



Maternal Stress and Allergic Diseases in Children: A systematic review

Katarzyna Smejda¹, Agnieszka Brzozowska¹, Daniela Podlecka¹, Kinga Polanska², Joanna Jerzynska^{1*}

¹Department of Pediatrics and Allergy, Medical University of Lodz, Copernicus Memorial Hospital in Lodz, Poland

²Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland

Article Info

Article Notes

Received: October 9, 2019

Accepted: November 15, 2019

*Correspondence:

*Dr. Joanna Jerzyńska MD, PhD, Department of Pediatrics and Allergy, N. Copernicus Memorial Hospital, Medical University of Lodz, Poland; Email: alergol@kopernik.lodz.pl.

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Keywords:

Prenatal stress
Maternal stress
Asthma
Wheezing
Atopic dermatitis
Allergic rhinitis
Food allergy
Children

Abstract

During pregnancy, women are more prone to stress and at risk of distress due to deep hormonal and physiological changes. The aim of this systematic review was to examine whether maternal stress during pregnancy increases the risk of atopic diseases in the children.

A review of the literature was performed using three databases: PubMed, Web of Science, EBSCO. We limited the results to human-subject studies published in English between January 2010 and September 2019. This systematic review suggests a relationship between maternal stress during pregnancy and allergic diseases in the child. The findings highlight the importance of the implementation of stress reduction programs for pregnant women and those in their postpartum period within communities in order to enable these individuals to relieve stress effectively.

Introduction

The information flow between the fetoplacental and maternal compartments is necessary for normal fetal development. Environmentally induced alterations in these signaling networks can negatively influence development, impacting lung organogenesis and programming future respiratory disease. Placental oxidative stress (OS) and maternal and fetal HPA axis functioning and cortisol production play key roles. Maternal stress impairs the placenta's tight regulation of fetal cortisol exposure, also stimulates secretion of placental corticotrophin-releasing hormone (pCRH), which plays a fundamental role in fetal HPA axis development and acts to increase fetal cortisol¹. Women with higher cumulative lifetime stress have elevated pCRH, specifically in the second half of gestation, and their offspring have elevated cortisol^{2,3}. Increased fetal cortisol activates fetal stress responses (i.e., HPA axis, catecholamines and neurotrophins) and induces a T helper type 2 cell predominance⁴.

The natural history of atopic diseases begins in utero⁵. A pivotal mediator triggered in response to stress is the release of glucocorticoids (GC). GC may affect gene expression through binding to GC receptors, thus affecting fetal development in general, and allergic vulnerability in particular. A series of recent findings also indicate that MPS may affect the fetus programming of immune functions and lead to vulnerability of the immune system. MPS (maternal prenatal stress) may hinder the gradual process in the offspring's cytokine production towards a Th1 type immune response⁶.

The aim of this systematic review was to examine whether maternal stress during pregnancy increases the risk of atopic diseases in the children.

Methods

Search strategy

A comprehensive literature search was conducted in September 2019. A review of the literature was performed using three databases: PubMed, Web of Science, EBSCO. We limited the results to human-subject studies published in English between January 2010 and September 2019. The search strategy and inclusion and exclusion criteria were developed among the total group of authors after which the two first authors individually conducted the literature search and identified the relevant studies based on the described inclusion and exclusion criteria. The combination of keywords used for the literature search is shown as follows: “maternal stress” or “prenatal stress” or “periparum stress” or “eczema” or “atopic dermatitis” or “asthma” or “wheezing” or “allergic rhinitis” or “food allergy”.

Study criteria

The inclusion criteria were as follows: (i) language: English language full length, original publications in peer reviewed journals, (ii) objectives: children between the ages of 0 and 18, (iii) design: cross sectional and case-control studies as well as prospective cohort studies, (iv) exposure: stressors (negative life events, daily hassles and job strain) and negative emotions (distress, anxiety and depressive symptoms) experienced by the mother during pregnancy and (v) outcome: specific disorders grouped into the following four outcomes: atopic dermatitis, allergic rhinitis, food allergy, asthma and wheeze.

