REVIEW ARTICLE

Maternal Exposure to Polycyclic Aromatic Hydrocarbon (PAH) and Its Effects on Pregnancy Outcomes: A Systematic Review

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Keywords:
polycyclic aromatic hydrocarbon; pregnancy outcome; intrauterine growth; maternal exposure; air pollution

ABSTRACT

Background: In the natural environment, polycyclic aromatic hydrocarbons (PAHs) are predominantly associated with fine particulate matter ($PM_{2.5}$) suspended in the ambient air. These tiny particles can be inhaled by humans and subsequently deposited in the respiratory system, where they can penetrate the bloodstream and accumulate in target organs, including the placenta. This condition resulted in placental dysfunction, which can lead to adverse pregnancy outcomes. Therefore, this study aims to systematically review the scientific published articles on maternal exposure towards PAHs during pregnancy and the effect on adverse pregnancy outcomes. **Methods:** This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic article search was performed using three online databases: PubMed, Scopus, and ProQuest to identify articles published from 2000 to 2022. A thorough article search identified eight studies suitable for inclusion in this review, as well as two additional studies discovered through the snowballing technique. All the included studies underwent quality assessment by using the NIH quality assessment tool. **Results:** A total of 948 articles were screened, of which ten full-text articles met the inclusion criteria for final evaluation. The most frequently reported adverse pregnancy outcomes across the selected studies were fetal growth restriction, including reduced birth weight and birth length, decreased head circumference, small for gestational age (SGA) and preterm delivery. PAH-DNA adducts in the cord blood were significantly associated with prenatal exposure to PAHs. PAHs exposure appears to have the most adverse impact on embryonic development during the first trimester. Seven articles recorded high quality (score range from 11 to 12.5 points) and only three articles recorded fair quality (score range from 8.5 to 10.5 points). **Conclusion:** Our findings indicate that maternal exposure to PAHs could negatively impact pregnancy outcomes. While this review enhances the understanding of the observed relationship, only a limited number of studies have explored the underlying biological mechanism. The appropriate measures to protect and limit the maternal exposure to PAHs, particularly in the first trimester, must be implemented. These include providing clinical advice to the expectant mothers on reducing exposure to tobacco smoke and poor air quality, encouraging appropriate dietary modifications, as well as reinforcing governmental efforts to strengthen environmental regulations.

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs), also known as polynuclear aromatic hydrocarbons (PNAs), refer to a class of chemical compounds that consist only of hydrogen and carbon (Abdel-Shafy & Mansour, 2016). Due to their tiny size, PAHs that attach to $PM_{2.5}$ can penetrate the bloodstream and accumulate in the target organ, including the placenta, which can cause placental dysfunction and lead to adverse pregnancy outcomes (Abdel-Shafy & Mansour, 2016; Perera et al., 2005a). Several PAHs have been shown to cause cancer, including naphthalene, chrysene, B[*a*]P, dibenzo[*a,e*]pyrene, dibenzo[*a,l*]pyrene and anthanthrene (Dybing et al., 2013).

PAHs can enter the human body through the lungs during breathing, by drinking contaminated water, and by consuming food, dirt, or dust particles that contain PAHs. PAHs can reach the human body through multiple routes of exposure, under normal environmental conditions, when the body comes into contact with dirt or dust that contains PAH (Mohd Radzi et al., 2016).

The elevated levels of B[a]P exposure during pregnancy lead to birth abnormalities and low birth weight, as shown in mice's laboratory experiments (Kim et al., 2013). Studies by the U.S. Center for Children's Environmental Health have found that maternal exposure to PAHs was correlated with adverse pregnancy outcomes such as reduced birth weight, premature birth and impaired infant growth (Perera et al., 2005b).

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Elevated levels of B[a]P were associated with the decline in the thickness of the placenta and were able to impair the placental structure and function, and lead to reproductive adverse consequences by crossing the placental barrier (Al-Saleh et al., 2013). Elevated levels of PAH-DNA adducts are related to the restriction of fetal and child growth (Tang et al., 2006). The accumulation of PAHs more easily occurred in fetal tissue than in the placenta and maternal tissue. The difference in enzyme function resulted in lower metabolism of PAHs in the fetal tissue (Anderson et al., 2000).

