Paediatric Respiratory Reviews 21 (2017) 38–46

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-Symposium: Maternal Diseases effecting the newborn

Air pollution during pregnancy and lung development in the child

Insa Korten [1,2], Kathryn Ramsey [3,4], Philipp Latzin [1,*]

[1] Division of Respiratory Medicine, Department of Pediatrics, Inselspital, University of Bern, Switzerland
[2] University Children's Hospital (UKBB), Basel
[3] Cystic Fibrosis Research and Treatment Center, University of North Carolina at Chapel Hill, USA
[4] Telethon Kids Institute, University of Western Australia, Australia

EDUCATIONAL AIMS

The reader will come to appreciate that:

- Air pollution in pregnancy leads to adverse birth effects.
- Air pollution in pregnancy influences postnatal lung development and respiratory health.
- There is interplay of direct and indirect impacts of prenatal air pollution on lung health.
- Environmental and epigenetic factors and individual exposure may contribute to the heterogeneous effects in different subjects.

ARTICLE INFO

Keywords:
air pollution
pregnancy
lung function
lung development
respiratory health
infant mortality

SUMMARY

Air pollution exposure has increased extensively in recent years and there is considerable evidence that exposure to particulate matter can lead to adverse respiratory outcomes. The health impacts of exposure to air pollution during the prenatal period is especially concerning as it can impair organogenesis and organ development, which can lead to long-term complications. Exposure to air pollution during pregnancy affects respiratory health in different ways. Lung development might be impaired by air pollution indirectly by causing lower birth weight, premature birth or disturbed development of the immune system. Exposure to air pollution during pregnancy has also been linked to decreased lung function in infancy and childhood, increased respiratory symptoms, and the development of childhood asthma. In addition, impaired lung development contributes to infant mortality. The mechanisms of how prenatal air pollution affects the lungs are not fully understood, but likely involve interplay of environmental and epigenetic effects. The current epidemiological evidence on the effect of air pollution during pregnancy on lung function and children's respiratory health is summarized in this review. While evidence for the adverse effects of prenatal air pollution on lung development and health continue to mount, rigorous actions must be taken to reduce air pollution exposure and thus long-term respiratory morbidity and mortality.

INTRODUCTION

Exposure to air pollution *in-utero* has long-term implications for respiratory health. Exposure events during pregnancy can significantly influence foetal and postnatal development and maturation. Germ and foetal cells are particularly sensitive to external exposure events due to their faster rates of replication, faster differentiation and higher sensitivity to surrounding signals compared with mature cells [1]. Prenatal environmental exposures may lead to an impaired organ development resulting in long term complications and disease in later life [2]. There is also growing evidence that environmental factors may affect gene expression permanently with trans-generational effects of intrauterine exposures. Children whose grandmothers smoked during pregnancy have a higher risk of developing asthma, independent of the smoking activity of the mother [3]. These data suggest an interplay

* Corresponding author. Division of Respiratory Medicine, Department of Pediatrics, Inselspital and University of Bern, Freiburgstrasse 31, 3010 Basel, Switzerland. Tel.: +41 31 29353.
E-mail address: philipp.latzin@insel.ch (P. Latzin).

http://dx.doi.org/10.1016/j.prrv.2016.08.008
1526-0542/

of environmental and epigenetic effects [4,5], and thus exposure events might influence prenatal development heterogeneously in individuals.

The importance of air pollution on respiratory health is amplified through its broad exposure. Although the health impact of air pollution on the individual might be smaller than other dangerous exposures, such as tobacco smoke, its significance as an environmental toxicant is ubiquitous as it cannot be avoided and affects large numbers of individuals. Evidence on the effects of prenatal exposure to tobacco smoke [6] and adverse effects of air pollution on neonatal health in general are reviewed elsewhere in detail [7–10]. Exposure to air pollution during pregnancy plays also an important role in lung development and has been shown to affect respiratory health in different ways. Lung disease is a leading cause of morbidity and mortality world-wide, therefore, the effect of air pollution on lung health is of great interest, especially from a public health point of view [11]. This review will summarize current epidemiological evidence on the effects of air pollution exposure during pregnancy on lung function in childhood and children's respiratory health. As premature birth, lower birth weight and impaired development of the immune system could be associated with later respiratory disease in life, we also briefly summarize the influence of air pollution on these risk factors in this review.

