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AIR POLLUTION, INFLAMMATION AND PRETERM BIRTH: A POTENTIAL MECHANISTIC LINK

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Abstract

Preterm birth is a public health issue of global significance, which may result in mortality during the perinatal period or may lead to major health and financial consequences due to lifelong impacts. Even though several risk factors for preterm birth have been identified, prevention efforts have failed to halt the increasing rates of preterm birth.

Epidemiological studies have identified air pollution as an emerging potential risk factor for preterm birth. However, many studies were limited by study design and inadequate exposure assessment. Due to the ubiquitous nature of ambient air pollution and the potential public health significance of any role in causing preterm birth, a novel focus investigating possible causal mechanisms influenced by air pollution is therefore a global health priority. We hypothesize that air pollution may act together with other biological factors to induce systemic inflammation and influence the duration of pregnancy. Evaluation and testing of this hypothesis is currently being conducted in a prospective cohort study in Mexico City and will provide an understanding of the pathways that mediate the effects of air pollution on preterm birth. The important public health implication is that crucial steps in this mechanistic pathway can potentially be acted on early in pregnancy to reduce the risk of preterm birth.

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Keywords

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Introduction

Preterm birth is defined as birth before 37 weeks of pregnancy and it is a very common occurrence; the prevalence of preterm birth was reported to range from 6.2 to 11.9% worldwide, but in some places, prevalence is even higher (1). Efforts to provide preventive or curative interventions have had minimal success. On the contrary, the problem seems to follow a worryingly increasing trend in several countries(2). Preterm birth is a major contributor to both perinatal and early neonatal mortality rates, especially in developing countries. (3, 4). In addition, surviving infants may have long term morbidity, including disability, which can have a major impact on their families (4). Air pollution has been identified as a potential risk factor for preterm birth, but research to date has had several limitations. Nonetheless, the U.S. Institute of Medicine, based on a 2007 review of 21 published studies on air pollution and preterm birth, acknowledged the role of air pollution in the etiology of preterm birth (2). We hypothesize that air pollution may act together with other biological factors to induce systemic inflammation and influence the duration of pregnancy.

Air pollution and preterm birth

Epidemiologic studies evaluating the association between air pollution and preterm delivery have had varying results for specific pollutants and gestational windows (5–12). In Beijing, China, an inverse relationship was observed between gestational age, total suspended particles (TSP) and sulfur dioxide (SO_2) concentrations during pregnancy (13). A study based in Vancouver, British Columbia, Canada, evaluated the gaseous pollutants carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2) and SO_2finding that only SO_2 and CO exposures during the last month of pregnancy were associated with preterm birth (9). In Los Angeles, California, evidence for a positive association between preterm delivery and particulate matter less than 10 microns in aerodynamic diameter (PM_{10}) and CO exposures during both the first gestational month and late pregnancy was observed, but no association was seen for NO_2 and O_3 (8). Subsequent studies in the Los Angeles population found modification of the pollution-preterm association by neighborhood socio-economic status (5), and continued associations with preterm delivery for exposures during the first trimester to particulate matter less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) and both early and late-pregnancy CO exposure, with strengthened associations when exposure misclassification was reduced by the use of time-activity information from the women under study (11). By contrast, another study in the state of California found that $PM_{2.5}$ but not CO was associated with preterm delivery (14). In the Czech Republic, trimester-specific exposures to oxides of nitrogen (NOx), $SO_2$and TSP were evaluated; the strongest associations observed were for first-trimester exposure to NOx and TSP, but little evidence for a NOx association was seen, and later trimester exposures showed weak associations for all pollutants (7). Exposures to SO_2 early in gestation were related to preterm birth in Labin, Croatia, but other pollutants were not evaluated (15). A study in Taiwan assessed exposure on the basis of proximity to a petrochemical plant and found a higher rate of preterm birth among women living in a more polluted versus less polluted region (16). In Pennsylvania, PM_{10} and SO_2 in the last 6 weeks of gestation were associated with preterm birth, controlling for gaseous co-pollutants (17). A study in Inchon, Korea which evaluated CO, $NO_2SO_2$and $PM_{10}$with exposure estimated using geo-statistical methods accounting for residential address, found significantly elevated risks of preterm delivery for all four

