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Maternal Exposure to Environmental Risk Factors and Risk of Adverse Health Outcomes in Offspring: An Overview

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Abstract

Exposure to environmental risk factors are common events in pregnant women and it can affect several health outcomes adverse in the offspring. Many observational studies, systematic reviews and meta-analysis have documented the aforementioned association. This narrative review highlights the results of previous studies about different types of adverse health outcomes during infancy, childhood, adolescent and adults that are related to maternal exposure to leading environmental risk factors e.g. smoking, alcohol consumption, infection and air pollution. Also, the review outlines the potential biological plausibility of the association. Hope this review will help to highlights the bivariate association between maternal health during pregnancy and child health as well as further researches to ascertain the potential mechanisms.

Key Words: Adverse Outcomes, Pregnancy, Maternal Health, Offspring, Overview.

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1- INTRODUCTION

Maternal exposure to environmental risk factors is a common event during pregnancy. Statistics show the prevalence of maternal exposure to environmental risk factors such as smoking (1), infection (2), alcohol consumption (3) and air pollution (4, 5) was remarkable and concerning. Regardless of the negative impact of exposure to these risk factors for the mother, it can threaten the child health during infancy, childhood, early adolescent, adolescent and adults. The association between maternal exposure to environmental risk factors and adverse health outcomes in the offspring have been more attention by researchers over the last decades. Some of them provide robust scientific evidence e.g. effect of maternal smoking during pregnancy (MSDP) on the attention-deficit/hyperactivity disorder (ADHD) (6) or effect of maternal infection during pregnancy (MIDP) on the autism spectrum disorders (ASD) (7). However, the evidence about these risk factors and some adverse health outcomes in offspring are sparse, mixed and conflicting e.g. MSDP and bone mass (8) or MSDP and cardiovascular risk factors (9). More robust and valid methodologically studies to identify environmental risk factors during pregnancy is a vital issue which helps prevent and interventional strategies to be targeted. In this study, we aimed to narratively review the published previous studies on maternal exposure to leading environmental risk factors and adverse health outcomes in the offspring.

2- MATERIALS AND METHODS

The major databases including PubMed, Web of Science and Scopus were searched to evaluate maternal exposure to environmental risk factors and risk of adverse health outcomes in offspring. The key words searched were environmental risk factors including: alcohol, smoking, air pollution and infection and adverse health outcomes. The articles were determined by two researcher independently (MN and MN). Disagreements between researchers were resolved by discussion between two authors. Also variables extracted from studies by two authors.

3- RESULTS

3-1. Maternal smoking during pregnancy

Maternal smoking during pregnancy (MSDP) is still a considerable health problem in many countries with the highest burden in the European Region (1). Children born to mothers who smoke during pregnancy tend to have a wide range of adverse health outcomes compared to those born to non-smoking mothers. The biological mechanism of adverse health outcomes related to MSDP can be attributed to the substances contained in cigarette products, such as nicotine, which cross the placental and affects fetal development. To have a valid inference it is necessary to distinguish the effect of tobacco smoking and e-cigarettes and cannabis use on adverse health outcomes from each other. Moreover, the association will be studied according to subgroups such as gestational age, smoking level e.g. no smoking, light smoking, heavy smoking any important confounders. However, in the following, we overview the published studies that evaluated the effect of MSDP as a whole concept on adverse health outcomes in offspring.

3-2. Maternal smoking during pregnancy and infant outcomes

MSDP has been found to have hazardous effects on infant health including a higher rate of sudden infant death syndrome (10), stillbirth (11), both low birth weight (LBW) and head circumference (12), preterm birth (13, 14) and fetal growth restriction (15). It has been highlighted in

the literature that prenatal smoking can influence maternal intervillous space and volume and surface area of fetal capillaries (16) which can lead to some adverse outcomes e.g. low birth weight. Moreover, it suggested that infant outcomes are mediator factors in the causal pathway MSDP-neuropsychiatric disorders. For example, MSDP mediated LBW and preterm birth that are two important risk factors of neuropsychiatric disorders (17).