Fetal vulnerability to high exposure to PAHs varies at different gestational ages throughout the gestational period (Wang et al., 2014). Other epidemiologic studies have found that the rate of fetal growth is regulated throughout the first trimester, resulting in a progressively greater deficit as the pregnancy progresses (Milani et al., 2005; Smith, 2004; Neufeld et al., 1999). Implantation and initial placentation during the first trimester are two critical events that are vulnerable to placental disruption (Erickson & Arbour, 2014). PAH exposure in the early stage of gestation can disrupt the early proliferation of trophoblast endovascular cells and prevent them from infiltrating into the fetal envelope. This condition leads to further disturbance of placental development and may restrict the supply of oxygen and nutrients to the fetus (Smith, 2004; Chaddha et al.,2004; Ritz & Wilhelm, 2008).

Compared to adults, developing fetuses and also neonates are more susceptible to the effects of the toxicology of PAHs, and when compared to non-pregnant women, pregnant women are at a higher risk (Jedrychowski et al., 2013). They are especially at risk because, from mother to fetus, PAHs can pass through the placenta (Polanska et al., 2014). Given the susceptibility of developing fetuses and neonates, this systematic review aims to examine maternal exposure to PAHs during pregnancy, its association with adverse pregnancy outcomes, and to identify the gestational period of greatest vulnerability to PAHs exposure.

MATERIALS AND METHODS

Study Design

This study was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Search Strategy

A bibliographic search was conducted using the online databases of PubMed, Scopus, and ProQuest, accessed through the IIUM Library account, and employing a backwards snowballing technique. Keywords that were used include “maternal exposure”, “prenatal exposure”, “polycyclic aromatic hydrocarbon*”, “adverse pregnancy outcome*”, “intrauterine growth”, “fetal growth retardation”, “pregnancy”, “cord blood”, “maternal serum”, “placenta”, “biological samples”. The Boolean operators of the connective terms, such as AND, OR, and NOT, have been used in the search strategy to obtain comprehensive results.

Selection Criteria

From the identified articles, studies that met the following eligibility criteria were selected based on: (i) articles published in the English language with full-text access from year 2000 or later; (ii) human epidemiological studies with several study designs (cohort, cross-sectional and case control studies) and (iii) studies reported on maternal exposure to PAHs during pregnancy and the effect on pregnancy outcomes. Retrieved articles that did not meet these criteria were excluded from the list. Only the final shortlisted articles went through the data analysis process and quality assessment procedures.

Article Screening and Data Extraction

Two reviewers independently performed article selection to ensure relevance and adherence to the criteria of the study. Any discrepancies between reviewers were resolved through discussion until consensus was achieved. The selection of articles based on the PRISMA guideline comprises four phases: (i) identification, (ii) screening, (iii) eligibility and (iv) included studies.

For the first level of screening, the titles and abstracts of the articles were reviewed, and duplicates of research articles across databases were removed. The articles that passed the initial screening were further evaluated based on the inclusion and exclusion criteria. Then, the data from the selected articles, including study objectives, methodology, number of participants, results, discussion of the findings, mechanism of action, and primary outcomes of the studies, were extracted and reviewed (as shown in Table 1).

Quality Assessment

The quality assessment of the selected studies was performed using the National Institutes of Health (NIH) quality assessment tool, designed for evaluating cohort, cross-sectional and case-control study designs (NIH, 2014). This tool assesses key aspects of study quality, including the strength of the study objectives, the credibility of the

study, the findings and discussion, and the participant's evaluation or the population involved in the study. The quality assessment comprises 14 questions for cohort and cross-sectional studies, and 12 questions for case-control studies. Each question can be scored as 1 for "yes", 0.5 for "no" and 0 for "not applicable", "cannot be determined" or "not reported". The total scores were summed up and categorised as follows: good quality (11–14 points), fair quality (7.5–10.5 points), and poor quality (0–7 points).