pollutants in the first trimester, and for CO and NO_2 in the third trimester (12). In Brisbane, Australia, O_3 and PM_{10} exposures in the first trimester were associated with preterm birth, whereas NO_2 and finer, light-scattering particles were not (18). The biological mechanisms which have been proposed to be on the pathway between air pollution and preterm delivery may occur during various points in pregnancy (9). However, the direct casual pathways mediating this process are not widely understood.

Inflammatory cytokines and preterm birth

Many of the known mediators of normal labor are pro-inflammatory cytokines. As a result, the instigation of an inflammatory response in the intrauterine space, even without infection, could provoke labor independent of the gestational age and maturity of the fetus (19), and cytokines play an important role in this process (20). Furthermore, although normal labor is accompanied by activation of the inflammatory system, this transitory phenomenon does not affect the health of the mother or the fetus. Nevertheless, if the inflammatory response becomes chronic, as in the case of a chorio-decidual infection, this condition may affect the duration of pregnancy, altering the normal timing and synchronization of the activation of labor tissular components, including uterine contractility, and/or the integrity of the fetal membranes and/or the competence of the cervix.

Clinical and experimental studies corroborate that inflammatory mediators, such as the Interleukin 1-β (IL-1β); Tumor Necrosis Factor-α (TNF-α); interleukin-6 (IL-6) and interleukin 10 (IL-10), associated with infection or not, can trigger the premature onset of labor. Intra-amniotic infusion of IL-1β causes uterine contractility in non-human primates (21) and this cytokine mediates the activation of the myometrium after inoculation of live bacteria in the choriodecidual space in a non-human primate experimental model (22). IL-1β is also a key mediator for degradation of the extracellular matrix support in the fetal membranes (23–26). IL-6 and TNF-α are pro-inflammatory cytokines involved in systemic inflammation, and evidence for a link between elevated serum levels of IL-6 as well as TNF-α and increased risk for preterm delivery is available (27–29). High serum concentrations of IL-10 were inversely associated with preterm delivery (30).

Cellular sources of these cytokines have been traced to local populations inside the choriodecidual space, just inside the maternal/fetal interface (25, 31), making this site a potential target for environmental factors such as infection, air pollutants, and other agents that may trigger inflammation. This virtual microenvironment is enriched with special subsets of leukocytes that may react with blood-borne compounds appearing at different times during pregnancy, resulting in the abnormal local and/or systemic triggering of the signaling network that leads to preterm labor or premature rupture of the membranes (PROM) (32).

Hypothesis: Inflammation is the pathway linking air pollution and preterm birth

Air pollution is composed of distinct gaseous compounds and particulate matter, which is comprised of suspended aggregates of transition metal oxides, ammonium nitrate and sulfate saltsas well as other organic materials. (33). In addition to concentration and size, particle toxicity is also influenced by composition. On the one hand coarse fraction particles that range from 2.5 to 10 μm in diameter ($PM_{2.5–10}$), are released from natural sources and may include microbiological components(33). When inhaled, PM_{10} and $PM_{2.5–10}$ or larger particles are either removed or are deposited on the ciliated epithelium in the tracheobronchial region (34). On the other hand fine fraction particles ($PM_{2.5}$) are mostly associated with anthropogenic, combustion-related emission sources. These smaller particles can potentially deposit deep into the lungs and may enter the circulatory system which may

allow particles to reach the intrauterine compartment or induce systemic inflammation (33, 35).