3-3. Maternal smoking during pregnancy and neuropsychiatric disorders

The association between MSDP and a range of neuropsychiatric disorders has been the focus of previous studies. According to a meta-analysis of observational studies, MSDP has been associated to an increased risk of Attention-Deficit/Hyperactivity Disorder (ADHD) in children (6, 18) and autism spectrum disorder (ASD) (19). The association between MSDP and other neuropsychiatric disorders has been sparse and resulting in controversial findings. For example, in a cohort of 1,680,219 mother-child pair, a positive association between MSDP and severe mental illness including bipolar disorder and schizophrenia spectrum disorders was found but it was non-significant (20). In another study, children exposed to maternal smoking during pregnancy had an about 2-fold increased risk for bipolar disorder (21, 22). These conflicting results were found for Tourette Syndrome (TS) and Chronic Tic Disorders (CTD) because both positive (23) and null association (24) were reported and for obsessive-compulsive disorder (OCD) that positive (25) and negative (26) association have been yielded. The association between MSDP and TS/CTD comorbid with ADHD (24, 27) and OCD (25) also were examined in previous studies however, it was rare and methodologically limited. The biological mechanisms underlying association between MSDP and neuropsychiatric disorders still not completely defined, however, the role of in utero nicotine exposure on fetal brain development have been reported (28, 29).

3-4. Maternal smoking during pregnancy and Type 1 diabetes mellitus

Most observational studies (30-32) suggest an inverse association between maternal smoking during pregnancy and T1DM with relative risks ranging from 0.30 to 0.90. In contrast, some studies (33, 34) showed a positive association between maternal smoking during pregnancy and T1DM. It is noteworthy that the effect of maternal smoking during pregnancy on the risk of T1DM may be different from that on the islet autoimmunity (35, 36) and it is needed that to be distinguished from each other. In two studies by Stene et al. (37), and Johansson et al. (38) considered islet autoimmunity as the outcome and these two studies suggest a negative association between maternal smoking during pregnancy and islet autoimmunity. Novel potential biological mechanisms e.g. epigenetics should be considered when observing an association between maternal smoking during pregnancy and the risk of T1DM in offspring. For example, it argued that immune function (39) and DNA methylation (40) in the offspring may be influenced by maternal smoking during pregnancy.

3-5. Maternal smoking during pregnancy and childhood cancer

Constituents and metabolites including polycyclic hydrocarbons, N-nitroso compounds, their precursors, and nicotine from mother smoker can cross the placenta. There is additional support from in vitro and animal studies for tumor-inducing by nicotine (41, 42). Although biological plausibility of the association between MSDP and risk of childhood cancer has been mentioned in the literature, however, there is inconsistency

and variation in strength and direction of effect measure for the aforementioned association. For example, in one meta-analysis positive association was found for lymphoma, brain and central nervous system and no association bone, soft tissue tumour, renal, hepatic, germ cell and leukaemia (43). In another meta-analysis non-Hodgkin lymphoma (NHL) positively associated with maternal smoking (any vs. no) during pregnancy but the risk was not statistically significant for Hodgkin lymphoma (HL) and any lymphoma (44).

3-6. Maternal smoking during pregnancy and respiratory disorders

Studies have shown that in utero exposure to nicotine may be associated early immune dysregulation and changes in lung branching morphogenesis (45, 46) which lead to increased small airway function reducing lung function in childhood and adolescents (47). For example, in one study negative association was found between MSDP and forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio but not for FEV1 (48). In following the previous studies have demonstrated that MSDP wheezing and development of asthma symptoms in childhood, adolescents and adults (47, 49-52). In the previous studies the effect of MSDP on asthma and wheezing after adjusting the covariates such as sex, atopy, or maternal history of asthma were examined (47, 49). In another interaction between MSDP and prematurity on childhood wheezing have been reported (52) or in another study the effect of prenatal from postnatal MSDP on childhood wheezing and asthma were distinguished from each other (51).

