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Air Pollution is Adversely Affecting Fetal Health by Causing Birth Defects, Premature Birth and IUGR: A Wake-Up Alarm!

Sanjay Kulshrestha*

Department of Pediatric Surgery, Sarkar Hospital for Women and Children, Delhi Gate, Agra, India

***Corresponding author:** Sanjay Kulshrestha, Department of Pediatric Surgery, Sarkar Hospital for Women and Children, Delhi Gate, Agra, India, Tel: +919897078456; E-Mail: drsankul2008@gmail.com

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Abstract

Air pollution has become one of the most serious threat to human health globally killing 1.1 million people in India alone. T he most recent victim is innocent human fetus which is developing serious disorders like birth defects, premature deliver y, IUGR or even fetal deaths due to exposure to gaseous and particulate air pollutants during pregnancy. Sometime there may be a genetic change due to air pollut ion that may not cause any obvious malformation or birth defects immediately but these babies are more prone to certain diseases like cardiac or metabolic disorders later in life. Short-term and long-term exposure to particulate air pollution may alter intrauterine environment or "genetic programming" of subsequent health, causing changes in gene expression that may be linked to later childhood and adulthood diseases. Recent reports and researches from various countries on air pollution causing adverse outcome of pregnancy are very alarming. If we believe these reports, in India 6.5 million babies of IUGR and 170,000 babies of birth defects are delivered every year due to air pollution. Researchers have not only established relationship of air pollution with different fetal disorder but also proved the relationship of different pollutants with a particular fetal disorder like birth defects, premature birth or IUGR and relationship with time of exposure during pregnancy versus type of disorder. We need to take some urgent measures to protect our fetuses during pregnancy by taking som e short and long term actions. These include some multicentric research and survey at national level in India to establish relationship of air pollution with adverse outcome of pregnancy and on the basis of that health authorities should take appropriate actions to prevent or minimize such pollution related diseases in fetuses during pregnancy.

Keywords: Air pollution and fetal disorders, Birth defects, Premature birth, Fetal growth retardation

Introduction

Air pollution has become an established epidemic globally. Many serious reports are pouring in from all over the world that shows the situation is becoming from bad to worse. Out of many relevant international reports on ambient air pollution, the

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two most recent and detailed reports on air pollution that need to be considered are from Lancet [1] and state of Global air by Health Effects Institute [2]. These reports have confirmed that air pollution is responsible for 6.1 million deaths globally and out of these total deaths, 50% belongs to China and India alone! In India particulate matter 2.5 air pollution is responsible for 1.1 million deaths or in other words two people in India are dying every minute due to air pollution. The most worrying fact is that air pollution is now not only affecting from a pediatric to the geriatric population but it has also started affecting the unborn i.e. human fetus, increasing chances of birth defects, fetal growth retardation, and premature birth. Sometime there may be a genetic change in the fetus that may not cause any obvious malformation or disorder immediately but these babies are more prone to certain diseases like cardiac or metabolic disorders later in life or in adulthood.

During the last 30 years various studies have come up from many countries and if we believe them, approximately 25% of babies delivered in India suffer IUGR [3] that would mean every year out of 26 million babies delivered every year in India, 6.5 million suffer IUGR due to air pollution and similarly if we believe the reported incidence of birth defects occurring due to air pollution as 10% of total, that would mean out of total 1.7 million babies of birth defects delivered every year in In dia [4], 170,000 babies develop such defects due to air pollution. In this article author is trying to make an evidenced-based detailed analysis of various recent reports on air pollution from all over the world regarding its severity, effects on the fetus, mechanism of air pollutants causing fetal diseases and what actions have to be taken to prevent this adverse outcome of pregnancy. To explain fetal health problems due to air pollution, it would be convenient to discuss this issue under the following heads.

1. Air Pollution and Birth Defects

Although there are several risk factors which contribute to birth defects like genetic factors, environmental factors, chemicals, drugs, infections, maternal diseases, etc, however, studies have shown that maternal exposure to air pollutants can have developmental or teratogenic effects leading to birth defects.

Studies from developed countries

Most recently, a study from California showed an increased number of Neural Tube Defects (NTD) in babies delivered to women who had high exposures to carbon monoxide (CO), nitrogen oxide (NO), or nitrogen dioxide (NO_2) and high prenatal exposure to PM_{10} [5]. A report from Ohio has established a relation between *p*ericonceptional exposure to air pollution and the risk of congenital malformations. This report examined data on birth defects for nearly 290,000 babies in Ohio and compared this to air pollution measurements that were taken simultaneously near mothers' homes [6]. A study by new Stanford University linked early maternal exposure to high levels of air pollution to NTDs. According to Analysis of air quality and birth defect data for women living in one of the country's smoggiest areas of California's San Joaquin Valley, found a positive correlation between NTD and maternal exposure to CO, NO, and NO_2 during pregnancy [7].