Results

During pregnancy, women are more prone to stress and at risk of distress due to deep hormonal and physiological changes.

Asthma and Wheezing

Rusconi et al studied 2314 mother-child pairs recruited in the Piccolipiù birth cohort in Italy. Maternal mental health problems extending from pregnancy to the first year after delivery are associated with development of both wheezing and infections. As wheezing is mostly triggered by infections, increased infection susceptibility could represent a possible common biologic mechanism. This study confirms the importance of early-life exposures on childhood health⁷. Lee et al also proved that high levels of perinatal anxiety affected the development of respiratory tract infection, especially bronchiolitis in offspring⁸. Maternal stress during pregnancy might affect fetal lung development and subsequently predispose to childhood asthma. An increased risk of asthma was found in infants of pregnant women with severe stress. Bakhtadze et al suggest intrauterine effects of maternal factors during

pregnancy on the presence of childhood asthma. Maternal severe stress during pregnancy can trigger wheezing and asthma of their child⁹.

Childhood asthma was associated with maternal lifetime major depressive symptoms, in addition to symptoms of anxiety/depression during pregnancy and 6 months after delivery. Maternal negative life events during pregnancy and 6 months after delivery were also associated with asthma¹⁰.

In a study of 370 mother-child pairs from Polish Mother and Child Cohort, premature stress, described by life events as stress factors (SRRS), increased the risk of wheezing independently from other predictors of wheezing (previously determined in this cohort), such as: number of infection and paternal smoking. This study also showed significant positive association between perceived stress (PSS) score in mothers during pregnancy and the risk of recurrent RTI in the first year of life. This association, however, was not significant after adjustment with statistical predictors of this outcome determined in this cohort previously. Psychological stress during pregnancy increases the risk of childhood wheeze and asthma^{11,12}.

Brew et al analyzed the population of children born in Sweden from July 2006 to December 2009 (n = 360 526). The objective was to determine whether there is a critical, sensitive or cumulative exposure period of maternal depression or anxiety for childhood asthma risk. Maternal depression or anxiety in four exposure periods were investigated: preconception, pregnancy (in utero), postnatal and current. Testing each exposure period as a ‘critical period’ revealed an association between maternal depression or anxiety and offspring asthma of approximately the same magnitude for each exposure period. Exposure to depression or anxiety at any single period was associated with offspring asthma for exposure during two periods. However, exposure to more than two periods did not increase the risk of asthma¹³. Bose et al identified two sensitive windows (7-19 and 33-40 wk gestation), during which increased nitrate (NO₃-) was associated with greater odds of asthma, specifically among boys born to mothers reporting high prenatal stress. Prenatal NO₃- exposure during distinct sensitive windows was associated with incident asthma in boys concurrently exposed to high prenatal stress¹⁴.

Lee et al demonstrated that the highest level of prenatal stress was associated with lower levels of forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and forced expiratory flow between 25% and 75% (FEF_{25%-75%}) after covariate adjustment; effects were similar for postnatal stress considered separately. In sex-stratified analyses, high postnatal stress was associated with lower FEV₁, FVC, and FEF_{25%-75%} in boys but not girls, although the interaction term was not significant. These are the first

prospective data that link perinatal stress with reduced child lung function. High levels of stress in the prenatal and postnatal periods were associated with symmetric reductions in FEV1 and FVC consistent with impaired lung growth. These data indicate that children exposed to the highest levels of pre- and postnatal maternal stress have on average a 133mL (9.2%) and 128mL (8.9%) reduction in FEV1 and a 142mL (9.0%) and 148mL (9.4%) reduction in FVC, respectively, at age 7, compared to their counterparts experiencing lower stress in these critical periods. Given that lung function growth patterns are established by 7 years of age, these findings have lifelong implications¹⁵.

