outcomes, caregiver report of ever wheeze, and wheeze in the past 12 months were obtained from the International Study of Asthma and Allergies in Childhood survey administered at 48 months. Associations between prenatal and postnatal NLE scores and wheeze were analyzed using a modified Poisson regression approach adjusting for covariates.
Results: In separate models, higher maternal psychosocial stress during pregnancy (relative risk [RR], 1.12; 95% CI, 1.00–1.26) and postnatally (RR, 1.21; 95% CI, 1.08–1.35) were associated with increased risk of wheeze in the past 12 months with an evident exposure-response relationship. There was a significant interaction between postnatal stress and sex in relation to current wheeze. In a sex-stratified model, the association between postnatal stress and risk of wheeze in the past 12 months was stronger in girls (RR, 1.35; 95% CI, 1.13–1.61) than in boys (RR, 1.11; 95% CI, 0.97–1.27) (P for interaction = .04).
Conclusion: Prenatal and postnatal stress in mothers was associated with wheeze in preschool-aged children, and the effect of postnatal stress was stronger in girls. Understanding the temporal- and sex-specific effects of stress may better inform prevention strategies.

Introduction

Childhood wheezing is an important contributor to morbidity and health care use in Latin America.[1,2] The study of environmental risk factors for the development of childhood wheezing and asthma in Latin America is an increasing area of interest.[3,4] Identifying critical exposure windows for prevalent risk factors can provide insight into the mechanisms through which these exposures lead to respiratory disease in childhood and ultimately inform the timing of public health interventions.

Although asthma and childhood wheeze are heterogeneous conditions, inflammation is a central pathologic feature.[5] Psychosocial stress leads to the activation of systems involved in the regulation of inflammatory processes (ie, hypothalamic-pituitary-adrenocortical [HPA] axis, autonomic nervous system) and alterations in innate and adaptive immune responses.[6] Hormones and neuropeptides released after the activation of stress response systems are involved in inflammatory[7] and airway responses,[8] so the study of psychosocial stressors as environmental risk factors for respiratory disease might be particularly relevant.

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Disclosures: Authors have nothing to disclose.
Funding Sources: The Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) project was funded by National Institutes of Health (NIH) grant R01 ES021357 (Dr R.O. Wright, principal investigator). Phenotyping and biostatistical support was funded by NIH grant P30 ES023515. During preparation of the manuscript, Dr R.J. Wright was supported by NIH grant R01HL095606, and Dr Rosa was supported by NIH grant T32 HD049311-09. The PROGRESS project also receives support and partial funding through the National Institute of Public Health/Ministry of Health of Mexico. We thank the American British Cowdray Hospital in Mexico for providing research facilities.

http://dx.doi.org/10.1016/j.anai.2015.12.025
1081-1206/

An increasing number of prospective epidemiologic studies have found associations between increased prenatal maternal stress or stress correlates (eg, maternal anxiety) and early asthma phenotypes.[9–13] In Boston, Massachusetts, children whose mothers reported higher numbers of negative life events (NLEs) during both the prenatal and early postnatal periods were 3 times more likely to have recurrent wheeze by 2 years of age when compared with mothers with low stress during both periods.[9] An inner-city cohort study in New York City reported associations between prenatal maternal demoralization, a broad measure of maternal psychological functioning, and increased risk of transient and persistent wheeze in children.[12] Another multisite US inner-city cohort study reported associations between prenatal perceived stress and wheeze in 1-year-old infants.[14] Maternal pregnancy-specific hassles were associated with a composite measure of respiratory illnesses during infancy.[15] In a study in the Netherlands, maternal distress assessed using the Brief Symptom Inventory during pregnancy was associated with increased odds of wheezing in children followed up to 6 years of age; maternal distress examined postnatally was not associated with child wheeze.[13] A recent study linked higher intrafamilial adverse childhood experiences with increased odds of asthma diagnosis in children in the National Survey of Children's Health.[16] Overlapping evidence suggests that exposure to stress may be an important contributing factor to respiratory morbidity in Latin America because of the high prevalence of intimate partner violence,[17] local violence,[18] perinatal depression,[19] and lack of data on stress-reduction strategies.[4] Despite increasing evidence in this area, similar studies in Latin American countries are lacking.