RESULTS

Bibliographic Search

The articles search retrieved 948 articles from the databases, and 12 additional articles were retrieved using the snowballing method. After removing the duplication, 607 articles were screened based on titles and abstracts. Then, 70 articles were assessed by referring to their full texts to examine the eligibility of the criteria based on the inclusion and exclusion criteria. Sixty articles that did not fulfil the inclusion criteria were excluded from the final selection. Finally, 10 articles were included in this systematic review. The final number of studies identified, included, and eliminated was summarised and recorded in the PRISMA Flow Diagram in Figure 1.

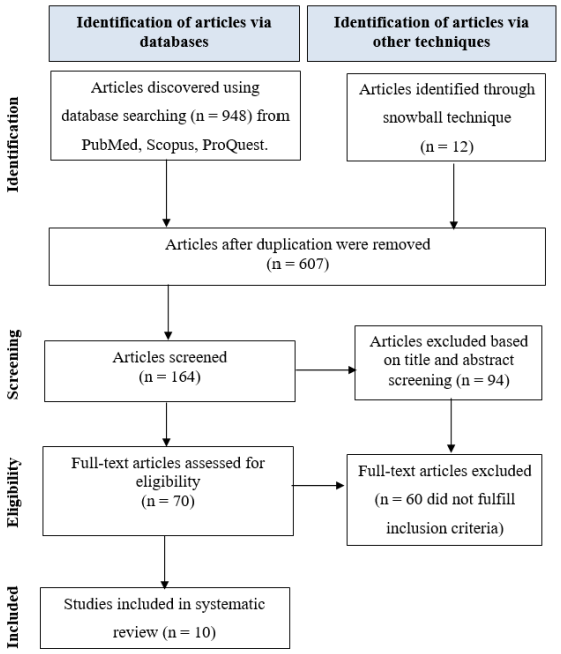

Figure 1: PRISMA Flow diagram for article selection

Overview of the Selected Articles

Table 1 presents a summary of the characteristics and principal findings of the selected articles in this systematic review. The selected studies have been published between 2000 and 2018. Among the 10 selected articles, eight were prospective cohort studies and two were case-control studies. The studies by Agarwal et al. (2018), Jedrychowski et al. (2017), Polanska et al. (2010), Choi et al. (2008), Singh et al. (2008), and Perera et al. (2005) have addressed maternal exposure to PAHs and adverse pregnancy outcomes, whereas studies by Jedrychowski et al. (2013), Zhang et al. (2016), and Gladen et al. (2000) primarily focused on the accumulation of PAHs in biological samples. Only a study by Choi et al. (2012) specifically examined the most vulnerable period to PAHs exposure during pregnancy.

Accumulated PAHs in Biological Samples

The studies in Poland utilised data from a previously established birth cohort of infants in Krakow (Jedrychowski et al., 2017; Jedrychowski et al., 2013; Choi et al., 2012) Four studies analysed and measured PAHs level through the sample that have been collected from the personal air monitor (Jedrychowski et al., 2017; Jedrychowski et al., 2013; Choi et al., 2012; Choi et al., 2008), three studies assessed the level of PAHs through placental tissue samples (Agarwal et al., 2018; Singh et al., 2008; Gladen et al., 2000), one study observed PAHs level within variety biological samples (maternal serum, umbilical cord serum and placenta) (Zhang et al., 2016), one study through umbilical cord blood and maternal blood (Perera et al., 2005) and one study through concentration of 1-hydroxypyrene (1-HP) in urine (Polanska et al., 2010).

