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REVIEW PAPER/*PRACA POGLĄDOWA*

The impact of particulate matter on prenatal and infant child development

Wpływ pyłu zawieszonego na rozwój prenatalny i niemowlęcy dziecka

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ABSTRACT

Introduction: Smog is formed by the interaction of various oxides, metals, and volatile organic compounds with solar radiation and fog. In Poland, the primary sources of pollution emissions come from road transport and combustion processes from municipal and residential sources. One of the air pollution parameters is particulate matter (PM), a complex mixture of solid particles and liquids.

Aim: The study discusses the most severe effects of particulate matter on child development.

Material and methods: Literature search was performed using the medical database PubMed in time period from 2007 to 2021 using the following MESH-terms: air pollution, child, particulate matter, low birth weight, asthma, environmental pollutions, respiratory system.

Results: The harmful effects of air pollution on foetal growth and the development of the child's internal organs and its endocrine system are presented in this paper. In the prenatal phase, endocrine-disrupting compounds (EDCs), by mimicking or even blocking the action of specific human hormones, may affect the endocrine balance of oestradiol and progesterone, which have a significant influence on the child's organ development. Air pollution can trigger and exacerbate asthma in children who already have it, while the role of air pollution in asthma development is debatable. Components of air pollution, including PM0.1, can penetrate the blood-brain barrier and activate inflammatory protein markers IL-6 and TNF-α, and induce inflammatory microstates.

Conclusions: Even a slight reduction in air pollutant emissions has a positive effect on a child's health.

KEY WORDS

air pollution, foetus, particulate matter, asthma, respiratory tract, low birth weight.

STRESZCZENIE

Wprowadzenie: Smog powstaje w wyniku oddziaływania różnych tlenków, metali i lotnych związków organicznych z mgłą i promieniowaniem słonecznym. W Polsce podstawowe źródła emisji zanieczyszczeń pochodzą z transportu drogowego oraz procesów spalania ze źródeł komunalnych i bytowych. Jednym z parametrów zanieczyszczenia powietrza jest pył zawieszony (PM), będący złożoną mieszaniną cząsteczek stałych i cieczy.

Cel: Omówienie najpoważniejszych skutków oddziaływania pyłu zawieszonego na rozwój dziecka.

Materiał i metody: Do wyszukiwania piśmiennictwa wykorzystano medyczną bazę danych PubMed w przedziale czasowym od 2007 do 2021 roku, używając następujących haseł MESH: *air pollution*, *child*, *particulate matter*, *low birth weight*, *asthma*, *environmental pollutions*, *respiratory system*.
Wyniki: W pracy przedstawiono szkodliwy wpływ zanieczyszczeń powietrza na wzrost płodu, rozwój narządów wewnętrznych dziecka oraz jego układu endokrynnego. W fazie prenatalnej związki zaburzające gospodarkę hormonalną (EDCs), poprzez naśladowanie lub nawet blokowanie działania ludzkich hormonów, mogą naruszać równowagę estradiolu i progesteronu, które mają istotny wpływ na rozwój narządów dziecka. Zanieczyszczenia powietrza mogą zaostrzać astmę u dzieci, które już na nią chorują, natomiast rola zanieczyszczeń powietrza w rozwoju astmy nie jest w pełni zbadana. Składniki zanieczyszczeń powietrza, w tym PM0,1, mogą przenikać przez barierę krew–mózg i aktywować białkowe markery zapalenia IL-6 i TNF-α oraz indukować mikrostany zapalne.
Wnioski: Nawet niewielkie ograniczenie emisji zanieczyszczeń powietrza ma pozytywny wpływ na zdrowie dziecka.

SŁOWA KLUCZOWE
zanieczyszczenie powietrza, płód, pył zawieszony, astma, drogi oddechowe, niska masa urodzeniowa.

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INTRODUCTION

Smog is formed by the interaction of various oxides, metals, and volatile organic compounds with solar radiation and fog [1]. In Poland, the main sources of emissions come from road transport and combustion processes from municipal and residential sources [2]. Particulate matter (PM), which is one of the air pollution parameters that is often identified with it, is a complex mixture of solid particles and liquids. Carcinogenic compounds such as benzo[a]pyrene (a group 1 carcinogen), as well as compounds of toxic metals (e.g. lead, cadmium, nickel) and metalloids (e.g. arsenic) can be adsorbed by the particles. PM10 particles are microscopic particles of solid or liquid matter suspended in the air with a diameter of no more than 10 μm; similarly, PM2.5 comprises particles with a diameter of no more than 2.5 μm. There is also a fraction of PM0.1, with a diameter below 0.1 μm, which is considered to be the most dangerous for health because no natural barrier can stop them. PM serves as a carrier for the substances mentioned above, which easily enter the bloodstream in the case of PM2.5. In recent decades, numerous epidemiological and experimental studies have indicated the pleiotropic adverse effects of exposure to particulate matter on human health [3–9].

