A review on effect of air pollutants on fetal development and pregnancy outcomes

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ABSTRACT:

Developing fetus is connected to the mother by placenta to receive oxygen and nutrients. Maternal exposure to ambient air pollution not only affects maternal health but also provides a pathway for many toxic pollutants to cross the placental barrier and interrupt biochemical milieu. There are numerous scientific studies available describing possible negative health impact of air pollutants on reproductive health, pregnancy outcomes and fetal development yet no toxic effect is available recently. Studying the pollutants exposure effect on fetal development is crucial for the underlying mechanism between prenatal exposure and pregnancy outcomes. Present review meticulously provides the compiled data of 40 most recent studies with possible action mechanism of air pollutants on pregnancy outcomes and fetal development to find a better solution to exterminate or reduce the problem.

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Review

Air pollution in the present scenario is considered the major inducer of harmful health effects, especially by emitting harmful gases (SO_2, NO_X, NH_3, CO, and CO_2), polycyclic aromatic hydrocarbons (Naphthalene, Anthracene, Phenanthrene, Fluoranthene, Benzo(b)fluoranthene, Benzo(k)fluoranthene, Benzo(a)pyrene, Dibenzo(a,h)anthracene, and Indeno(1, 2, 3-cd) pyrene), Volatile Organic Compounds (Benzene, Toluene, *o-m-p* Xylene, Ethylbenzene etc.), Particulate Matter (PM_{10} and $PM_{2.5}$, $PM_{0.1}$) as well as combustion-derived nanoparticles (both Petrol Exhaust Nanoparticles, PENPs and Diesel Exhaust Nanoparticles, DENPs) [1] causing not only environmental issues [2] but also cause health hazard *via* blood circulation, inhalation and cause asthma, pharyngeal and laryngeal cancer, tuberculosis, nutritional deficit, cardiovascular and other endocrine disorders, adverse pregnancy outcomes, neonatal abnormality and mortality too [1, 3].

Pregnancy outcomes are important indicators

of the maternal as well as newborn and infant health. Stillbirth, low birth weight (LBW) and impaired growth directly reflect the abnormal maternal health [4]. In the last few years, there is an increasing research trend towards exploring the possible adverse effects of ambient air pollution on maternal health and birth outcomes. Previous attempts were made to critically review the correlation between air pollutant exposure and maternal health but the problem is increasing exponentially day by day and there is no recent data is available to scientifically validate the same and as the problem is increasing very speedily there is an urgent need to monitor the risky consequences of pollutant exposure. This review compiled the data of 40 recent most population-based pregnancies and fetal growth studies worldwide (Table 1).

Table 1. Effect of different air pollutants on pregnancy and fetal outcome

S. No.	Objective of study	Pollutant name	Effect	References
1	Traffic-related air pollution (TRAP) and childhood obesity	NO_X	Increase in prenatal non-freeway NO_X was associated with 33% higher leptin and 9% high molecular weight adiponectin levels in cord blood. Leptin levels were found 71% higher in mothers who resided near to major roadways (75 m). Increased leptin level and altered infant weight was related to only female infants not males	[5]
2	Continuous 24-48 hours exposures of $PM_{2.5}$ and other air toxicants on maternal birth weight, child acute respiratory infections as well as adult chronic respiratory and lung impairments	$PM_{2.5}$ and air toxicants	The association between $PM_{2.5}$ and air toxicants exposure, maternal birth weight, child acute respiratory infections as well as adult chronic respiratory and lung impairments were examined. Peripheral and cord blood samples were also collected to investigate gene-environment interactions	[6]
3	24 h household $PM_{2.5}$ exposure during pregnancy	$PM_{2.5}$	$PM_{2.5}$ exposure in pregnancy was associated with 4 g decrease in birth weight while 2% increase in its prevalence.	[7]
4	Association between prenatal exposure to $PM_{2.5}$ and its constituents and preterm delivery	$PM_{2.5}$ and PM_{10}, ammonium, chlorine, sodium, nitrate, vanadium and bromine	Increased risk of preterm delivery with full gestational exposure to $PM_{2.5}$ and its constituents; preterm delivery were observed for blacks, Asians and older mothers	[8]
5	Impacts of air pollution on small gestational age (SGA) birth weight, LBW and preterm birth	CO, NO_2, NO, O_3, SO_2, $PM_{2.5}$ and PM_{10}	Exposure to all air pollutants was associated with SGA; proximity to highways was related with 26% increase in SGA and 11% increase in LBW. $PM_{2.5}$ exposure with preterm births was observed at <37 weeks and for other pollutants at <30 weeks of gestation	[9]
6	Exposure to environmental contaminants during pregnancy	-	Environmental contaminants' exposure during pregnancy resulted in deregulation of genetic and epigenetic mechanisms of prenatal growth. Alteration of fetal development signaling led to various transgenerational disorders; necrotic, apoptotic and inflammatory reactions to fetal nucleic acids	[10]