Kozyrskyj et al proved that postpartum depressive symptoms had a 1.5-fold significant association with childhood asthma between the ages 6-8. This was independent of male sex, maternal asthma, non-immigrant status, low household socioeconomic status, being firstborn, low birthweight, low family functioning and urban-rural residence, of which the first 4 covariates elevated the risk of asthma. At age 9-10, an association was no longer evident¹⁶. In turn, Ramratnam et al. showed that maternal depression was significantly associated with recurrent wheezing in children. These associations were also significant when considered in a longitudinal analysis of cumulative stress and depression. Neither stress nor depression was significantly related to aeroallergen sensitization or antiviral responses¹⁷. Elbert et al observed no association of maternal psychiatric symptoms during pregnancy with allergic sensitization. Maternal overall psychiatric, depressive and anxiety symptoms during pregnancy were associated with an increased risk of inhalant allergy only¹⁸. Also, in the study of Rae et al postnatal psychological distress and intimate partner violence were associated with both presence of wheeze and recurrent child wheeze¹⁹. Trump et al evaluated genomic regions altered in their methylation level due to maternal stress based of whole genome bisulfite sequencing data of 10 mother-child-pairs. High maternal stress was associated with an increased risk for persistent wheezing in the child until the age of 5. Both mothers and children showed genome-wide alterations in DNA-methylation specifically in enhancer elements. Deregulated neuroendocrine and neurotransmitter receptor interactions were observed in stressed mothers and their children. In children but not in mothers, signals required for lung maturation in the prenatal period were epigenetically deregulated and could be linked with wheezing later in children's life²⁰. Increased prenatal stress in Mexican women enhanced the association between PM2.5 exposure in early pregnancy, and child wheeze at 48 months of age²¹.

Allergic Rhinitis

In opposite to the numerous studies underlining the association between perinatal maternal stress and the link

of lower respiratory diseases, the information concerning the association between maternal stress and allergic rhinitis is scar. Most recently Andersson et al. performed a systematic review of existing epidemiological studies examining prenatal maternal stress and risk of atopy-related outcomes in children (asthma, wheeze, atopic dermatitis, allergic rhinitis, and immunoglobulin E (IgE) expression) with the majority of studies documenting a significant exposure-response relationship for all conditions²².

Assessing the clinical status of children at age of 8,5 year at average, De Marco et al found an association between the prevalence of maternal stress and increased risk of all allergic diseases (for allergic rhinitis -OR: 1.753, 95%CI:1.08-2.84)⁵. In a systematic review and meta-analysis, Flanigan et al proved that maternal exposure to any type of stress (anxiety, depression) correlated to an increased risk of subsequent allergic rhinitis in the offspring (OR 1.36 95% CI 1.08-1.71)²³. Exposure to stress during last trimester of pregnancy, had the greatest impact compared to the first and second trimester. In a study of Hartwig et al, when asthma, atopic dermatitis and allergic rhinitis were analyzed separately, the authors found that the odds of children to develop allergic rhinitis at age of 14 years, significantly increased with increase number of experienced events in the prenatal life in the last trimester; however after adjustment for confounders, this association did not reach the level of significance²⁴.

The results of Cheng et al on a 1152 pregnant women and their offspring at age of 3,6,9 and 12 months of age showed that maternal anxiety during pregnancy was associated with an increased risk of infantile rhinitis in their infants (OR 1.42 95% CI 1.04-1.93), however no significant association between prenatal depression and infantile rhinitis was found²⁵.

Tsuji et al state, that maternal psychological stress affects the inflammatory response in their allergic children. They found significant relationships between maternal psychological stress and IL-6 and IL-8 mRNA expressions in children with asthma and allergic rhinitis²⁶.

Food Allergy

Maternal stress in fetal and early life has been associated with the development of respiratory allergies, but no studies exist about food allergy. Secretory Immunoglobulin A (sIgA) plays a critical role to infant gut mucosal immunity. Delayed IgA production is associated with greater risk of allergic disease. Kang et al investigated differences in infant fecal sIgA concentrations according to the presence of maternal depressive symptoms during and after pregnancy. Twelve percent of women reported clinically significant depressive symptoms only prenatally, 8.7% had only postpartum symptoms and 9.2% had symptoms both

pre and postnatally. Infants born to mothers with pre and postnatal symptoms had significantly lower median sIgA concentrations than those in the reference group (4.4 mg/g feces vs. 6.3 mg/g feces; $p = 0.033$). The odds for sIgA concentrations in the lowest quartile was threefold higher when mothers had pre and postnatal symptoms. Postnatal symptoms were not associated with fecal sIgA. Infants born to mothers with depressive symptoms appear to have lower fecal sIgA concentrations, predisposing them to higher risk of allergic disease²⁷. In the Polish cohort study, no relationship was found between maternal stress during pregnancy and food allergy in children¹¹.