Inflammation may underlie the air pollution-preterm link and can be a consequence of direct stimulation of inflammatory cells or mediated by oxidative stress. Ambient pollutants have been associated with systemic inflammation in several studies and this may include the intrauterine milieu (36–38). Inhalation of particulate matter can cause an increase in markers of inflammation, as shown in both *in vivo* and *in vitro* studies (33, 39). Although less information exists about the specific effects of particulate matter components versus its aggregate, compositional trace elements (40, 41) and transition metals contribute to cardiopulmonary injury and inflammation in healthy animal models (42). Direct exposures of cultured cell lines to ambient particles have shown that particle composition is linked to differential toxicity and ability to provoke proinflammatory responses (43, 44).

Physio-pathological effects associated with particulate exposure both *in vivo* and *in vitro* include inflammatory effects such as airway inflammation, recruitment of monocytes and macrophages, cytokine release and activation of T-cells and β lymphocytes (43, 45), and cytotoxic effects including apoptosis, necrosis, genotoxicity, generation of reactive oxygen species, and thrombosis (33, 46, 47). Particle toxicity occurs when macrophages phagocytize particles and subsequently present the antigen to helper T-cells. In addition, macrophages release cytokines that attract other immune cells, producing a generalized inflammatory response to the inhaled particle and generation of reactive oxygen species. Metals and metal oxides such as vanadium, nickel, and lead can contribute to particle toxicity. Phagocytosis of metal oxides, especially vanadium oxide, by alveolar macrophages stimulates the release of IL-1β. IL-1β in turn induces the release of platelet derived growth factor receptor (PDGF-Rα), which plays an important role in the proliferation of other cytokine-releasing cells (48). Particles also induced DNA breakage *in vitro*suggesting that transition metals also have a genotoxic effect (46). A recent study identified two cellular response profiles related to the main particle emission source (49). Samples from a region in which soil components predominated resulted in a cell profile characterized by cell toxicity, whereas samples associated with high temperature combustion sources (i.e., vehicular emissions) resulted in a proinflammatory profile. Interestingly, larger effects were induced by PM_{10} than by $PM_{2.5}$.

Endotoxins (such as lipopolysaccharide) are liberated from the cell walls of gram-negative bacteria and often are found in suspended particles (43). Endotoxin exposure is associated with a Th-1 type response and the concurrent release of cytokines such as TNF-α, IFN-γ, IL-6, IL-8, and IL-12 (50). In Mexico City, concentrations of endotoxin in particles can range from 11–18 units/milligram of particulate, with the larger fraction of the total endotoxin being contained within the insoluble fraction of the particles (43). Increased levels of endotoxins in particulate samples have been shown to be correlated with increased cellular concentrations of E-selectin *in vitro* (46). E-selectin, which plays a role in monocyte adhesion and recruitment, is synthesized and released by endothelial cells in response to increased cytokine output and is believed to play an important role in airway inflammation. The coarse particle fraction contains higher concentrations of endotoxin than the fine fraction and accordingly, in the same study, coarse fraction was more strongly associated with cytokine release *in vitro* (44). Thus, particle composition may be a better predictor of particulate toxicity than size, and endotoxin is an influential particle component in inducing the inflammatory effects of exposure.

Choriodecidual microenvironment

A complex mix of cells, including decidual cells and leukocyte subsets such as monocytes, lymphocytes and NK cells, composes the borderline between the pregnant woman and the fetus. These cells preserve immune tolerance along gestation, but as the end of pregnancy

approaches, several changes, including the arrival of specific subsets of lymphocytes, are coincident with the induction of labor (51, 52). This virtual space or choriodecidua constitutes a microenvironment located both in the placenta and in the fetal membranes and contains all cellular elements needed for establishing an inflammatory response when contact with air pollutant constituents, air pollutants triggered systemic inflammation or other environmental insults is established. Cells in this microenvironment are located in the proximity of effector tissues of labor including the myometrium, fetal membranes and the cervix, and can thus modulate the functional responses of these tissues. An intricate network of signaling, composed of primary signals such as IL-1β and TNF-α, appears to initiate the sequence of events leading to labor, a sequence resembling the initial phases of inflammation(25). This initial signaling elicits the secretion of a secondary wave compounds by local cells, resulting in the production of prostaglandins, oxytocin and matrix metalloproteinases. This secondary wave mediates the activation of the myometrium, inducing it to make effective contractions and cause the degradation of extracellular matrix both in the cervix and fetal membranes, resulting in cervical ripening and rupture of the fetal membranes.