7	Effect of high ambient air pollution exposure on low fertility rate and early pregnancy loss	PM_{10}, NO_2, SO_2, O_3 and CO	Cumulative pregnancy rate in multiple IVF cycles was 51.3% per person. Air pollution exposure during periods 1 (start of COS to oocyte retrieval) and 3 (embryo transfer to hCG test) was generally associated with IVF outcomes. Increased NO_2 and CO during period 1 were associated with decreased intrauterine pregnancy probability. PM_{10}, NO_2 and CO levels during period 3 were also inversely related to intrauterine pregnancy.	[11]
8	Exposure to air pollutants and inhalable environmental elements during pregnancy and after birth and childhood-onset systemic lupus erythematosus (cSLE) diagnosis	PM_{10}, SO_2, NO_2, O_3 and CO	An increased frequency of maternal occupational exposure during pregnancy to volatile vapor and smoking (maternal and/or secondhand) was related to cSLE development.	[12]
9	Relation of prenatal exposure to air pollutants, smoking with pregnancy complications and adverse birth outcomes	NO_X	NO_2 and CALINE4-derived NO_X exposure increased the risk of high uterine artery resistance in later pregnancies. Smoking also increased the risk of higher uterine resistance and contributed to bilateral notching in mid-pregnancy	[13]
10	Placental biomarkers of PAH exposure and glutathione-S-transferase biotransformation enzymes in obstetric population	PAHs and Pb	Maternal serum folate levels were inversely related to PAHs-DNA adducts. Maternal Pb exposure was significantly correlated with cord-blood Pb levels. Maternal serum folate levels were negative predictor of total DNA-PAH adducts levels in placenta.	[14]
11	Associations between cause-specific stillbirth and prenatal exposure to air chemical pollutants and $PM_{2.5}$	Air chemical pollutants and $PM_{2.5}$	Stillbirths due to impaired fetal growth were increased following gestational exposure to $PM_{2.5}$	[15]
12	Residential pollutant exposure and pregnancy outcomes	NO_X, O_3, $PM_{2.5}$ and PM_{10}	Traffic exhaust were related to 2-6% increase in low birth weight, 1-3% increase in small gestational age affecting fetal growth	[16]
13	Pollutant exposure risk for neonatal development, intrauterine growth retardation, preterm birth, low birth weight, reduced birth size and congenital malformation	CO, NO_2, PM_{10} and $PM_{2.5}$	Exposure-mediated pregnancy complication is associated with reduced birth weight and increased probabilities of low birth weight, chromosomal aberrations, decreased neurological development as well as high risk of chronic diseases	[16,17]
14	Effect of estimated daily air pollutants exposure, temperature and greenness on newborns	-	Higher environmental pollutants exposure led to poorer fetal birth-weight, head-circumference and gestational age at birth	[18]
15	Association between air pollution exposure and birth weight	NO_2 and PM_{10}	Non-significant variations were observed in birth weight	[19]
16	Exposure effect of $PM_{2.5}$ on preterm birth	$PM_{2.5}$	8.3% preterm births were observed during the 3rd trimester	[20]

17	To identify association of pregnancy loss with common pollutant exposure	$PM_{2.5}$, O_3 and sulfate compounds	Increased incidence of pregnancy loss was 28% were identified; increase in average whole pregnancy ozone and $PM_{2.5}$	[21]
18	Associations between air pollution and various birth outcomes	NO_2 and $PM_{2.5}$	$PM_{2.5}$ was not significantly associated with spontaneous preterm birth. NO_2 in second trimester was negatively associated with spontaneous preterm birth. Spatial exposures brought about significant reduction in OR of $PM_{2.5}$ and NO_2	[22]
19	Evaluation of mother-infant pairs using spatio-temporal models and stationary monitors for exposure to ambient air pollution	$PM_{2.5}$	Increased risk of preterm birth and reduced fetal growth in an urban area. $PM_{2.5}$ increase during pregnancy was associated with preterm birth. Increased lower birth weight, an IQR increase in modeled and monitored $PM_{2.5}$ was 12.1 g and 15.9 g	[23]
20	Air pollution effects in pregnancy	-	Adverse effect of air pollution on respiratory and cardiovascular systems, also associated with type 2 diabetes; Embryonic and fetal organs are vulnerable to air pollutants mediated damage; increased risk of negative gestational outcomes, preterm delivery and low fetus birth weight	[24]
21	Correlation between household cooking fuels and risk of stillbirth	Household cooking fuels	Characteristic risk for stillbirths of firewood as cooking fuel in India was 11% and 1% for kerosene cooking. Women who cook with firewood, risk factors were significantly associated with occurrence of stillbirth	[25]
22	Air pollutant exposure during pregnancy	$PM_{2.5}$, NO_2 and O_3	Exposure was responsible for maternal asthma, gestational diabetes, heart disease, hypertension, low birth weight, pre-existing diabetes, preeclampsia, preterm birth, and small gestational age	[26]
23	Exposure to high pollution fuels	-	Use of high pollution fuels resulted 92 g reduction in mean neonatal birth weight as compared to low pollution fuel. Full adjusted OR for below average birth size risk was 1.29	[23]
24	Pollutant exposure during pregnancy and effect on intrauterine environment and fetal heart rate	-	Change in fetal heart rate, increased cesarean sections, neonatal asphyxia, cerebral palsy and even fetal death during delivery following pollutant exposure	[27]
25	To evaluate secondary health data for neonatal mortality rate (NMR) following exposure to cow dung/crop residues/firewood as fuel	Cow dung/crop residues/firewood	Mean rural NMR was 4.2% live births and urban NMR was 3.31%. Household air pollution (HAP) was 92.2% in rural areas as compared to 40.8% in urban areas. HAP was strongly associated with NMR for urban and rural areas combined.	[28]
26	Association between maternal exposures to environmental SO_2 and total suspended particulates and risk of low birth weight	SO_2 and total suspended particulates	Exposures to SO_2 and total suspended particulates yielded adjOR between VLBW and maternal exposures to high levels of air pollution	[29]
27	Air pollution exposure during pregnancy; maternal asthma and neonatal respiratory outcomes	PM_{10}, $PM_{2.5}$, SO_2, NO_2 and CO	Transient tachypnea of the newborn (TTN), asphyxia, and respiratory distress syndrome risk were increased during preconception and I trimester after PM_{10}, CO, NO_X, O_3 and SO_2 exposure	[30]