All seven PAHs were detected in all placentas, except benzo[a]pyrene, which was undetected in one placental sample (Gladen et al., 2000). Maternal serums had the highest concentration of total PAHs levels (1290 ng g-1 lipid), followed by umbilical cord serums (1150 ng g-1 lipid) and lowest in placenta samples (673 ng g-1 lipid) (Zhang et al., 2017). B[a]P exposure during pregnancy causes DNA damage in the biological samples of maternal and cord blood (Jedrychowski et al., 2013). PAH-DNA adducts in the cord blood were shown to be significantly related to tertiles of B[a]P exposure (non-parametric trend z = 3.50, p <0.001) (Jedrychowski et al., 2013).

Maternal Exposure to PAH and Effects on Pregnancy Outcomes

A case-control study conducted in India by Agarwal et al. (2017) found that preterm birth groups (0.485 ± 0.675 µg/L) had significantly higher levels of B[a]P in the placental samples, compared to full-term delivery groups (0.124 ± 0.436 µg/L). Similarly, a case-control study by Singh et al. (2008) reported that mothers with preterm deliveries had significantly higher carcinogenic PAH benzo(b)fluoranthene, with concentrations of 61.91 ± 12.43 ppb in the preterm birth group compared to 23.84 ± 7.01 ppb in the full-term delivery group.

Table 1: Study characteristics and principal findings of selected studies

Author	Study Characteristics	Methodology	Principal Findings
Agarwal et al. (2018)	Case-control study. Sample population: 55 controls (full-term delivery), 29 cases (preterm delivery). Not trimester-specific exposure. Measure the relationship between PAH exposure and preterm delivery.	Interview, 30g of placental tissues, hospital records.	**Level of B[*a*]P** Preterm birth groups: (0.485 ± 0.675 µg/L) Full-term delivery groups: (0.124 ± 0.436 µg/L). **Level of GSH in cases than in controls** Significantly lower ($p < 0.05$) **Level of MDA in cases than in controls** Significantly higher ($p < 0.05$)
Zhang et al. (2016)	Prospective cohort study. Sample populations: 95 participants. Not trimester-specific exposure. Measure PAH in biological samples.	Questionnaire, 286 individual samples of maternal blood, umbilical cord blood and placentas.	**ΣPAH15** Maternal serum: 1290 ng g^{-1} lipid Cord serums: 1150 ng g^{-1} lipid Placentas: 673 ng g^{-1} lipid **B[a]Peq** Maternal serum: 22.4 ng g^{-1} lipid Cord serums: 20.4 ng g^{-1} lipid Placenta: 3.2 ng g^{-1} lipid
Jedrychowski et al. (2017)	Prospective cohort study. Sample populations: 455 participants. 2nd trimester. PAH exposure and birth weight, birth length and head circumference.	Questionnaire, wearing a personal air monitor during the 2nd trimester for 2 days. Maternal and child hospital records.	**Birth weight (g)** PAH: (β = -0.20, $p = 0.004$) $PM_{2.5}$: (β = -0.02, $p = 0.757$) **Birth length (cm)** PAH: (β = -0.17, p = 0.025) $PM_{2.5}$: (β = -0.04, p = 0.453) **Head circumference (cm)** PAH: (β = -0.13, p = 0.086) $PM_{2.5}$: (β = -0.06, p = 0.277)
Choi et al. (2012)	Prospective cohort study. Sample population: 344 participants. 2nd trimester ($n = 344$), each trimester ($n = 77$). PAH exposure and reduction in FGR, birth weight, birth length and birth head circumference.	Questionnaire and wearing a personal air monitor during the 2nd trimester and each trimester for 2 days. Medical record and calculation of fetal growth ratio (FGR, %) of newborns.	**Reduction in each trimester** **FGR** 1st: (-3%, 95% CI, -5 to -0%) 2nd: (-1%, 95% CI, -2% to 1%) 3rd: (0%, 95% CI, -3% to 1%) **Birthweight** 1st:(-105 g, 95% CI, -188 to -22g) 2nd: (-36 g, 95% CI, -76 to 4 g) 3rd: (-44 g, 95% CI, -123 to 36 g) **Birth length** 1: (-0.78 cm, 95% CI, -1.30 to -0.26 cm) 2nd : (-0.24 cm, 95% CI, -0.49 to 0.01 cm) 3rd : (-0.57 cm, 95% CI, -1.07 to -0.07 cm) **Birth head circumference** 1st: (-0.11cm, 95% CI, -0.39 to 0.17 cm) 2nd : (-0.13 cm, 95% CI, -0.26 to 0.00 cm)
Polanska et al. (2010)	Prospective cohort study. Sample population: 449 mother-child pairs. 2nd trimester. PAH exposure and birth weight, birth length, head circumference, ponderal index and cephalisation index.	Questionnaire, urine samples of 20-24 weeks pregnant women, saliva samples once each trimester. medical records of newborns.	**Birth weight (g)** (β = -158.3, p = 0.01) **Birth length (cm)** (β = -0.70, p = 0.05) **Head circumference (cm)** (β = -0.50, p = 0.05) **Ponderal index (g/cm^3)** (β = -0.02, p = 0.60) **Cephalisation index (cm/g)** (β = 4.2, p = 0.01)