Alviani et al in a small number study (N=32) found the presence of antenatal stressor increased the likelihood of childhood food allergy by 73% (OR: 1.73; 95% CI: 0.62-4.82, $p = ns$). They also noticed that there was a trend for higher numbers of stressful events in the food-allergic group, which did not reach statistical significance. It should be underlined that the level of significance could be different in case of larger population studied²⁸.

Polloni et al investigated the relation between perinatal stress and the development of severe food allergy in childhood, comparing patients to their siblings. The authors found a significant difference in the number of bereavements occurred during food allergic children pregnancy compared to siblings ($p = .039$). Bereavements in most cases occurred in the last trimester of pregnancy. Comparing mothers' report of pregnancies with food allergic children and healthy children, a significant higher total number of stressful events emerged, especially bereavements²⁹. Authors also state pregnancies with allergic children were reported by mothers as significantly harder than with their healthy children ($p < .05$)²⁹.

Atopic Dermatitis

Some cohort and registry studies have found associations with maternal stress and childhood atopic dermatitis (AD). Study performed in two general population - based cohorts (Cohort for Childhood Origin of Asthma and Allergic Diseases (COCOA) and Panel Study of Korean Children revealed that prenatal maternal distress increased the risk of AD in offspring in both cohorts independently³⁰. In COCOA both prenatal maternal depression and anxiety scores were positively related to predicted probability of AD. According to authors, the main pathophysiological mechanism are the abnormal steroid levels and oxidative stress³⁰.

A study of Larsen et al based on the Danish National Birth Cohort and (data from 32 104 pregnancies) proved that maternal exposure to self-reported high job strain during pregnancy was associated with 15% higher odds of atopic dermatitis among 7-year-old children (OR 1.15, 95% CI 1.02–1.31)³¹. Similar findings were found by an Australian

cohort study, in which the authors revealed the likelihood of asthma and AD at age of 14 years, was significantly increased in children of mothers who had experienced adverse life events during the second half of gestation²⁴. There are not fully understood mechanisms, which stress may affect the development of atopic diseases. Wen et al concluded that elevated cIgE (cord blood IgE), LT- α and Fc ϵ RI- β genotypes, and maternal stress during pregnancy were associated with ever having physician - diagnosed AD in 2-yr-old children and increased the predictive ability for AD after taking into account gender, maternal education, and parental atopic history³².

Also in a systematic review of Andersson et al showed that children of mothers who had stress during pregnancy had significantly higher risk of AD²². De Marco et al found an association between the prevalence of maternal stress and increased risk of all allergic diseases (for Atopic dermatitis -OR: 1.53, 95%CI:1.11-2.10)⁵. In a systematic review and meta-analysis of Flanigan et al. proved that maternal exposure to any type of stress (anxiety, depression) correlated to an increased risk of atopic dermatitis in offspring, but only depression and work stress were significant³³. Exposure to stress during the last trimester of pregnancy had the greatest impact compared to the first and second trimester.

Sidbury et al showed that working in professional or technical occupations increased the risk of childhood AD in addition to work stress during pregnancy. The mothers of children with AD had a longer working time than those without AD³⁴. The results of LISA cohort study suggest that the presence of stress - related maternal factors during pregnancy increased the risk of childhood AD during the first 2 years of life. Beyond the second year, this risk was not observed, suggesting that other factor say override the influence of prenatal stress³⁵.