28	Pregnancy trimester-specific exposure to ambient air pollutants and respiratory health outcomes in the first two years of life	CO and PM$_{2.5}$	Trimester-specific air pollution modified the BMI and respiratory health in growing up; children of first trimester PM$_{2.5}$ exposed overweight/obese mothers had an adjusted incidence rate ratio 1.85, 1.76 and 1.90 in quartile 2–4 for bronchiolitis/bronchitis (term ii), ear infection in the first year of life	[31]
29	Relationship between PM$_{2.5}$ exposure during pregnancy and post-neonatal mortality	PM$_{2.5}$	PM$_{2.5}$ exposure increased the risk factor for total mortality, respiratory syndrome and sudden infant death syndrome (SIDS) mortality	[32]
30	To evaluate adverse pregnancy outcome, infant respiratory and circulatory problems	PM$_{10}$ and PM$_{2.5}$	Maternal serum, urine as well as umbilical cord blood, tissue and placental tissue analyze using 8-hydroxydeoxyguanosine (8-OHdG), a biological indicator of oxidative stress	[33]
31	*In utero* particulate matter exposure in adulthood	PM$_{10}$ and PM$_{2.5}$	*In utero* PM$_{2.5}$ exposure caused acute inflammation, chronic matrix remodeling, as well as alterations of Ca^{2+} handling proteins, resulting in cardiac dysfunction	[34]
32	Association between exposure to indoor biomass fuel sources, second-hand tobacco smoke and adverse health outcomes in early infancy	Wood and/or dung as primary indoor biomass fuel sources	Exposure to wood and/or dung as primary fuel source was associated with 49% increase in LBW risk, 34% increase in respiratory illness incidence and 21% increase in six-month infant mortality risk. Exposed neonatal also had 45% and 30% respective increase in risks of underweight and stunting.	[35]
33	Exposure effect of PM and other ambient pollutants on 200 pregnancy outcomes	PM and other ambient pollutants	Maternal biological samples i.e. hair samples, urine samples (for 8-oxo-deoxyguanosine), blood samples for transcript markers and biomarkers of pre-eclampsia as well as neonatal blood samples for transcript markers were analyzed as predictors for pregnant women and neonatal at risk	[36]
34	Maternal exposure to PM$_{10}$ in association with birth weight, fetus growth, shape and gestational age at birth	PM$_{10}$	PM$_{10}$ exposure caused significant lower birth weight (39.0g, preterm births) and (24.0g, term births); reduction in fetal growth among term and moderately preterm births were also observed	[37]
35	To compare the effect of traffic-related air pollution exposure and preeclampsia, preterm birth and very preterm birth	CO, NO, NO$_2$, NO$_X$ and PM$_{10}$ and PM$_{2.5}$	Pollutant exposure elevated risks for preeclampsia, preterm birth, and very preterm birth from maternal exposures. Increased risk of preterm birth and very preterm birth were also positively associated with PM$_{10}$ and PM$_{2.5}$ exposure	[38]
36	PM$_{2.5}$ exposure in pregnant females and adverse birth outcome using a gap-filled satellite	PM$_{2.5}$	PM$_{2.5}$ exposure was associated with a 12.85 g decrease in term birth weight, increased risk of preterm birth and term LBW.	[39]
37	Effects of prenatal and postnatal exposure to PM on Kawasaki disease (KD)	Suspended particulate matter	The Odd ratios of PM exposure were 1.59 for prenatal exposure and 1.41 for postnatal exposure suggestive of an increased risk of Kawasaki disease	[40]
38	Exposure effect of traffic air pollutants during pre-pregnancy or early pregnancy and birth defects	NO$_2$, PM$_{10}$ and PM$_{2.5}$	Exposure to high level of NO$_2$ and PM$_{10}$ increased the risk on birth defects ($P<0.05$) during pre-pregnancy or early pregnancy	[41]