Choi et al. (2008)	Prospective cohort study. Sample population: African American (n=224) and Dominican women (n=392). 3rd trimester. PAH exposure and SGA, FGR < 85% and preterm delivery.	Questionnaire, wearing a personal air monitor for 2 days. Medical record.	**Preterm delivery** African American (n = 205): (OR = 4.676, *p* = 0.001) Dominican (n = 351): (OR = 0.523, *p* = 0.229) **SGA** African American (n = 201): (OR = 1.94, *p* = 0.03) Dominican (n = 336): (OR = 0.82, *p* = 0.53) **FGR** (full term only) African American (n = 194): (OR = 2.15, *p* = 0.03) Dominican (n = 341): (OR = 0.80, *p* = 0.40)
Jedrychowski et al. (2013)	Prospective cohort study. Sample population: 362 2nd trimester. PAH-DNA adducts in cord blood.	Questionnaire, wearing a personal air monitor for 2 days. Maternal blood and umbilical cord blood were collected.	**Cord blood concentrations of PAH–DNA adducts (per 10^8 nucleotides)** ≤ 1.15 ng/m^3 : (0.24, 95% CI 0.22 to 0.26) 1.16-5.69 ng/m^3 : (0.25, 95% CI 0.25 to 0.27) > 5.69 ng/m^3 : (0.30, 95% CI 0.27 to 0.32) (*z* = 3.50, *p* < 0.001) **Maternal blood concentrations of PAH-DNA adduct (per 10^8 nucleotides)** ≤ 1.15 ng/m^3 : (0.25, 95% CI 0.23 to 0.27) 1.16-5.69 ng/m^3 : (0.26, 95% CI 0.24 to 0.28) > 5.69 ng/m^3 : (0.27, 95% CI 0.25 to 0.30) (*z* = 1.63, *p* = 0.103)
Singh et al. (2008)	Case-control study. Sample population: Control (*n* = 31), cases (*n* = 29) Not trimester-specific exposure. Compare the placental PAH levels in the preterm delivery group with the control group of normal delivery.	Interview, collection of placental tissues and medical record.	**PAHs (ppb)** **Naphthalene** Full-term: 249.62 ± 47.55 Preterm: 374.32 ± 75.90 **Acenaphthylene** Full-term: 58.72 ± 42.50 Preterm: 99.09 ± 46.72 **Phenanthrene** Full-term: 377.78 ± 79.54 Preterm: 468.64 ± 105.40 **Anthracene** Full-term: 25.81 ± 8.08 Preterm: 33.26 ± 11.15 **Fluoranthene** Full-term: 208.6 ± 21.93 Preterm: 325.91 ± 45.14* **Pyrene** Full-term: 296.43 ± 91.55 Preterm: 187.24 ± 84.94 **Benzo(k)fluoranthene** Full-term: 29.85 ± 22.34 Preterm: 11.25 ± 7.15 **Benzo(b)fluoranthene** Full-term: 23.84 ± 7.01 Preterm: 61.91 ± 12.43* **Benzo(a)pyrene** Full-term: 8.83 ± 5.84