Increasing evidence from animal models indicates that the timing of stress exposure (prenatal vs postnatal) is important and that critical windows of vulnerability may differ by sex of the offspring for a number of developmental outcomes.[20,21] For example, one study found that male offspring of dams exposed to stress early in the prenatal period revealed maladaptive behavioral stress responsivity in a series of tests.[22] In another study, females had increased anxiety-related behavior after exposure to prenatal stress, whereas males had decreased memory for novel objects and novel spatial locations.[23] Although mechanisms have not been fully elucidated, studies suggest that sex-specific effects can arise through differential placental effects and fetal sex hormones.[24,25] For example, one recent study looking at prenatal socioeconomic adversity and epigenetic changes in placenta, found sex differences in methylation of 11β-hydroxysteroid dehydrogenase type 2, the enzyme responsible for the conversion of cortisol into inactive cortisone, suggesting that prenatal environmental cues may affect fetal programming to respond to stress postnatally in a sex-specific manner.[26]

Epidemiologic studies considering sex-specific effects of perinatal stress on childhood respiratory disorders are sparse and have yielded mixed results. In a large study using electronic records in Sweden, boys born to women who experienced bereavement, defined as the loss of a close family member during the second trimester, were found to have higher risk of asthma.[27] Another small study looking at subjective distress experienced during pregnancy due to the 1998 Quebec ice storm found that only girls had higher odds of lifetime wheezing, physician diagnosis of asthma, and asthma medication use by 12 years of age.[28] However, these studies were limited by their inability to examine prenatal and postnatal stress concurrently and adjust for other important confounders.

We examined whether higher maternal stress, assessed in pregnancy and postnatally, was associated with increased likelihood of wheeze in children enrolled in a Mexico City pregnancy cohort followed up to 4 years of age. Specifically, we first examined the effects of prenatal and postnatal stress in separate models. Next, we mutually adjusted for prenatal and postnatal stress. Finally, we examined joint effects of exposure to increased stress in both pregnancy and at 4 years of age. We also examined whether temporal effects of perinatal stress differed relative to the child's sex.

Methods

Study Population

The Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) project recruited pregnant women who were receiving health insurance and prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social [IMSS]) between July 2007 and February 2011. The IMSS provides health care to affiliated private sector employees, most of whom are low- to middle-income workers, and their families. Women were eligible to participate in the study if they met the following criteria: less than 20 weeks gestation, greater than 18 years of age, planned to stay in Mexico City for the next 3 years, had access to a telephone, had no medical history of heart or kidney disease, did not consume alcohol daily, and did not use any steroid or antiepilepsy medications. After birth, 815 mother-child dyads had at least 1 follow-up visit, and 417 had all the necessary covariates for these analyses. There were no significant differences between participants who had all necessary covariates when compared with those who did not by mother's age at delivery, maternal asthma, child's sex, or prenatal ETS exposure (eTable 1). Procedures were approved by institutional review boards at the Harvard School of Public Health, Icahn School of Medicine at Mount Sinai, and the Mexican National Institute of Public Health. Women provided written informed consent.

Measures of Psychosocial Stress

The Crisis in Family Systems—Revised (CRISYS) survey, which has been validated in Spanish,[29] was administered by a trained psychologist during the second or third trimester of pregnancy and during the 48-month visit. The CRISYS questionnaire assesses life events across 11 domains: financial, legal, career, relationship, home safety, neighborhood safety, medical issues (self and others), home, prejudice, and authority. Participants rated life events occurring in the past 6 months as positive, negative, or neutral. Previous research has found increased vulnerability across multiple domains; therefore, domains with 1 or more NLE were summed into an NLE domain score, with higher scores indicating greater stress.[9,30]

Outcome Measures

The validated Spanish version of the International Study of Asthma and Allergies in Childhood questionnaire was administered starting at the 48-month visit. Ever wheeze was determined based on caregiver response to the question, "Has your child ever had wheezing or whistling in the chest at any time in the past?" and current wheeze was defined based on response to the question, "Has your child had wheezing or whistling of the chest in the past 12 months?"

Covariates

Child's sex, mother's age at delivery, and mother's report of ever having asthma were collected through questionnaires. Exposure to environmental tobacco smoke was ascertained during pregnancy (during the second or third trimester) and during the 48-month visit through report of any smoker in the home during these periods. Exposure to particulate matter 2.5 μm and less in diameter ($PM_{2.5}$) was estimated for each woman during pregnancy and