39	Air pollution exposure during pregnancy and risk assessment for next generation	$PM_{2.5}$	Increased offspring child systolic BP percentile and risk for elevated BP were observed following $PM_{2.5}$ concentration at ≥13 $\mu g/m^3$ during third-trimester (4.85 percentile increase in child SBP).	[42]
40	Air pollutant exposure during three months preconception, gestational weeks 3-8 and orofacial defects	PM_{10}, $PM_{2.5}$, CO, SO_2 and NO_X	Preconception, CO and PM_{10} were significantly associated with cleft palate, while SO_2 was associated with cleft palate ± without cleft palate; NO_X and $PM_{2.5}$ were also linked with risk.	[43]

Inclusion Criteria

Original, full-text articles, clinical studies, and reviews were considered in the study. Studies were included if women were exposed with environmental toxic pollutants during pregnancy (e.g., maternal age and gestational age (preterm and very preterm birth), pre-eclampsia, season of birth, birth weight and size, head circumference). Relationship between toxic environmental pollutants (particulate matter, SO_2, NO_X, O_3, volatile organic compounds, polycyclic aromatic hydrocarbons and HCHO) released from vehicular emission, industrial processes, tobacco smoke/e-cigarette, incense burning and frequency of cesarean sections (C-sections), preterm birth, neonatal asphyxia, cerebral palsy and fetal death were studied.

Exclusion Criteria

Studies which were not in English language OR of irrelevant population OR Irrelevant exposures OR irrelevant outcomes OR of patients with previously reported risk factors were excluded in the study.

Therefore, from 108 records identified through database synthesis, we included 40 studies in the qualitative synthesis.

Air pollutants induced cellular toxicity, DNA damage, and apoptosis

Carbon monoxide (CO)

CO toxicity occurs due to the synergistic effect of tissue hypoxia as well as direct CO-mediated cell damage [44]. The affinity of CO to hemoglobin is approximately 210 times more than O_2. Exposure to the small environmental concentration of CO may form carboxyhemoglobin and compromises cellular oxygen availability and subsequent lethality. CO poisoning has been reported to develop long-term neurological effects as CO perturb the mitochondrial cytochrome-*c*-oxidase or Complex IV by binding to prosthetic group heme a3, resulting in shut down of oxidative phosphorylation, similarly to cyanide and nitric oxide and causing abnormal ATP synthesis rate and cell signaling [45-50].

Ozone (O_3)

O_3 is a powerful oxidant, invades an unpaired electron of polyunsaturated fatty acids of the cell membrane to form ozonides and unstable zwitterions or trioxolane which further generate lipo-hydroperoxides, aldehydes, and H_2O_2. This pathway commences generation of lipid radicals and auto-oxidation of membranes and further causes DNA damage leading to impaired cellular function [51]. High-level ozone (O_3) exposure is a possible risk factor for late Alzheimer's disease onset [52]. Ambient ozone and fine particulate matter exposure is a risk factor for developing asthma, chronic obstructive pulmonary disease, atherosclerosis and diabetes [53, 54]. Ambient O_3 exposure is directly associated with oxidative-damage, diminished antioxidant defence and pro-inflammatory response in skin [55].

Sulfur dioxide (SO$_2$)

SO$_2$, a sensory irritant mainly penetrates the upper airways and can cause oxidative stress and DNA damage in multiple organs (brain, heart, kidney, liver, spleen, and testis) including lungs by disintegrating cell membrane [56-58].

Nitrogen oxide (NO$_X$)

Exposure to elevated NO$_X$ leads to inflammation of the mucous membrane and rigidness of respiratory tracts. Exposure has reported to adversely affect natural killer cells and T-lymphocytes (mainly CD8$^+$ determinant cells) causing weakened adaptive immunity against viral infection [59].

Particulate Matter (PM)

Nuclear membrane translocation of PM though is difficult to damage nuclear DNA due to size-specific nuclear transportation; by this non-oxidative mechanism several aberrant DNA adducts are generated. Lesion generated by polycyclic aromatic hydrocarbons (PAHs) and oxidative stress cause oxidative DNA damage, strand breaks (SB) and cytogenetic markers [60, 61] directly associated with increased inflammatory responses (GM-CSF, IL-6, IL-8, TNF-α), lipid peroxidation rate and alterations in cellular metabolism accompanied by activation of phospholipase A2, DNase II, the caspase-activated DNase (CAD) [62], endonuclease G (EndoG) [63], apoptosis-inducing factor (AIF) [64] leading to cell death [65-69].