			Preterm: 13.85 ± 7.06 **Dibenzo(a,h)anthracene** Full-term: 22.03 ± 17.06 Preterm: 15.33 ± 7.06
Perera et al. (2005)	Prospective cohort study. Sample population: 369 Not trimester-specific exposure. Birth weight, birth length and head circumference.	Healthy singleton pregnant women, proximity to the WTC site, 18-39 years old, non-smokers, pregnant on 11th September 2001 and due to give birth within 41 weeks of that day.	**Natural log transformed** **Adducts in cord blood** Birth weight: (β = 0.03, *p* = 0.18) Birth length: (β = 0.001, *p* =0.96) Head circumference: (β = 0.01, *p* = 0.27) **Cord adducts x ETS** Birth weight: (β = -0.11, *p* = 0.03) Birth length: (β = 0.01, *p* = 0.53) Head circumference: (β = -0.04, *p* = 0.04)
Gladen et al. (2000)	Prospective cohort study. Sample population:200 Not trimester specific exposure PAH level in placenta and birth weight.	Questionnaire, placental samples and medical records for pregnancy and delivery.	**Median concentration (ng/g dry weight)** Benz[*a*]anthracene: 1.15 Benzo[*b*] fluoranthene: 0.86 Benzo[*g,h,i*] perylene: 0.73 Benzo[*a*]pyrene: 0.91 Chrysene: 1.38 Dibenz[*a,h*]anthracene: 0.73 Indeno[1,2,3-*c,d*]pyrene: 0.74 Total of seven PAHs: 7.36

Vulnerable Gestational Period of PAHs Exposure

A study conducted by Choi et al. (2012) was one of the earlier studies that investigated the specific period of fetal susceptibility to PAHs exposure on adverse pregnancy outcomes. This study measured exposure to eight airborne PAHs in all participants during the second trimester, and measurements were also conducted once per trimester for a subgroup. During the first trimester, one natural-log unit increase in prenatal exposure of PAHs, associated with the most significant decrease in the fetal growth ratio (FGR) (-3%, 95% CI, -5 to -0%), decrease in birth weight (-105g, 95% CI, -188 to -22g) and decrease in birth length (-0.78cm, 95% CI, -1.30 to –0.26cm) (Choi et al., 2012).

A study by Jedrychowski et al. (2017) and Choi et al. (2008) monitored PAH exposure using personal air monitoring throughout the second and third trimesters of pregnancy, respectively. Prenatal exposure to PAHs during the second trimester significantly affected fetal development, particularly birth weight. The standardised effect of PAHs on birth weight was ten times greater (β = −0.20, *p* = 0.004) compared to the effect of $PM_{2.5}$ (β = −0.02, *p* = 0.757) (Jedrychowski et al., 2017). Prenatal PAHs exposure is significantly related to the development of SGA (95% CI, 1.1-3.5; *p* = 0.03) and preterm birth (95% CI, 1.8–11.9; *p* = 0.001) among African Americans (Choi et al., 2008).

Quality Assessment of the Selected Articles

The National Institute of Health (NIH) tool has been used to assess the quality of the selected studies. The majority (seven out of eight) of prospective cohort studies (Jedrychowski et al., 2017; Jedrychowski et al., 2013; Choi et al., 2012; Polanska et al., 2010; Choi et al., 2008; Perera et al., 2005; Gladen et al., 2000), as shown in Table 2, were recorded as “good quality” with the scores ranging between 11 and 12.5. Two case-control studies (Agarwal et al., 2018; Singh et al., 2008), as shown in Table 3, were assigned a “fair quality” rating, with identical scores of 8.5. The highest score (12.5 out of 14) was obtained by Choi et al. (2012), who measured comprehensive exposure to PAH throughout the pregnancy period, with measurements taken more than once for a subset of participants for each specific trimester.