3-7. Maternal smoking during pregnancy and other adverse health outcomes

The association between MSDP and other adverse health outcomes has been the focus of previous investigations, however, they are few with inconsistent results. For example, the effect of MSDP on bone mineral density and bone fracture (8, 53), later smoking by adolescent (54), criminal outcomes (55), child and adolescent sleep outcomes (56), short stature and obesity in adult daughters (57), tooth development e.g. missing or hypodontia (58, 59), vision difficulties (60), cardiovascular risk factors (9, 61) and reproductive outcomes(62).

3-8. Alcohol consumption during pregnancy

Alcohol consumption is one of the health-related risk factors during pregnancy. Despite the significant effects of alcohol consumption in pregnancy on fetal health, its prevalence in the world is remarkable. Result s of the meta-analysis on 62 studies showed that global prevalence of alcohol consumption during pregnancy was 9·8% and the estimated prevalence of fetal alcohol syndrome (FAS) in the general population was 14·6 per 10.000 people (63). Following alcohol consumption during pregnancy, a number of risk factors will threaten the health of the fetus or child including stillbirth, spontaneous abortion, premature birth, intrauterine growth retardation, FAS and low birth weight (64-66). High alcohol consumption during pregnancy can seriously affect the developing embryo. Its severity varies from severe side effects including FAS to smaller side effects such as low birth weight, IUGR and reduction in IQ (64, 67). In general, the side effects of alcohol consumption during pregnancy is in relation to effects on the developing embryo and fetus and anomalies of the organ systems (68). However, the severity of side effects depend on amount of alcohol ingested the length of period using alcohol and the developmental stage of the embryo and fetus.

3-9. Alcohol consumption during pregnancy and anomalies of the organ systems

Nearly one third of children born from alcoholic mothers have shown some signs of congenital cardiac problems (69, 70). Also the positive correlation between alcohol consumption and oral clefts have been demonstrated previously (71). In the conducted study by Chen et al. increased risk of alcohol-related neural tube defects was observed (72). In another study, the side effects of alcohol consumption in the second month of pregnancy on the renal function of infants were observed (73). Linneberg et al. showed that in mothers who consumed four or more drinks per week at 30 weeks of gestation the risk of atopic dermatitis in early infancy increases (74).

3-10. Alcohol consumption during pregnancy and behavioral and developmental changes

Helen et al. in their longitudinal prospective study on 1,529 pregnant women found that the rate of somatoform disorders, substance dependence, paranoid, passive aggressive, anti-social and other personality disorders more than double in adults exposed to one or more binge alcohol episodes in utero (75). Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurobehavioral disorders of childhood that positively is in correlation with alcohol consumption during pregnancy (76). Alcohol in pregnancy may affect intellectual ability that together with attention span and behavior are being considered higher functions of the cerebral cortex. Results of the study on 7 year-old school children born from mother with history of alcohol consumption during pregnancy showed the negative effect of alcohol on IQ (77). In the systematic review of 33 studies regarding the relation between alcohol consumption during pregnancy and mental health outcomes including: anxiety/depression, emotional problems, total internalizing problems, total problem score, and conduct disorder, results showed that more than half of the analyses indicating a positive association of prenatal alcohol exposure and offspring mental health problems (78). In overall, the teratogenicity of alcohol is related with increased oxidative stress; Disturbed glucose, protein, lipid and DNA metabolism; impaired neurogenesis and increased cellular apoptosis, especially of neural crest cells (68).

3-11. Maternal infection during pregnancy

One of the common environmental risk factors during pregnancy is an infection or indicators of infection e.g. chorioamnionitis, fever, amniotic fluid foul or uterine tenderness. A high prevalence of maternal bacterial and viral infections was reported from conducted studies from low/middle-income (2), and high-income countries (79). Maternal infection during pregnancy (MIDP) can induce a great negative impact on the fetus and neonate and in following adverse health outcomes in the offspring during childhood, adolescent and adult (80, 81). Two most common route transmission of infection from mother to fetus are a) hematogenous spread e.g. TORCH infections; Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections and b) ascending infection via the uterine cervix to the amniotic fluid such as different types of viremia, bacteremia or parasitemia e.g. Escherichia coli, Candida Albicans, Parvovirus B19, Varicella zoster virus, and Plasmodium falciparum. To have a valid inference it is necessary to subgroup the effect of MIDP on adverse health outcomes in the offspring according to type and site of infection, gestational age e.g. preterm from the term, time of infection occurring e.g. during pregnancy, in delivery (perinatal) and breastfeeding (postnatal), however, we overview the effect of MIDP as a whole on adverse health outcomes in offspring.