Other factors during pregnancy may add or potentiate inflammation

We may postulate that any factor contributing to activation of the choriodecidual cells, such as the above described environmental pollutants, may induce the development of labor. If this is happening before the normal terminus of pregnancy, it may appear as preterm labor. The association of inflammation and preterm delivery is complex since several interacting factors resulting in the elicitation of the inflammatory response may contribute to preterm labor onset; some of these factors are perhaps acting at different periods of gestation. Here, we propose that in addition to air pollutants, factors such as local or systemic infections, oxidative stress, nutritional status, genetic background, and obesity during pregnancy have a common inflammation-mediated pathway potentially leading to preterm labor. This perspective enriches our central hypothesis, making the induction of inflammation a central communicating mechanism between the mentioned factors and the development of preterm labor. We propose that the total inflammatory response leading to the induction of the mechanisms of preterm labor results from a combination of factors.

Infection and preterm labor

Systemic, cervico-vaginal and/or intrauterine infections are considered a direct explanation of preterm birth (53, 54). The patho-physiologic model linking infection and preterm birth proposes that the pathogenic microorganisms become established in the ecosystem of the cervix and vagina and can progressively colonize the internal regions of the reproductive tract (19). Chorio-decidual infections confined to this virtual space can acquire chronic characteristics, and elicit a local inflammatory response that remains subclinical yet still affects the intra-uterine environment, influencing the functions of reproductive tissues.

Although air pollution does not directly cause infections, it may increase maternal susceptibility to infections due to impaired immune function and enhanced inflammation (55, 56). Alterations in the immune system could alter vaginal flora and promote pathogens associated with bacterial vaginosis, a risk factor for preterm delivery (57). A range of infections, from genitourinary and intra-amniotic infections to maternal systemic infections and periodontal disease, are associated with preterm delivery etiology (58).

Oxidative stress and diet

Oxidative stress may also mediate inflammation and preterm delivery associations (18, 59), and oxidative stress is a common result of exposure to gaseous and particulate pollutants. Reactive oxygen species generated within the cell can lead to oxidative stress, apoptosis or

even necrosis. Oxidative stress can occur due to synergy between nitrogen oxides and SO_2manifested in the adverse effects of NO_x metabolites. Reactive sulfur species are oxidative stressors whose actions on antioxidants and enzymes could affect the embryo in its earliest phase of growth and development (15, 59). Particulate matter may contribute to systemic oxidative stress, since combustion-derived particles (41) and/or their transition-metal constituents (e.g. iron, copper, chromium, and vanadium) may have oxidative activities (15). In addition, organic compounds in particles may activate inflammatory cells capable of generating reactive oxygen and nitrogen species (42). Ozone is also a plausible contributor to oxidative stress; toxicology studies have shown increases in both lipid peroxidation products and inflammatory cytokines after ozone exposure (60, 61). Controlled human exposure studies also support an inflammatory response to ozone exposure (62).

Antioxidant vitamins, including vitamins C and E, are a primary line of defense against oxidative stress. The source of these vitamins is the diet and vitamin supplements and special recommendations for pregnant women have been established (63). Hence, nutritional status may play a role in the control of the effects of the inflammatory pathway. Anti-oxidant vitamins E and C have been proposed as possible preventive agents for PROM and a clinical trial showed that vitamin C reduces the risk of PROM (64). There is also evidence that anti-oxidant vitamins reduce impacts of air pollution on lung function and other parameters that are hypothesized to be influenced by the oxidative stress resulting from pollution exposure (65, 66). Thus, we consider these vitamins as important potential modifiers of any association between air pollution/inflammation and preterm delivery.