DISCUSSIONS

Maternal Exposure to PAHs and Adverse Pregnancy Outcomes

Reduction in Birth Weight, Birth Length and Head Circumference

In 2005, Perera et al. reported no significant relationship between maternal exposure to PAHs during pregnancy and fetal growth reduction (Perera et al., 2005a). This finding contrasts with their earlier study in 1998, which demonstrated a significant association between PAH-DNA adducts and birth weight (Perera et al., 1998). However, in the 2005 study, by a similar research group, a significant association was only observed when environmental tobacco smoke (ETS) exposure was included in the analysis, corresponding to a two-fold increase in the concentration of cord blood adducts (Perera et al., 2005b).

Table 2: Checklist for Quality Assessment for Prospective Cohort Study (Source: NIH Study Quality Assessment Tools)

Criteria	Prospective Cohort Study							
	Gladden et al. (2000)	**Perera et al. (2005)**	**Choi et al. (2008)**	**Polanska et al. (2010)**	**Choi et al. (2012)**	**Jedrychowski et al. (2013)**	**Zhang et al. (2016)**	**Jedrychowski et al. (2018)**
Q1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q2. Was the study population clearly specified and defined?	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Q3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	C/D	Yes
Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No
Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	C/D	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q10. Was the exposure(s) assessed more than once over time?	No	No	No	No	Yes	No	No	No
Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q12. Were the outcome assessors blinded to the exposure status of participants?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Q13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	C/D	Yes	Yes
Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Summary Quality	**Good**	**Good**	**Good**	**Good**	**Good**	**Good**	**Fair**	**Good**

Legends: C/D: Cannot Be Determined; N/A: Not Applicable

Table 3: Checklist for Quality Assessment for Case-control Study (Source: NIH Study Quality Assessment Tools)

Criteria	Case-control Study	
	Singh et al. (2008)	Agarwal et al. (2018)
Q1. Was the research question or objective in this paper clearly stated and appropriate?	Yes	Yes
Q2. Was the study population clearly specified and defined?	Yes	Yes
Q3. Did the authors include a sample size justification?	No	No
Q4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes	Yes
Q5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Yes	Yes
Q6. Were the cases clearly defined and differentiated from controls?	Yes	Yes
Q7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	N/A	N/A
Q8. Was there use of concurrent controls?	Yes	Yes
Q9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	C/D	C/D
Q10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Yes	Yes
Q11. Were the assessors of exposure/risk blinded to the case or control status of participants?	N/A	N/A
Q12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Yes	Yes
Summary Quality	**Fair**	**Fair**

Legends: C/D: Cannot Be Determined; N/A: Not Applicable

Tobacco smoking could be the most critical contributor to PAH exposure, and the exposure is not a significant health factor without it (Polanska et al., 2010). The combination of elevated DNA adducts and ETS exposure was associated with a 7% decrease in birth weight and a 3% decrease in head circumference (Perera et al., 2004).

In more recently published studies, prenatal PAHs exposure has been shown to significantly reduce birth weight, birth length, and head circumference (Jedrychowski et al., 2017; Polanska et al., 2010). In terms of impact size between PAH and $PM_{2.5}$, PAH have a greater impact size when compared to $PM_{2.5}$ (Jedrychowski et al., 2017). PAHs exposure during pregnancy causes DNA damage, leading to the induction of apoptosis, antiestrogenic effects, and binding to human aryl hydrocarbon receptors (AHR), resulting in the generation of P450 enzymes. These then interact with growth factor receptors, resulting in inefficient placentation as well as reduced oxygen and nutrient exchange to the fetus (Herbstman et al., 2012; Perera et al., 2011; Page et al., 2002).

SGA and Preterm Birth

1-In-unit increase in prenatal exposure to PAHs was significantly associated with a 2-fold increased chance of being born small for gestational age (SGA) or FGR less than 85% and an increased chance of premature delivery by five times in African Americans (Choi et al., 2008). This observation was consistent with a previous study that found SGA to be associated with PAH exposure in infants in the Czech Republic (Dejmek et al., 2000). Although the mean PAHs exposure in the sample was only one-third of that reported in the Czech Republic, the estimated risk of being born SGA among African Americans was significantly higher than that observed in the Czech population (Dejmek et al., 2000).