LUNG AND AIRWAY DEVELOPMENT

Lung morphogenesis and development of airways begin at 4-7 weeks of gestation and reaches the alveolar phase at around 36 weeks of gestational age. Alveolarisation continues until adolescence or even early adulthood [12], thus, compared to other organs, the maturational process of the lung takes place over a relatively long time period. During early pregnancy, cellular differentiation and branching morphogenesis can be disturbed, whereas in late pregnancy, an impairment of structural and functional growth of the lung can occur [2]. Environmental exposures, including air pollution, can lead to a disturbed alveolarisation and thus impairment of lung development and function after birth [13,14]. In addition, repair mechanisms of the developing lung tissue are not as efficient as those of the mature lung and therefore, the immature lung is more vulnerable to respiratory insults [2]. Evidence exists for a negative effect of postnatal air pollution exposure on lung function outcomes. Large epidemiological studies have shown that increased exposure to outdoor air pollutants during early postnatal life is associated with reduced lung growth and impaired development in children [11,15,16]. Evidence for an effect of prenatal exposure to outdoor air pollution on lung development and respiratory health is less well established, but some studies exist and those will be summarized in the following sections.

AIR POLLUTION DURING PREGNANCY AND LUNG FUNCTION IN CHILDHOOD

A number of studies, in both unselected and in asthmatic children, have reported associations between maternal exposure to different pollutants during pregnancy and impaired lung function during infancy and childhood. Those studies are summarized in Table 1.

In the BILD (Basel-Bern infant lung development cohort) study [17], a prospective birth cohort study of unselected infants, air pollution exposure was assessed during pregnancy and lung function measurements were performed at the postnatal age of five weeks in 241 neonates [18]. Increased minute ventilation, higher respiratory rate and tidal breathing flows in newborns were associated with higher maternal PM_{10} exposure during pregnancy, with the association strongest for the last trimester of pregnancy [18]. This suggests that prenatal exposure to air pollution may affect lung development. Importantly, the exposure to air pollution during the comparably short postnatal period was also assessed, but no consistent association for the examined pollutants was found, indicating that prenatal exposure had a greater influence on lung development. While this is the only study to investigate the association between prenatal air pollution exposure and lung function in infancy, a number of studies have examined associations with lung function later in childhood. One study in 620 children in the USA showed that higher NO_2 and benzene levels in pregnancy were associated with decreased lung function parameters (forced expiratory volume (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF)) at the age of 4.5 years [19]. Results were mainly driven by a high association in the second trimester and were significant after adjustment for maternal and paternal smoking during pregnancy. Postnatal and current air pollution exposure measurements were not associated with lung function measures, thus supporting the findings of the BILD study. Other studies have investigated the effect of prenatal air pollution exposure on pulmonary outcomes in childhood. A number of studies by Jedrychowski and colleagues used Personal Environmental Monitoring Samplers (PEMS) to monitor individual exposure to air pollution, although this method did not allow for indoor and outdoor pollution to be distinguished. In one study, exposure to prenatal and residential polycyclic aromatic hydrocarbons (PAH) was associated with a decrease in FEV_1 and forced expiratory flow 25-75% (FEF_{25-75}) when measured between 5 and 9 years of age in non-asthmatic children. The results suggested a possible additive effect of prenatal and postnatal exposure of PAH on lung function outcomes [20]. Both parameters showed significant associations if analysed in the same model, although further studies might be needed to clearly disentangle pre- and postnatal effects. The authors also demonstrated reduced FVC and FEV_1 values at the age of five years, if mothers were exposed to higher $PM_{2.5}$ during pregnancy [21]. A limitation of these studies is that $PM_{2.5}$ was only measured at one time point, in the second trimester of pregnancy, and postnatal exposure was not assessed. Investigation into prenatal and early childhood air pollution exposure on lung function in asthmatic children at 6-11 years of age showed consistent evidence for negative associations between prenatal exposure to air pollution and FVC, PEF and FEV_1 [22]. The strongest effects were found for NO_2 in the second trimester and PM_{10} in the first trimester of pregnancy, while CO seemed to have the strongest effect post-natally.

In summary, there is some evidence for an adverse impact of prenatal air pollution exposure on lung function in infancy and childhood in both unselected and asthmatic children. Effects were seen using various lung function measurements and remained significant after taking postnatal air pollution exposure as well as tobacco exposure into account. Nevertheless, data remains scarce. It is unclear which stage of pregnancy the developing lung is most vulnerable to air pollution exposure. In addition, publication bias may be a factor as no negative studies have been published. Further air pollution research is needed to better understand the specific effects of different pollutants at various stages of lung development.

AIR POLLUTION DURING PREGNANCY AND RESPIRATORY HEALTH IN CHILDREN

If prenatal exposure to air pollution leads to impaired lung growth and airway development, it is likely that air pollution also leads to increased respiratory morbidity in those children. Indeed, a number of studies have found associations between prenatal exposure to air pollution and respiratory symptoms (detailed results are presented in Table 2). Jedrychowski and co-authors