AIM

This paper discusses the most severe effects of particulate matter on child development. The aim of the study was to signal the problem and conduct a literature review of the described issue.

MATERIAL AND METHODS

Literature search was performed using the medical database PubMed in time period from 2007 to 2021 using the following MESH-terms: air pollution, child, particulate matter, low birth weight, asthma, environmental pollutions, and respiratory system.

RESULTS

PRENATAL PERIOD

Exposure to air pollution during the foetal period has significant consequences, adversely affecting foetal growth and the development of the child's internal organs [10–13]. In the prenatal period, dynamic cell proliferation occurs, and the child's ability to defend itself against pollution is severely limited. During pregnancy, it is worth noting that women's minute lung ventilation

and respiratory frequency increase, favouring the deposition of contaminants in the adipose tissue. A possible pathomechanism is a placental malfunction caused by deposited pollutants, which induces oxidative stress and consequently oedema and inflammation [14]. The transport of oxygen and nutrients to the foetus is reduced. The most noticeable change is the significantly lower birth weight of children. Jedrychowski *et al.* conducted a study among more than 300 non-smoking women living in the Krakow metropolitan area, who delivered a baby between 34 and 42 weeks of pregnancy. During the second trimester of pregnancy, PM concentrations in exhaled air were measured for 3 days using a PEMS device (Personal Environmental Monitoring Sampler). Women in Krakow exposed to PM2.5 levels above 35 μg/m^3 during pregnancy gave birth to children with birth weight lower by 128 g on average, head circumference lower by 0.3 cm on average, and body length lower by 0.9 cm on average [15]. Similar results were obtained in studies conducted in other scientific centres [16, 17].

Oxidative stress and inflammation induced by PM2.5-related pollutants accumulating in the placenta may be responsible for the genesis of reduced body weight. Ongoing inflammatory processes cause endocrine pathologies, disrupting the pituitary-adrenal-placental system [18]. Another proposed mechanism suggests that components associated with PM2.5 and smaller particles may affect the placenta through activation of NK cells. PM particles also impede oxygen exchange between the placenta and the foetus and over-activate the immune system, causing further inflammatory reactions. In in vitro experimental studies, the possibility of induction of apoptosis induced by processes initiated by PM2.5 accumulation has been reported [19].

Reactive oxygen species associated with oxidative stress affect mitogen-activated kinases (MAPKs) – these molecules are involved in directing cellular responses to various stimuli such as mitogens, osmotic stress, heat shock, or pro-inflammatory cytokines. They are also involved in the activation of apoptosis mechanisms; the same group of scientists in studies on rats proved the damaging effect of PM2.5 on testicular tissues and the deterioration of mitochondrial integrity of the spermatocytes of male rats [20]. It has also been shown that PM2.5 can disrupt G2/M checkpoints by interfering with processes in early trophoblasts. This may cause a reduction in the number of trophoblasts in utero and translate directly into the lower birth weight of the child [21].

Air pollutants significantly affect the endocrine system; an example of this action is endocrine-active compounds (EDC). These compounds mimic the action of hormones and, in some cases, can block the action of actual human hormones. They can affect hormone balance in the prenatal phase, especially oestradiol and progesterone, which significantly influence development of the child's organs. Heavy metals, diesel pollution, or pesticides can act very similarly to EDCs. Wójtowicz *et al.* demonstrated the direct effect of EDC compounds on the synthesis of hormones [22]; similar studies have confirmed the blocking effect of PM2.5 on chorionic gonadotropin and hence impaired synthesis of progesterone [23].

In addition, PM particles can activate toll-like receptors (TLRs), which play a crucial role in initiating the innate immune response. Receptors activated by PM2.5 can induce metabolic pathways, including changes in foetal glucose metabolism. In addition, air pollution particles cause changes in cord plasma insulin levels early in life. They may be a risk factor for developing metabolic diseases such as glucose intolerance or insulin-dependent diabetes later in life [24].