Oxidative stress and ROS production following pollutant exposure

Oxidative stress is referred to as a disproportion between the appearance of ROS in the biological system and system's capacity to completely balance redox potential, repair the damage and/or detoxify the reactive intermediates. The repair mechanism includes decreased oxidant species production or increased free radical scavenger levels (vitamin C or glutathione) or antioxidant enzymes *i.e.* catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD). Air Pollutants are responsible for ROS production and degenerating intracellular compartment as well as the fluid of respiratory tract, epithelial lining fluid, cytochrome P$_{450}$, cytoplasm, and mitochondria. Pollutants exposure is associated with oxidative damaged deoxynucleotides in blood and urine. Increased physicochemical surface properties of PM causes increased ROS-oxidative stress. High surface area to volume ratio of PM provide more surface for transition metals or organic compounds to get attach and causing aberration mitochondrial signaling mediators and enzymes, misbalanced intracellular Ca^{2+} homeostasis and activation of activator protein-1 (AP-1), mitogen-activated protein kinases (MAPK) and nuclear factor κB (NF-κB), upregulation of pro-inflammatory gene expression and cytokines [70]. Acute pollutant exposure diminishes the anti-oxidative status either by depleting the free radical scavengers or by decreasing antioxidant enzymes activity [71-74].

Effect of pollutants on pregnancy and fetal growth

International scenario

High ambient air pollution exposure was found to be linked with a low fertility rate and early pregnancy loss in women. Increased exposure to PM$_{10}$, CO, and NO$_2$ during Controlled Ovarian Stimulation (COS) and after embryo transfer is inversely proportional to decreased intrauterine pregnancy. 6621 cycles of 4581 patients with one or more fresh IVF cycles were analyzed and found cumulative pregnancy in multiple IVF was 51.3% per person. To evaluate patients' individual exposure to air pollution four exposure peri-

ods were measured including: 1): start of COS to oocyte retrieval, 2): oocyte retrieval to embryo transfer, 3): embryo transfer to hCG test and 4): start of COS to hCG test. Cox-proportional hazard ratios (HRs) were evaluated probabilities of pregnancy loss and intrauterine pregnancy for an IQR increase in each air pollutant concentration during each period. Increased NO_2 and CO during period 1 were associated with decreased intrauterine pregnancy. PM_{10}, NO_2 and CO levels during period 3 were negatively linked with intrauterine pregnancy. Both PM_{10} and NO_2 exposure during period 3 showed pregnancy loss [11]. Associations between cause-specific stillbirth and prenatal exposure to air chemical pollutants and $PM_{2.5}$ were quantified using Positive Matrix Factorization by Ebisu et al. 2018 on nested case-control study design (n=32262). The odds ratio per interquartile range for stillbirths due to impaired fetal growth was increased following gestational exposure to $PM_{2.5}$ though; no association was established between stillbirths caused by maternal complications and pollutant exposure [15]. To explore the exposure effect of $PM_{2.5}$ on preterm birth in China 426246 pregnant women were enrolled for birth outcome study in National free pre-pregnancy checkups project. The gestational exposure to $PM_{2.5}$ was alienated into the first trimester, second trimester, third trimester and entire pregnancy. Cox proportional hazards regression was used for evaluation of exposure effect by considering maternal age, alcohol use, education level, occupation, second-hand smoking, pre-pregnancy BMI, number of previous pregnancies, coastal areas and season of conception. The study found that 35261 (8.3%) preterm births were most significant during the third trimester and $PM_{2.5}$ exposure at 10 µg/m³ was significant during the first trimester and second trimester. Subgroup analysis revealed that women

who were having age more than 30 years, had low education level, worked as planters, had the male baby, had previous pregnancies, not living in coastal areas and conceived baby in winter was more sensitive to $PM_{2.5}$ exposure [20]. Exposure effect of air pollutants on the timing of incident pregnancy loss (from ovulation) was evaluated in 343 singleton pregnancies in a multisite prospective cohort study. The total evaluated pregnancy loss was 98 out of 343. Adjusted Cox proportional hazards models revealed an interquartile range increase in average pregnancy, ozone (HR-1.12), $PM_{2.5}$ (HR-1.13) and sulfate compounds (HR-1.58) exposure caused faster pregnancy loss. It was evidenced that pollutant exposure throughout pregnancy was associated with loss, but outlining specific heightened vulnerability period provides larger preconception [21]. Mother-infant pairs (n=61640) were evaluated using spatial-temporal models and stationary monitors for exposure to ambient air pollution and found associated with a higher risk of preterm birth and reduced fetal growth in an urban area. For average $PM_{2.5}$ increased IQR (2.5 µg/m³) during pregnancy was associated with 1.04 ORs of preterm birth. For lower birth weight, an IQR increase in modeled and monitored $PM_{2.5}$ was 12.1 g and 15.9 g [23]. Exposure to $PM_{2.5}$, NO_2, and O_3 in 818400 singleton live births during pregnancy was evaluated and was found that exposure was responsible for modification of maternal asthma, gestational diabetes, heart disease, hypertension, pre-existing diabetes, pre-eclampsia, preterm birth, low birth weight, and small gestational age. Interquartile range increases in $PM_{2.5}$, NO_2, and O_3 during entire pregnancy were associated with 4%, 8.4% and 2% increase in the OR of preterm birth. For pregnancy exposure to $PM_{2.5}$ and NO_2 among

