

Maternal Exposure to Ambient Particulate Matter (PM_{2.5}) During Embryonic Cardiac Development Leads to Hypoplastic Left Heart Syndrome

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Background Information

Congenital heart defects are present in about 1% of all live births, and within that 1%, the incidence of hypoplastic left heart syndrome (HLHS) ranges from 4.8% to 9%.¹ The cause of HLHS, as well as how to prevent the condition, remains unclear.² However, in recent years, there has been increasing awareness of HLHS. Even so, without surgery, the condition is still fatal within the first few weeks of life.²

In utero, the embryonic heart begins to develop around the third week of pregnancy and the fetal heartbeat is detected between 21 and 22 days after conception.³ HLHS is a severe condition related to a grouping of cardiac malformations including hypoplasia of the left ventricle, a narrowed aortic arch, and an open foramen ovale between the left and right atria.³ Due to severe underdevelopment, or sometimes nonexistence of the left ventricle, the left side of the heart is unable to properly supply the body with oxygenated blood.² When oxygen-saturated blood reaches the left atrium, it is shunted through the open foramen ovale and mixed with desaturated blood in the right atrium.³ For the first several days of life, the right side of the heart may be able to adequately oxygenate the body, as some of this mixed blood is shunted from the pulmonary artery to the aorta through the open ductus arteriosus.² However, this structure typically closes shortly after birth, resulting in the heart's inability to supply the body with oxygenated blood.² This leads to common signs and symptoms of HLHS including cyanosis, dyspnea, a weak pulse, and a pounding heart.⁴ Current research on the topic suggests that HLHS may be genetically complex, inheritable, and likely linked to teratogenic drugs and environmental and seasonal influences.⁵ After careful exploration of embryonic development and the factors that contribute to mutagenic states, we decided to further analyze the association between HLHS and environmental and seasonal factors.

Hypothesis and Rationale

After examining seasonal trends of various pollutants, we hypothesize that hypoplastic left heart syndrome (HLHS) is caused by maternal exposure to high levels of PM_{2.5} in the atmosphere during embryonic cardiac development. Particulate matter (PM) consists of microscopic solid particles or liquid droplets that are either emitted directly into the air or formed from secondary reactions involving gaseous pollutants that combine in the atmosphere.⁶ These airborne particles tend to be measured in two size ranges: less than or equal to two microns (PM_{2.5}), and less than or equal to ten microns (PM₁₀); however, PM_{2.5} is considered to be a more significant health concern than PM₁₀, due to its smaller size and ability to deeply enter the respiratory tract.⁶ While some particulate matter may come from natural and organic sources such as natural fires, agriculture, and human activities, PM_{2.5} is derived mainly from combustion-related sources.⁷ Major sources of PM_{2.5} emission include motor vehicles, power plant emissions, and bushfires.⁸

Various studies have reported seasonal trends with the incidence of HLHS births by month.⁹ *Figure 2.1* displays the seasonality of HLHS, where an increase of children born with HLHS can be seen in the summer months.⁹ This means that, if carried to full term, conception

would transpire during the fall months and cardiac development would occur in the winter months. Correspondingly, *Figure 2.2* displays the seasonality of PM_{2.5} levels in the air, where higher levels are measured in the winter months and lower levels are measured in the summer months.¹⁰ A side-by-side comparison of the graphs illustrates an inverse relationship. Following our hypothesis, babies conceived in the fall undergo cardiac development in the winter (weeks three through eight of pregnancy)³ and are exposed to the highest levels of PM_{2.5} throughout the year. If PM_{2.5} is causing HLHS, it would make sense that a higher incidence of babies with HLHS are born in the summer, when PM_{2.5} levels are at their lowest.^{9,10}

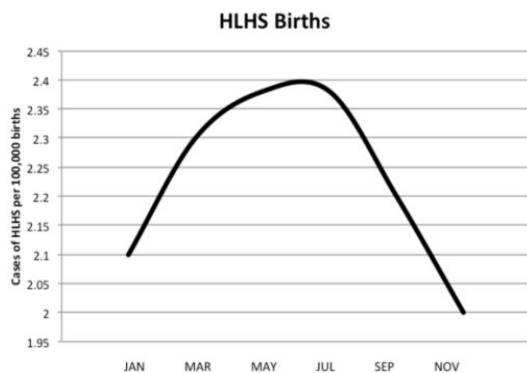


Figure 2.1. Seasonality of HLHS.⁹ Indicates an increase of HLHS births in the summer months and a decline of HLHS births in the winter months.

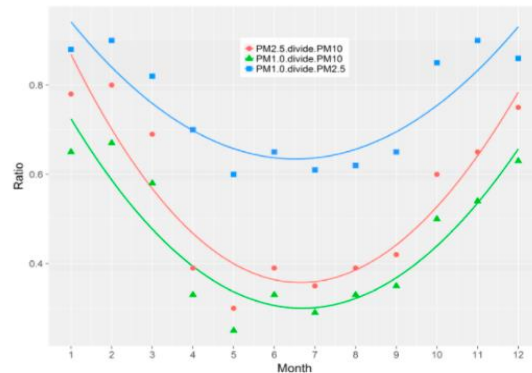


Figure 2.2. Seasonality of PM_{2.5} levels (as shown in red).¹⁰ Indicates higher levels of PM_{2.5} in the winter months and lower levels of PM_{2.5} in the summer months.