The effect of air pollution on gene methylation, which results in changes in the expression of individual genes, has also been demonstrated. It is suspected that the most significant role in harmful methylation is played by polycyclic aromatic hydrocarbons, such as benzo[a]pyrene, the concentrations of which have been exceeded in Polish cities for many years. The greatest damage is observed in Treg (regulatory) lymphocytes, responsible for suppressing an over- or autoreactive immune response. Consequently, plasma IgE and IFN-γ levels increase, and IL-10 expression decreases [25]. Prunicki *et al.* showed that it was by such a mechanism that the incidence of asthma was significantly increased in the children included in the study [26]. This hypothesis is confirmed by studies of placenta samples exposed to PM2.5 particles, in which an increase in placental Alu-marker DNA mutation was noted [27].

On the other hand, analytical studies conducted on abortive material indicate significantly higher cadmium and lead content in the tissues of foetuses from pregnant mothers living in urban agglomerations compared to those associated with rural areas [28]. Also, studies on the chemical composition of cord blood have indicated higher lead and cadmium content for urban populations [29]. It is known from other studies that exposure to toxic metals, also associated with particulate matter, is higher in urbanized regions [30–33]. Exposure to PM has also been linked to a higher risk of spontaneous miscarriage [34].

RESPIRATORY SYSTEM

Children are particularly vulnerable to smog due to their shorter and narrower airways, frequent mouth breathing, not fully mature detoxification system, and insufficient filtration in the nasal passages. In addition, statistically they spend more time outdoors and show significantly more physical activity compared to adults. Per kilogram

of body weight, a child has higher minute ventilation than an adult, while their airways are closer to the ground (due to their height) making them more exposed to traffic pollution. The child's respiratory system fully develops between 3 and 8 years of age.

At the same time, the immune system is still immature; preschool children are on average diagnosed with 8–10 respiratory infections per year. Each infection causes a decrease in the efficiency of mucociliary clearance. Decreased ciliary movement means that airborne contaminants can persist longer in the airways. If the epithelium is damaged during infection, the basement membrane is exposed, making it easier for pollutants, especially those associated with PM2.5, to penetrate the tissues. The differentiation of the respiratory system begins at about the 4th week of foetal life through the abdominal protrusion of the intestinal tube. In the glandular phase lasting from the 6th to about the 17th week of foetal life, dichotomous divisions of primary bronchi begin. It is now suspected that air pollutants entering the foetus may affect the growth of the tracheobronchial tree and large blood vessels [35].

Later prenatal exposures may, in turn, influence lung capillary development and lung capacity in the tubular and saccular phases. It has been shown that long-term exposure to low concentrations of PM2.5 is more harmful than a 1-day exposure to repeatedly exceeded permissible concentrations; in addition, a slight decrease in FEV1/FVC% was observed among children aged 6–10 years compared to a control sample [36]. Air pollutants, even after a short exposure of a few hours, affect the airway mucosa; in a study in which healthy young people were exposed for 5 hours to air pollution, 3 different measures of oxidative potential were significantly associated with markers (exhaled nitric oxide and IL-6) of airway and nasal inflammation [37].

It is currently accepted that an increase in PM concentrations of 10 μg/m^3 translates into a 1% increase in respiratory illnesses. An increase in respiratory infections among children was observed 7 days after an increase in PM2.5 concentration by 10 μg, and infections on average persisted for 28 days [38].

Exposure of healthy children to temporarily elevated air pollutants lasting several hours usually results in irritation and minor inflammation that does not cause discomfort to the child. However, chronic exposure of children even to acceptable concentrations of pollutants (not exceeding WHO daily standards) results in a slower increase in absolute values of respiratory indices as the child grows up [39].

It is possible that during chronic exposure of young children to air pollutants, a partial remodelling of their airways may occur. The distance of residence of the child from large pollution sources is not without consideration. In a study conducted in Krakow, the frequency of respiratory symptoms was higher in children living up to 200 m from busy roads compared to children living more than 500 m away [40]. An extensive cohort study of pregnant women's exposure to air pollution was carried out in Krakow, followed by spirometric tests in the born children in their 5th year of life. The results of the study showed reduced forced vital capacity (FVC) in children with the highest exposure to PM2.5 and deficits in forced expiratory volume in the first second (FEV_1) [40].