women with pre-existing diabetes, increases of 10.6% and 23.8% in the OR of preterm birth were detected while the increases of 3.8% and 6.5% (P_{int}<0.01) were observed among women without this condition. For exposure to $PM_{2.5}$ during pregnancy, increase in OR of preterm birth was 8.3% more among women with pre-eclampsia than among women without preeclampsia (3.6%) (P_{int}=0.04). Exposure to O_3 during pregnancy among asthmatic women caused a stronger increase in the OR of preterm birth (12.0%) as compared to non-asthmatic women (2.0%) [26]. Pollutant exposure during pregnancy affects the intrauterine milieu further causing a change in fetal heart rate (FHR) resulting in increased cesarean sections (C-sections) [27]. The incidence of neonatal asphyxia, cerebral palsy and even fetal death during delivery is also attributed to increased pollutant contact.

Son et al. 2017 investigated the relationship between $PM_{2.5}$ exposure during pregnancy and post-neonatal mortality using model adjusted by sex, birth weight, gestational length, maternal characteristics, temperature and season of birth and relative humidity. The study included extended Cox proportional hazards modeling with duration-dependent covariates in 465682 births with 385 mortalities. Neonatal exposure to $PM_{2.5}$ was measured from birth to death. Risk factor for total mortality, respiratory syndrome and Sudden Infant Death Syndrome (SIDS) mortality per-inter-quartile-range increase were 2.66, 3.14 and 2.50 respectively [32].

To evaluate adverse pregnancy outcomes and infant respiratory and circulatory problems following PM_{10}, and $PM_{2.5}$ exposures, 2500 pregnant women with their infants were studied using 8-hydroxydeoxyguanosine (8-OHdG), a biological indicator of oxidative stress. Maternal serum, urine, umbilical cord blood and tissue and placental tissue were analyzed during all three trimesters [33].

To compare the effect of traffic-related air pollution exposure and pre-eclampsia, preterm birth (gestational age <37 weeks) and very preterm birth (<30 weeks) 81186 singleton births were studied and found at elevated risks from maternal exposure to traffic air pollutants (CO, NO, NO_2, NO_X and $PM_{2.5}$ and PM_{10}) [38].

To understand the exposure effect of traffic air pollutants including NO_2, PM_{10} and $PM_{2.5}$ during pre-pregnancy or early pregnancy and birth defects, a case-crossover study involving 4235 pregnant women were employed. The average ambient NO_2, $PM_{2.5}$, and PM_{10} respective concentrations appeared as 60.83 $\mu g/m^3$, 103.88 $\mu g/m^3$ and 104.94 $\mu g/m^3$. It was observed that exposure to a high level of NO_2 and PM_{10} increased the risk of birth defects (P<0.05) during pre-pregnancy or early pregnancy [41].

Pollutant exposure during pregnancy is considered as a potential risk issue for neonatal development, intrauterine growth retardation, preterm birth, low birth weight, reduced birth size and congenital malformations [16, 17]. Epidemiological research on maternal exposure to air pollutants and birth outcomes are suggestive of exposure derived pregnancy problems which are further associated with chromosomal aberrations, decreased neurological development as well as high risk of chronic diseases. The toxicity of pollutants also causes an inflammatory response to weaken both innate as well as adaptive immune response [72].

18-34 week pregnant women were involved in a questionnaire and household chemical (indoor pollutants, formaldehyde, NO_2, and VOCs) usage survey. In addition, gestational age, birth weight, and length and head circumference were collected from birth records. The association between

pollutants and pollution surrogates were detected using general linear models, controlling for maternal age, parity, maternal health, and season of birth. Only HCHO was associated with any of the birth outcomes. There was a 0.044 decrease in BW z-score (P = 0.033) and 0.05 decrease in HC z-score (P= 0.06) for each unit increase in HCHO. Although HCHO concentrations were very low, this finding is consistent with other studies of formaldehyde and poor birth outcomes [75].

Residential pollutant exposure was found directly related to pregnancy outcomes by producing small size for gestational age, preterm birth and low birth weight in a population-based cohort study. Pollution exposure was negatively associated with term birth weight [75]. In a similar study conducted by Smith et al. 2017 on 540365 singleton term live births and found average air exposure of NO_2 (41 $\mu g/m^3$), nitrogen oxides NO_X (73 $\mu g/m^3$), O_3 (32 $\mu g/m^3$), $PM_{2.5}$ (14 $\mu g/m^3$) and PM_{10} (23 $\mu g/m^3$). Interquartile range increases in NO_2, NO_X, O_3, $PM_{2.5}$ and PM_{10} from traffic exhaust were related to 2% to 6% increase in odds of term low birth weight, 1% to 3% increase in odds of term small for gestational age suggesting adversely affecting fetal growth [77].

A cross-sectional study performed by Milanzi and Namacha, 2017 using secondary data of 9124 respondents revealed exposure to high pollution fuels resulted in a 92 g reduction in mean birth weight [78].