Genetic background

The genetic profile controlling individual inflammatory response may be relevant to the inflammatory pathway toward preterm birth. An epidemiology study found that haplotypes of two pro-inflammatory cytokine polymorphisms were associated with preterm birth in a North Carolina-based birth cohort (67). Experimental research compared amniochorion tissues with hyperresponsive alleles of TNF-α and IL-1β to tissues with the more common alleles, and found that the hyperresponsive allele-carrying tissue secreted higher levels of cytokine when challenged with increasing doses of bacterial lipopolysaccharide (68). This implies an over-response to pro-inflammatory factors such as intra-uterine infection that may contribute to preterm birth in women with these polymorphisms. Similarly, in a case-control study among African-American women, carriers of the rarer (hyper-responsive) allele of a TNF-α polymorphism were more likely to have preterm delivery associated with PROM (69). Thus, hyper-functional polymorphisms in genes related to cytokines may confer greater capacity to mount an inflammatory response in the face of an infectious stimulus while simultaneously amplifying other responses. Similarly, the IL-1rα allele 2 (or an unknown allele strongly associated with it) coding for the antagonist of the IL-1 receptor has been suggested to have an important role in inflammatory response (70).

Obesity and inflammation

Maternal increased adiposity has been associated with increased risk of antenatal, intrapartum and postpartum complications. Since rates of obesity are still rising in the population of fertile women, we may expect an increase in the number of pregnancy-associated complications, both in the mother and in the babies. Preterm delivery is a serious concern in pregnancies involving obese women (71). Infants born to mothers with a body mass index (BMI) >35kg/m_2 are at increased risk of premature birth and neonatal death. In the past decade, the incidence of preterm delivery has risen, closely paralleling the rising rate of maternal obesity. There is a higher incidence of preterm delivery among obese women, as well as other obstetrical indications including PROM and preeclampsia (72). Some of these complications have been linked to the associated inflammation conditioned

by increased adiposity (73). Adipocytes produce several pro-inflammatory signals that elicit a general inflammatory response (74) which may eventually harm pregnancy as an additive or priming effect to other inflammation-inducing factors such as those mentioned previously. The increased baseline inflammation due to obesity may represent the starting point for a cascade of adversity, which increases risk for both maternal disease and neonatal complications.

Consequences of the hypothesis

Preterm birth continues to be a public health priority of global importance. Knowledge of the mechanisms of this outcome allows us to propose that the inflammatory pathway is a critical link between air pollution exposure and preterm labor. However, this response is also influenced and up-regulated by the presence of several other factors, usually present during pregnancy, involved in the induction/regulation of the inflammatory response. Observation of a relationship between air pollution exposure and preterm birth, as well as the mediating inflammatory pathway, may be useful in guiding treatment and prevention efforts in clinical settings. To evaluate this hypothesis, our research group - an international interdisciplinary collaboration - is conducting this proposed research in a prospective cohort study of 800 pregnant women in Mexico City (75); the study also has an *in vitro* component which evaluates the inflammatory processes of cells directly exposed to particulate matter. Such a complex study, considering all the potentially interacting factors, has been suggested to be conducted through an interdisciplinary collaboration among environmental and perinatal epidemiologists, geographers, obstetrics and gynecology specialists, molecular biologists and environmental toxicologists. The ongoing research will address many of the identified gaps in knowledge, including evaluation of various time windows during pregnancy; inclusion of the full range of monitored air pollutants; use of high-quality, ultra-sound confirmed gestational age data; examination of biomarkers of biologic response; and evaluation of particle composition for one component of the project. The practical implication is that we hope to be able to identify and treat at-risk patients early on during pregnancy to promote full term pregnancies and, in the long term, reduce preterm birth rates.

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