Barcelona is among the most polluted cities in Europe which are partly attributable to high traffic density. A study in Barcelona on 2,247 cases of congenital anomalies showed a statistically significant association of NOx with CHD and GIT anomalies [8]. A nationwide study of Israel found exposure to PM10 and NOx pollutants in pregnancies were associated with an increased risk of congenital malformations, with specific defects evident in circulatory system from PM10 and NOx exposure and genital organs from NOx exposure [9]. National Birth Defects Prevention Study (NBDPS) in USA found that

higher exposure to air pollutants related to car traffic was more common among mothers of babies born with certain types of CHDs [10].

Studies from developing countries

China is very extensively making serious researches to find a relationship between severe air pollution and adverse outcome of pregnancy. According to research in China, babies who were exposed to certain organic pollutants in the womb were at very high risk of NTDs. Environmental scientists at Peking University investigated levels of PAHs and other pollutants in the placenta in fetuses or newborns with NTDs and found the risk of a defect was 4.5 times greater where levels of PAHs were above the average of 597 nano-grams. This study is important: firstly, it is from an Asian country as China having more or less similar air pollution conditions as that of India. Secondly, it shows what is actually reaching fetus rather than just what is circulating in the mother's blood. Thirdly, researchers are using actual biomarkers in the blood rather than measuring pollutants level from the nearest pollution recording centers to see the mothers what they have been exposed to. Thus it showed correlation with the environmental level of pollutants with that of mother's blood level and to the actual presence in the placenta [11]. Another Chinese study from Wuhan observed associations between ozone and CHDs [12].

Study of Taiwan provides evidence that ozone and PM10 during first 3 months of pregnancy increases the risk of CHD and with per 10 ppb increase in O3 exposure during first 3 months of gestation among all births were associated with increased risk of CHDs like VSDs (31%), ASDs (16%), and PDA (19%) respectively [13]. A meta-analysis confirmed that continuous exposure to NO_2, SO_2, and PM10 at 3-8 weeks of gestation was related to increased risk of CHDs [14]. Similarly, two other studies in 2014 showed evidence that exposure to PM10, PM2.5, NO_2, and SO_2 may be associated with the risk of birth defects [15,16].

The National Population and Family Planning Commission of China shared its research that linked high rate of birth defects in-country to air pollution. Research commented, "every 30 seconds, a baby is born with physical defects in China, all thanks to the country's degrading environment". According to Drum Tower Hospital, environmental pollution accounts for 10 percent of the causes of physical defects in Chinese infants. They said the situation in China is alarming and recommended to start a high-level preventive plan in China [17]. Considering this fact, total babies of birth defects delivered in India at 1.7 million years, approximately 170,000 may be caused by air pollution. **TABLE 1** summarizes various fetal disorders by different pollutants:

TABLE 1. **Fetal disorders by different pollutants.**

S. No.	Pollutants	Fetal Disorders
1	Particulate Matter (PM)	a. maternal exposures to PM10 and PM2.5 are associated with 23% and 14%, respectively, the excess risk of PTB and LBW b. PM2.5 linked with risk of congenital anomalies [6] c. High prenatal exposure to PM10 with NTDs [5]
2	Carbon Monoxide (CO)	a. Exposure during the first 8 weeks increases risk of NTDs by two times [7] b. Associated with an increased risk of CHDs like VSD [12]
3	Nitrates NOx	a. NO, and NO_2 linked to increased risks for birth defects and link between NO2 and anencephaly was particularly strong [7,9] b. NO_2 and SO_2 are associated with CHDs [8]

4	Ozone (O_3)	a. As per study per 10 ppb increase in O3 exposure was associated with risk of VSDs (31%), ASDs (16%), and PDA (19%) respectively [18] b. There are associations between O_3 exposure and increased risk of CHDs [19] and pulmonary artery and valve defects [20]
5	Polycyclic aromatic hydrocarbons (PAH)	a. PAHs are chemicals formed during the burning of coal, oil, gas, garbage and high levels of PAHs in the placenta is associated with NTDs [11] b. Data from NBDPS of US have linked PAH with Oral Clefts [20]
6	Sulfur Dioxide SO_2	a. Associated with risk of aortic artery and VSD [18] b. A retrospective cohort study in China reported link of SO_2 with the risk of birth defects in general