Haifa Pregnancy Cohort Study (HPCS) conducted by Golan et al. 2018 on nearly 750000 newborns and estimated daily air pollutants exposure, temperature, and greenness. It was found that higher environmental pollutants exposure led to poorer fetal growth parameters likewise birthweight, head-circumference and gestational age at birth [18].

Maternal exposure to incense burning and hypertensive disorders as well as blood pressure of 10563 pregnant women were evaluated by He et al. 2018. It was found that incense smelling during late pregnancy was associated with increased hypertensive risk (relative risk, 1.84) and increased blood pressure (1.6 mmHg systolic blood pressure increase). Incense burning is found a well-established modifiable risk factor for hypertensive disorders [79].

Prenatal air pollution exposure is responsible for early age respiratory problems and is associated with increased maternal pre-pregnancy BMI. Children of first-trimester pregnant obese females (exposed to $PM_{2.5}$) had an adjusted wheezing incidence ratio of 1.85 (1.23-2.78), 1.76 (1.08-2.85) and 1.90 (1.10-3.27) in quartile 2-4. Additionally, second-trimester exposure was associated with bronchiolitis/bronchitis. First-trimester exposure to $PM_{2.5}$ was associated with ear infection in children with adjusted Odds Ratio (adjOR) 7.64 (1.18-49.37), 11.37 (1.47-87.97) and 8.26 (1.13-60.29) for quartile 2-4 and second-year with adjOR 3.28 (1.00-10.73) and 4.15 (1.05-16.36) for quartile 2-3 [32].

Van den Eeden et al. 2018 evaluated exposure effect of PM and other ambient pollutants on 200 pregnancy outcomes by biochemical changes in maternal, placental and cord blood. Samples i.e. maternal hair samples, urine samples for 8-oxo-deoxyguanosine, maternal blood samples for transcript markers and biomarkers of pre-eclampsia, neonatal blood samples for transcript markers were analyzed [36].

Xiao et al. 2018 evaluated the relationship $PM_{2.5}$ exposure in pregnant females and adverse birth outcomes using a gap-filled satellite in Shanghai, China. 132783 live birth records singleton evaluated for association with term birth weight and term low birth weight (LBW) and found whole-pregnancy $PM_{2.5}$ exposure was associated with a

12.85 g decrease in term birth weight, increased risk of preterm birth (OR 1.27) and increased risk of term LBW (OR 1.22). The scale of associations between $PM_{2.5}$ exposure during pregnancy and adverse birth outcomes was high [39].

Effects of prenatal and postnatal exposure to PM on Kawasaki Disease (KD) was studied using nation population data of 30367 participants (age group 6 to 30 months) at municipality levels. A multilevel logistic regression analysis for individual and municipality level was performed and found that children, who were exposed to higher Suspended Particulate Matter (SPM) level during pregnancy, were hospitalized for KD more than the others. The Odd ratios of PM exposure were 1.59 for prenatal exposure and 1.41 for postnatal exposure suggesting that early-life exposure to PM is associated with an increased risk of Kawasaki disease [40].

Air pollution exposure during pregnancy and risk assessment for the next generation was studied in 1293 mothers and their children of age between 3 and 9 years of age. Multivariable-adjusted cubic spline revealed increased offspring Systolic BP Percentile (SBP) and risk for elevated BP following $PM_{2.5}$ concentrations at ≥ 13 $\mu g/m^3$ during third-trimester (4.85 percentile increase in child SBP) [42].

National scenario

Tamil Nadu Air Pollution and Health Effects (TAPHE) study was organized into five components from pregnant mother-child cohort and adult cohort (n=1200 each cohort). Continuous 24-48 h. exposures of $PM_{2.5}$ were measured in household microenvironments together with ambient measurements. The association between $PM_{2.5}$ and air toxicants exposure, maternal birth weight, child acute respiratory infections as well as adult chronic respiratory and lung impairments were examined while adjusting multiple covari-

ates. In addition, a bio-repository of peripheral and cord blood samples was created to investigate gene-environment interactions [6].

Direct serial measurements of 24-h household $PM_{2.5}$ exposures during pregnancy were analyzed for LBW in an integrated rural-urban, mother-child cohort study in Tamil Nadu, India. First-trimester pregnant women (n=1285) from primary health care centers and urban health posts were kept in observation for each trimester until birth to collect antenatal care data and birth weight. A detailed questionnaire was provided to each mother on covariates related to household, socio-economic, demographic and maternal health characteristics. $PM_{2.5}$ exposure (10 $\mu g/m^3$) increase in pregnancy was associated with 4 g (95% CI: 1.08, 6.76 g) decrease in birth weight while 2% increase in its prevalence (OR=1.02; 95% CI:1.005, 1.041) following adjustment for infant sex, gestational age, maternal BMI, maternal age, history of previous LBW, season of conception and birth order [7].