Braig et al evaluated maternal hair cortisol concentrations at childbirth and the cumulative incidences of parent-reported child AD symptoms until age 2 years. Maternal stress and anxiety were associated with child AD symptoms³⁶. Letourneau et al found that prenatal pregnancy-specific anxiety and postnatal anxiety predicted AD independent of paternal support and maternal sensitivity³⁷. Also, in the Ulm SPATZ Health Study in Germany, psychosocial stress and anxiety during pregnancy were associated with child AD symptoms³⁸. El-Heis et al demonstrated that preconception perceived stress affecting health and stress in daily living were associated with an increased risk of offspring atopic eczema at age 12 months but not at 6 months, robust to adjustment for potentially confounding variables. Findings were similar for maternal psychological distress preconception. Low maternal mood between delivery and 6 months post-partum was associated with an increased risk of infantile atopic eczema at age 12 months, but no significant

association between post-natal mood and atopic eczema was seen after taking account of preconception stress³⁹. In our previous paper we didn't find any correlation between maternal stress during pregnancy and atopic dermatitis in children. Maternal overall psychiatric and anxiety symptoms during pregnancy were associated with an increased risk of eczema¹⁸.

Molecular Mechanism of Allergic Diseases Triggered by Mother's Stress

It has been proven that maternal stress can modify fetal cytokine profile, enhancing TH2 (allergic) immune responses characteristic of atopic asthma, such as interleukin 6 (IL-6), which has been associated with premature labor, can promote TH2 responses by stimulating production of IL-4 and IL-13, and TH17 pathway promotion⁴⁰. Perinatal maternal anxiety increases glucocorticosteroids in pregnant women, which can cross the placental barrier. As known, cortisol, also known as stress hormone, can down-regulate the HPA (hypothalamus, pituitary gland, and adrenal glands) axis by binding to glucocorticoid receptors and mineralocorticoid receptors. What is more, higher levels of glucocorticosteroids in fetus and offspring leads to higher levels of reactive oxygen species and increased oxidative stress is considered to be a crucial reason for alteration in the immune response⁴¹⁻⁴³. Maternal depression could affect child outcomes through altered placental function, epigenetic changes in the child, and stress reactivity⁴⁴. Maternal and fetus distress can also stimulate CRH (corticotrophin releasing hormone) secretion in the placenta, which leads to increased levels of this hormone in the fetal circulation with subsequent fetal HPA axis stimulation⁴⁵.

In several studies maternal stress during pregnancy was associated with raised cord blood specific and total IgE^{23,46-49}. On the other hand, we were able to find just one study reporting an alteration of cord blood cytokine profiles (IL-4,6,5,8,12 and TNF-alpha) in offspring of mothers exposed to stress during pregnancy⁵⁰. In an animal study, the number of total peripheral blood lymphocytes and the number of CD4+ and CD8+ lymphocytes decreased in offspring of stressed mothers^{20,45}. Trump et al suggested that prenatal maternal stress may cause epigenetic effects with DNA- methylation and alter gene expression in the placenta³³.

Limitations

The present review has some limitations that need to be acknowledged. First, the differences in the ethnic groups of the subjects and the methodology in the ascertainment of childhood allergic diseases among the included studies of this review could have contributed to the heterogeneity of the review findings. In addition, different methods used to assess maternal stress in individual studies. These factors

may result in the difficulties in drawing firm conclusions on the association between the experience of maternal stress and childhood allergic diseases risk.

Conclusion

This systematic review suggests a relationship between maternal stress during pregnancy and allergic diseases in the child. Most of the research confirms the importance of early-life exposures on childhood health. Although the existing evidence support a relationship of maternal prenatal stress with allergic predisposition of the offspring, further studies are needed to elucidate whether the association is dependent on the type of stress and whether it involves any type of allergic predisposition or not. The findings highlight the importance of the implementation of stress reduction programs for pregnant women and those in their postpartum period to relieve stress effectively. The effective psychological management of women with chronic distress may reduce offspring asthma risk. This is very important because reduced lung function in children exposed to elevated levels of pre- and postnatal maternal stress can predispose individuals to future chronic respiratory diseases.

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