2. Air pollution and IUGR, LBW, and PMB

There is growing evidence that in addition to congenital anomalies, this air pollution also affects fetal development like Low Birth Weight (LBW), Preterm Birth (PTB), Intrauterine Growth Retardation (IUGR) and Small-For-Gestational-Age (SGA). Recent studies have linked air pollution to gestational hypertension, and preeclampsia which may be related to a detrimental effect on placental growth and function. A meta-analysis of 41 such studies revealed that exposure to SO_2 was associated with PTB, exposure to PM2.5 or less was associated with LBW, SGA and PTB, coarse PM less than 10 μM was associated with SGA births [14].

A recent study from Cincinnati, USA revealed that exposure to high levels of small particle air pollution is associated with a high risk of PTB. The study identified a 19% increased risk with maximum risk during the third trimester [21]. The vast majority of births, 97%, occurred in very urban areas, where most monitoring stations are located and exposure levels likely to be highest [22]. A meta-analysis from Korea systematically reviewed to provide evidence on concentration based association between maternal exposure to PM and LBW and PTB. This systematic review has updated current scientific evidence and shows that a decrease in BW per 10 $\mu g/m^3$ increase in particulate matter (PM2.5 or PM10) during pregnancy; studies suggest that maternal exposures to PM10 and PM2.5 during pregnancy are associated with 23% and 14%, respectively, the excess risk of PTB [23]. An extensive population-based study conducted recently in Wuhan, China for a cohort study on 9.5 million cases found that 3%, 2%, 5% and 15% increase in the risk of PTB with each 5 $\mu g/m^3$ increase in PM2.5 and PM10 and 10 $\mu g/m^3$ increase in concentrations respectively [24]. This co-relation of PM 2.5 and low birth weight has also been established by a recent US study [25].

As far as Indian studies are concerned, we are not aware of any such report regarding the association of air pollution with adverse outcome of pregnancy in India. As per information by government, at present, there are no specific data on mortality and morbidity due to air pollution in India [26]. However, India was the part of a worldwide study from more than 3 million births in nine nations at 14 sites has shown that pregnant mothers exposed to air pollution emitted by vehicles are significantly more likely to have smaller babies in 25% [3]. In India 26 million babies are delivered every year and considering this fact, about 6.5 million newborns are affected with IUGR in India by air pollution.

3. Air pollution and fetal deaths and stillbirth

Studies are coming up showing air pollutants are closely related with fetal death and stillbirth. The largest study in this regards has come from China that examined in details about the relationship of different pollutants with that of fetal deaths that have appeared in textbook “Ambient Air Pollution and Health Impact in China-2017. It showed a high PM level equal or more than

0.996 mg/m^3 may increase risk of fetal death and Similarly, 1 ppb increase in SO_2, a 10-ppb increase in NO_2 and 10-ppb exposure in O_3 was significantly associated with stillbirth [24]. That was also supported by a US study that estimated that up to 2.2 per 1,000 Ohio stillbirths are potentially attributable to high levels of PM2.5 [27].

4. The actual mechanism of adverse health effect on the fetus by pollutants

How pregnant women's exposure to air pollutants induces the development of birth defects is still not clear and under research. The possible explanations or theories are (**TABLE 2**):

Placental insufficiency: Maternal exposure to ambient air pollution may affect placental growth and function. Air pollution-induced oxidative stress during pregnancy has been suggested as one possible mechanism behind pregnancy outcomes because it regulates the pulmonary and placental inflammation, the hemodynamic responses, thus transplacental oxygenation and transportation of nutrients.

Gestational hypertension and preeclampsia: Maternal PM10 exposure was associated with an increased risk of pregnancy-induced hypertension and preeclampsia. This may explain the relationships between air pollution and adverse birth outcomes.

Systemic inflammatory responses: Inflammation may be one other possible pathway through which air pollution may increase the risk of adverse birth outcomes. Some particles penetrate deeper into the lung and may exhibit systemic effects after entering the bloodstream triggering preterm delivery.