In the household survey to find the correlation between household cooking fuels and risk of stillbirth, 188917 women aged 15-49 were included. Robust standard errors were considered as literacy of parents, in home lighting fuel and cooking fuel used, gravida status, previous abortion history, antenatal checkup history of mother, age during last pregnancy (>35 years), fetus and other complications and premature delivery. The characteristic risk for stillbirths of firewood as cooking fuel in India was 11% and 1% for kerosene cooking. Women who cook with firewood, risk factors were significantly associated with the occurrence of stillbirth (1.24; 95% CI: 1.08-1.41) while kerosene fuel is associated with risk factors (1.36; 95% CI: 1.10-1.67) than those who cook with LPG/electricity. Kerosene lamp usage for home lighting was also associated with stillbirths compared to electric lighting (1.15; 95% CI:

1.06-1.25). By providing access to cleaner cooking fuel about 12% of stillbirths in India could be prevented [25].

Annual secondary health data of 1404337 live births of rural and urban areas from 284 districts of 09 Indian states were analyzed for neonatal mortality rate (NMR) following exposure to cow dung/crop residues/firewood as fuel. Socio-demographic, healthcare and behavioral aspects of the mother were considered as covariates during the study. The average rural NMR was recorded 42.4 out of 1000 live births and urban NMR was 33.1 out of 1000 live births. The proportion of household air pollution was 92.2% (P< 0.001) in rural areas as compared to 40.8% in urban areas, and the difference was statistically significant. HAP values were strongly associated with NMR (β = 0.22; 95% confidence interval [CI] = 0.09 to 0.35) for urban and rural areas combined. For rural areas separately, the association was significant (β = 0.30; 95% CI = 0.13 to 0.45) after adjustment which represents that HAP is associated with NMR in rural areas, but not in urban areas in India [28].

The association between exposure to indoor biomass fuel sources, second-hand tobacco smoke and adverse health outcomes in early infancy in a population in rural south India was observed by Tielsch et al. 2009. A population-based cohort of newborns from birth through 6 months was performed. Follow up visits for morbidity associated anthropometric measurements were performed bimonthly after delivery. 92.3% of 11728 liveborn infants resided in households and used wood and/or dung as a primary fuel source, such exposure was associated with 49% increase in LBW risk, 34% increase in respiratory illness incidence and 21% increase in six-month infant mortality risk. Exposed neonatal also had 45% and 30% increase in risks of underweight and stunting.

Exposure was also linked with adverse health outcomes except for accomplished growth [35].

Conclusion

Pollutant mediated oxidative stress and ROS production following exposure to various air pollutants causes harmful health effects. The biological system though possesses the repair mechanism i.e. antioxidants to neutralize the resulting cellular toxicity, DNA damage and cell death, yet repeated and/or severe pollutant exposure defense mechanism provide insufficient protection. During pregnancy, such exposure severely affects both the maternal organs as well as the neonatal milieu. Maternal pollution exposure during pregnancy is attributed to increased chances of cesarean section, intrauterine growth retardation, preterm birth or small gestational age, stillbirth, increased fetal heart rate, neonatal asphyxia, cerebral palsy, low birth weight, low birth size, congenital malformations, decreased neurological development, chromosomal aberrations casing teratogenic effects, respiratory syndrome likewise bronchiolitis/bronchitis, sudden infant death syndrome, elevated blood pressure and hypertension and increased risk to Kawasaki disease. Though studies are suggestive of adverse fetal and pregnancy outcomes following air pollutant exposure yet some research provides information about the gender-specific increase in leptin levels following NO_X exposure, no association between stillbirths and accomplished growth caused by maternal complications and pollutant exposure.

List of abbreviations

adjOR- Adjusted Odds Ratio; BMI- Body Mass Index; CAD- Caspase Activated DNase; CAT- Catalase; CI- Confidence Interval; CO- Carbon Monoxide; COS- Controlled Ovarian Stimulation; C-sections- Cesarean Sections; cSLE-Systemic

lupus erythematosus; DENPs- Diesel Exhaust Nanoparticles; EndoG- Endonuclease G; FHR-Fetal Heart Rate; GPx- Glutathione Peroxidase; GST-Glutathione-s-transferase; HAP- Household air pollution; HRs- Hazard Ratios; LBW- Low Birth Weight; MAPK- Mitogen Activated Protein Kinases; NF-κB- Nuclear Factor Kappa-B; NMR- Neonatal Mortality Rate; NO_2-Nitrogen Dioxide; NO_x- Nitrogen Oxides; OR- Odd Ratio; O_3- Ozone; PAHs- Polycyclic Aromatic Hydrocarbons; PENPs- Petrol Exhaust Nanoparticles; PM- Particulate Matter; ROS- Reactive Oxygen Species; SBP- Systolic BP percentile; SOD- Superoxide Dismutase; SPM-Suspended particulate matter; TTN- Transient tachypnea of the newborn; VLBW- Very Low Birth Weight; VOCs-Volatile Organic Compounds;8-OHdG- 8-hydroxydeoxyguanosine.

Financial supports

Competing interest

Authors report no competing interest.

Acknowledgements

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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