A similar study was carried out in Canada, with results similar to those in Poland, but higher FEV_1 and FEV_1/FVC deficits were observed among boys aged 6–18 years than in the same group of girls [41]. This result may be partly explained by boys' statistically longer time spent outdoors. It is suspected that such an outcome in the whole group of children studied results from the effect of pollution on the child's respiratory system after birth.

BRONCHIAL ASTHMA

While scientists agree that air pollution can trigger and exacerbate asthma in children who already have asthma, there is debate among researchers about the role of air pollution in the development of asthma. It is thought that constituent air pollutants such as nitrogen and sulphur oxides may be factors in the development of asthma but not the main determinant. However, an increased response to allergens during exposure to PM has been demonstrated. The likely mechanism is an increase in oxidative stress in endothelial cells, a shortening of their lifespan, and an imbalance between Th1 and Th2, which may predispose to childhood asthma development. Observations in France have shown a higher prevalence of asthma in children living in large urban centres with busy transport routes [42].

The analysis of available studies and observations shows that chronic exposure to every 2 μg/m^3 increases the risk of asthma by 14%. However, it is important to remember that there are also genetic factors underlying asthma, and not all studies unequivocally confirm the association of air pollution with the development of this disease [43].

PM also interferes with the bacterial flora of the respiratory tract, which provide an additional protective barrier. Bacteria of the respiratory microbiome can metabolize some of the components of pollutants, e.g. arsenic, changing their toxicity. Air pollutants affect the composition of the respiratory bacterial flora by changing its diversity and profile [44]. This has been confirmed by studies on the incidence of respiratory tract infections caused by *Staphylococcus aureus* and *Pseudomonas areuginosa*,

and people exposed to higher concentrations of PM2.5 were more frequently ill [45].

NERVOUS SYSTEM

Components of air pollutants, including PM0.1, can penetrate the blood-brain barrier and activate inflammatory protein markers IL-6 and TNF-α, and thus induce inflammatory microstates [46]. PM2.5 and smaller particles may enter the brain via 2 routes: penetrating the blood system and directly through the nasal mucosa. This has been confirmed by studies in mice using 10 nm gold nanoparticles. About 0.02% of nanoparticles enter the circulation from the alveoli, and air pollutants penetrate in the same way [47].

A study conducted in Krakow between 2001 and 2006 found that children whose mothers were exposed to concentrations of polycyclic aromatic hydrocarbons above 17.96 ng/m^3 during pregnancy had reduced Raven's matrices scores (the test measures non-verbal, abstract, and cognitive functioning). Raven's matrices reflect the level of general intelligence; the results of the 5-year-old children included in the study in Krakow corresponded to an average decrease of about 3.8 IQ points compared to the control group [40].

Thanks to deiodinase type 2 the conversion of thyroxine (T4) to triiodothyronine (T3) take place in glial cells. Next as a t3, hormone is transported to other neurons and oligodendrocytes – cells responsible for forming myelin sheaths. When T3 is taken up by the cells, it travels to the cell's nucleus and regulates the transcription of many genes. PM can affect thyroid hormone signalling, leading to reduced brain-derived neurotrophic factor (BDNF) and deregulation of GABAergic interneuron function. The consequence is reduced synaptogenesis and impaired neural networks [48]. Also, noradrenaline and dopamine, by binding to β2 and D1.2 receptors, are involved in the neurodevelopmental processes in the foetus. *In vitro* studies have shown that benzo[a]pyrene and other polycyclic aromatic hydrocarbons bind to β2AR receptors and activate downstream [49].

It has also been shown that heavy metals such as lead, a component of air pollution, can bind to transcription factors. A well-described example is the attachment of heavy metals to the AhR receptor, which can disrupt NMDA receptor regulation and consequently disrupt Ca^{2+} homeostasis and lower intracellular Ca^{2+} levels [50]. The demonstration by Calderón-Garcidueñas *et al.* [51] that children carrying the ε4 allele of the apolipoprotein E (APOE) gene, considered a risk factor for Alzheimer's disease, showed a higher number of marker proteins compared to the control group is extremely important. This finding suggests that air pollution may increase the risk of Alzheimer's disease in children predisposed to the disease by a genetic factor.

CONCLUSIONS

Air pollution, as outlined above, significantly affects a child's prenatal development. Even small reductions in air pollution emissions positively impact child health. Increasing public awareness can be a driving force for change at both national and local levels. Responsible pregnancy planning and deliberate reduction of maternal and then child exposure to major sources of pollution is also important.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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