The level of PAHs was detected higher in placental samples of the preterm birth group (cases) compared to the full-term delivery group (controls) (Agarwal et al., 2018; Singh et al., 2008). PAHs induce the formation of reactive oxygen species (ROS) that lead to lipid peroxidation in tissues (LPO) (Al-Saleh et al., 2013; de Almeida et al., 2007). Malondialdehyde (MDA), a LPO byproduct usually regarded as a key indication of the antioxidant defence system's failure, while glutathione (GSH) acts as an efficient non-enzymatic antioxidant molecule for evaluating PAH-mediated effects (Agarwal et al., 2018). Higher placental MDA levels and lower GSH placental levels in the preterm birth group compared to the full-term delivery group indicated an antioxidant defence failure in the detoxification of excess ROS (Agarwal et al., 2018). These findings were also reported in a prior study, which revealed that PAHs induced oxidative stress, as the study detected elevated MDA levels and lower GSH levels in the blood of the bronchial asthma group (cases) compared to the control group (Suresh et al., 2009).

Accumulation of PAHs in Biological Samples

PAHs and PAH-DNA adducts were detected in the biological samples, including placental tissues, maternal blood and cord blood (Jedrychowski et al., 2017; Zhang et al., 2017; Gladen et al., 2000). Increased prenatal exposure towards airborne PAHs was significantly associated with the formation of PAH-DNA adducts in the cord blood. Fetal DNA is more susceptible to DNA damage per unit of PAH exposure because of a greater rate of formation of the adducts and/or lower ability for DNA (Jedrychowski et al., 2013). PAHs were detected in significant amounts in maternal blood, umbilical cord blood, and placental tissues (Zhang et al., 2017). This finding suggests that the accumulation of PAH-DNA adducts may not necessarily occur, even when higher levels of PAH are detected in the biological samples. Instead of inducing DNA adduct formation, PAH exposure during pregnancy may also trigger oxidative stress or bind to estrogen receptor binding sites, thereby displacing natural estrogens (Ewa & Danuta, 2017; Plíšková et al., 2002; Vondráček et al., 2002).

Vulnerable Pregnancy Windows

Increased prenatal exposure to PAHs in the first trimester was associated with the most significant decrease in fetal growth ratio, birth weight, and birth length compared to the unit impacts of PAHs in the following trimesters (Choi et al., 2012). Other epidemiologic studies have found that fetal growth rate is regulated throughout the first trimester, resulting in a progressively greater deficit as the pregnancy progresses (Milani et al., 2005; Smith, 2004; Neufeld et al., 1999). An unfavourable intrauterine environment, especially early in pregnancy, is thought to activate the fetus's survival mechanism, which protects essential organs, such as the brain and heart, while inhibiting the development of other systems (Barker, 2006).

CONCLUSION

As a conclusion, PAH exposure during pregnancy can lead to the occurrence of adverse pregnancy outcomes, including low birth weight, reduced birth length, reduced head circumference, SGA and preterm birth. However, only a few studies have shown a significant

association between exposure and the outcome. This systematic review suggests that pregnancy is a vulnerable period in life, and environmental pollutants can have adverse effects on pregnancy outcomes.

The selected articles in this systematic review only examined the association between maternal or prenatal exposure towards PAHs during pregnancy and adverse pregnancy outcomes, but no studies specifically examined the biological mechanism involved to explain the observed relationship. Several included studies only postulated possible mechanisms based on previous studies, without providing laboratory or clinical evidence to support these postulations. Future studies could design *in vitro* experimental research that integrates the biological and mechanistic investigations to provide a comprehensive understanding of maternal exposure to PAHs and their effect on pregnancy outcomes. Additionally, this study only focuses on environmental exposure to PAHs, excluding dietary consumption and occupational exposure, which may be important confounders in this observation.

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