Mothers who are living in highly urbanized areas, especially where the population exceeds 100,000, are particularly susceptible to inhaling higher levels of PM_{2.5}.¹¹ PM_{2.5} enters the mother's body through the nasal and oral cavities, eventually reaching the alveoli and accessing the bloodstream via the pulmonary capillaries by diffusion.¹² Once in the bloodstream, maternal blood carrying PM_{2.5} particles flow through the placental artery and into the placenta.¹³ The fetus then receives this maternal blood from the placenta via the umbilical vein, which is then shunted into fetal circulation.¹³ Components of PM_{2.5} enter the uteroplacental vascular system, which may result in placental pathologic changes and decreased transplacental function.¹⁴ Consequently, pregnancy complications such as restricted fetal growth through one or more action mechanisms, including the umbilical cord, placenta, and fetal membranes may occur.¹⁴

In a study conducted by Sørensen et al., blood samples were taken from both men and women living in Copenhagen, Denmark, to test for PM_{2.5} exposure in a city where levels are dramatically prevalent, like many other highly populated cities.¹¹ The researchers found that exposure to PM_{2.5} in moderate concentrations can induce oxidative stress and increase red blood cell (RBC) concentration in peripheral blood.¹¹ Personal exposure, according to the study, appears more closely related to biomarkers like decreased clotting time and hemoglobin, lipid peroxidation, plasma proteins in the blood, and low birth weight—all of which are potentially related to cardiovascular disease and malformation.^{11,15} In infants with HLHS, similar

hematological pathology markers are shown.¹¹ Additionally, the study analyzed PM_{2.5} acting as an oxidant that lowers the partial pressure of oxygen, causing hypoxia with locally high levels of oxidative stress within the capillaries, producing “avascular, hypocellular ghosts.”¹⁵ In newborns with HLHS, this may be observed as cyanosis due to the lack of cardiac perfusion.⁴

Burton studied the epidemiologic effects of air pollution in urban environments in 2010 and drew a conclusion that ambient pollution (PM) is positively associated with an increased risk of human mortality.¹⁵ This is presumably caused by oxidative stress mediated by the inflammatory response of macrophage activity in releasing reactive oxygen species (ROS) into the tissues.¹⁶ The stress that ROS generates promotes endothelial dysfunction, induces oxidative injury to vascular cells, and oxidizes lipoproteins which function to trigger fibrin deposition.¹⁶ As a result, this pathway increases clotting in the blood.¹⁶ These processes could be an indication of abnormal parenchymal development of the vascular tissue.¹⁶ Previously, it was not understood how this process affected angiogenesis.¹⁶ However, leptin, a hormone found primarily in adipose cells, is also expressed in the placenta, indicating that if these structures within the embryo become dysregulated and oxidized by the ROS, then promotion of the inflammatory response of the tissue will occur as a direct result of the body’s immunologic response.¹⁶ Furthermore, this is associated with structural abnormalities of the cardiac tissue during embryonic development that leads to the occurrence of significant biomarkers of HLHS.¹¹

Significance and Innovation

McKinney et al. state that if left untreated, most newborns with HLHS die within the first few months of life due to the severity of defects.³ There are currently three options available for newborns born with HLHS: (1) no intervention with supportive care, (2) cardiac transplantation, or (3) a three-stage palliative repair resulting in a single right ventricle, with different portions of the pulmonary artery acting to facilitate both systemic and pulmonary circulation.³ The costs of these interventions are significant. According to a study by Dean et al., neonates with HLHS who undergo a cardiac transplant have an average length of stay of 87 days and charges of nearly \$600,000, while neonates undergoing a three-stage palliative repair have an average length of stay of 48 days, and charges of an estimated \$376,403.¹⁷ Following our hypothesis, these financial strains could be avoided by reducing PM_{2.5} exposure, thus preventing HLHS in utero.

To test this hypothesis, we propose that pregnant women who are at a higher risk for conceiving a child with HLHS (due to their increased exposure to PM_{2.5}) be tested for PM_{2.5} concentration in their blood. By using a vacuum pump with a membrane filter of 2.5-micron pore size, we could analyze the effects of PM_{2.5} on blood samples to determine if there is a definitive association between HLHS and PM_{2.5} exposure.¹⁸ Additionally, since HLHS can be diagnosed by fetal ultrasound, our findings could be compared with postpartum analysis of the newborn’s blood count to see if the child tests positive for biomarkers indicating signs of oxidative stress.^{3,11} The incidence of HLHS being caused by oxidative stress due to PM_{2.5} has not yet been linked to human data. However, promising findings concluding biomarkers of oxidative stress have been present in lab rats as a result of exposure to environmental pollutants, particularly PM_{2.5}, showing an increased prevalence of cardiovascular malformation.¹⁹

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