TABLE 2. **Possible mechanism of action of individual pollutants.**

S. No.	Pollutants	Possible Mechanism Of Action
1	Particulate Matter (PM)	a. PM can combine placental growth receptor and cause an inflammatory response to the placenta. b. PM2.5 has a toxic effect on chromosomes and DNA changing their number or structure including DNA mutations. c. Few potentially toxic elements such as plumbum, cadmium, nickel, manganese, vanadium, bromine, and PAHs are absorbed on the PM2.5 and easily enter the blood through lung alveoli [24].
2	Carbon Monoxide (CO)	a. It competes with O2 to combine with Hb resulting in a decrease in maternal oxygen-carrying capacity thereby insufficient intrauterine oxygenation. b. Cause changes in blood viscosity or can damage WBC, platelets or endothelial cells affecting fetal and maternal nutritional communication.
3	Sulfur dioxide (SO_2)	It is transformed into sulfite or hydrosulfite in the blood and transferred to the baby via the placenta. It affects fetal growth and even can cause fetal malformations or deaths.
4	Nitrates Nox	It enters into the blood in the form of nitrite and nitrate which can transform low iron Hb into meth hemoglobin leading to tissue hypoxia, hindering nutrition and oxygen exchange between the mother and fetus [24].

5. Time of exposure during pregnancy

Fetal period is the most critical period of human life because of rapid cellular proliferation, differentiation, and growth. Out of this total fetal period, the first 6-8 weeks are most important because this is the period of organogenesis. For congenital anomalies, it is of great importance to assess exposure during critical pregnancy weeks 3-8. Exposure after this period less likely to cause congenital anomalies but still pollutant can cause many other health problems in a fetus like IUGR, PTB, SGA or even fetal demise. A period even before conception is also important as it has been found if mother exposed to higher levels of PM2.5 one month prior to and after conception, a fetus is more likely to have a birth defect. A study on month-by-month exposure risk assessment reveals that pollutants can accumulate in a mother prior to conception and can cause malformations [6]. On the contrary study in Anqing city shows the second trimester is strongly associated with birth defects [28].

6. Long term effects of pollutants later in life

Some time the delivered newborn may look normal apparently, however, these babies might develop some genetic change or change in the immune system, that may cause certain disease like cardiac or metabolic disorders later in childhood or in adulthood. Short-term and long-term exposure to particulate air pollution may alter intrauterine environment causing changes in gene expression that may be linked to later childhood and adulthood diseases. The hypothesis is that environmental factors altering intrauterine environment during critical windows of development lead permanent changes in fetal structure, physiology, and metabolism which initially promote survival but later predispose to diseases in adulthood. Exposure to air pollution especially in third-trimester may cause intrauterine vitamin D deficiency which is critical for the normal development of the lung and immune system in the fetus. Air pollution has substantial long term adverse health effects like reduced stature, cardiovascular disease, type 2 diabetes and osteoporosis later in life [23].

7. Actions to be taken to safeguard fetus

First and foremost, we have to accept the fact that air pollution is an alarming threat to our fragile fetus. Therefore, we n eed to take some urgent short and long term measures in India to fight this biggest manmade disaster!

Long term actions: Government should initiate multicentric research to establish a relationship of air pollution with adverse outcome of pregnancy. On that basis, authorities should take appropriate actions to prevent or minimize such pollution-related diseases in fetuses. General measures to lessen the burden of air pollution in India need to be taken. The status of pollution, contents and contributing sources varies from country to country or even amongst different cities of the same country. Therefore we need to study it in details and to make ‘customized action plans’ to control this air pollution. In India, there is a need for a National Program for Air Pollution. Air Pollution is a ‘disease’ in an epidemic form and requires an aggressive National Program like that of polio, tuberculosis, AIDS, etc.

Short term actions: Health authorities to release advisories for pregnant ladies regarding “what to do and what not to do” to minimize effects of air pollution. Pregnant ladies should avoid busy roads with high traffic loads or during peak hours as vehicular exhaust pollution is one of the major sources of air pollution, use of Mask, Use of Air Purifiers

Conclusion

Air pollution is an established epidemic globally. The most worrying fact is that air pollution has also started affecting the human fetus, increasing chances of birth defects, IUGR, PMB or even fetal death. Since the present situation is very alarming especially in India or Asian countries, therefore we need to act fast considering it as an emergency. We need some long-term and short-term measures to safeguard fetal health against air pollution. There is a need for research at the national level to establish a relationship of air pollution with adverse outcome of pregnancy so that some guidelines for better management can be made. Besides, general measures to lessen the burden of air pollution in India, a National Programme for Air Pollution should also be considered. As a short term action, there is a need to release some advisories for pregnant ladies regarding “what to do and what not to do”.

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