3-12. Maternal infection during pregnancy and infant outcomes

Previous studies have shown that several MIDP including listeriosis (82), gonorrhoea (83) Chlamydia trachomatis (84) have been associated with preterm birth, however, there is a need to more studies to evaluate the effect of other infections e.g. cytomegalovirus (85), Zika virus infection (86) on the risk of preterm birth. Furthermore, it argued that viral infection may predispose the preterm delivery via coinfection and superinfection with other microorganisms (87, 88). In a pooled analysis of results from cohort studies maternal human immunodeficiency virus (HIV) infection may modify the risk of both low birth weight infant and preterm delivery (89). Untreated maternal syphilis may influence the different type of fetal loss or stillbirth, neonatal death, prematurity or low birth weight (90). Moreover, other infections such as gonorrhoea (91), influenza A virus (92), helicobacter pylori (93), parasitic disease such as malaria (94, 95). In a systematic review herpes simplex virus (HSV), and human cytomegalovirus (HCMV) were risk factors for premature birth, and stillbirth (96). Moreover, different types of sexually transmitted infections (STIs) (97, 98), influenza A virus (92), malaria (99) introduced as risk factors for stillbirth.

3-13. Maternal infection during pregnancy and neuropsychiatric disorders

Although the biological mechanisms of MIDP on brain impairment in the child are not well studied, however, it argued that MIDP and proinflammatory cytokines may lead to altered grey matter volume and white matter integrity and have short and long-term effects brain development (100). MIDP has been positively associated with several neuropsychiatric disorders and chronic developmental motor disability including ADHD (101, 102), ASD (7), schizophrenia (103), psychotic disorders (81), cerebral palsy (104, 105), epilepsy (106). Some evidence suggests an association between MIDP and depressive symptoms in adolescent offspring (107).

3-14. Maternal infection during pregnancy and other outcomes

It argued that MIDP could trigger the initial destruction to fetal beta cells and in following some outcomes such as Type 1 diabetes mellitus (T1DM) have been increased in the offspring (108). The epidemiologic studies about the association between MIDP and childhood cancer have been raised over the last decade. several plausible mechanisms genomic instability (109), immune tolerance and dysregulated immune function (110) might explain the association. The results from a meta-analysis provide robust evidence for an association between MIDP and a higher risk of childhood leukaemia (111). The evidence provides that MIDP could affect altered fetal immunologic development that leads to airway hyper-responsiveness conditions and the following asthma during childhood and adolescent (112). It is also mentioned in the literature that MIDP can predispose childhood infections because of the effect on genetic vulnerability or fetal programming (113).

3-15. Maternal indicators of infection during pregnancy and adverse health outcomes

Indicators of maternal infection that mainly evaluated in the studies were as follow; chorioamnionitis (clinical and histological), fever, placental infection, uterine tenderness, amniotic fluid foul, premature rupture of membranes, leukocytosis and antibiotics (114, 115). However, two main indicators were chorioamnionitis and fever during pregnancy. chorioamnionitis can vulnerable the low birth weight preterm infant to several adverse outcomes in infancy such as neurologic damage (116),

bronchopulmonary dysplasia (117), and later life such as cerebral palsy (114), asthma (118), mental and motor development (119), and ASD and ADHD (120). Previous studies have demonstrated that fever during pregnancy may be related to birth defects (121), oral clefts (122), neural tube defects (123), motor development (124), psychosis-like experiences (125), ADHD (102), ASD (126), CP (115), and seizures (127). Association between antibiotic prescribing in pregnancy and nonprogressive and chronic developmental motor disability e.g. CP, epilepsy (128), and febrile seizures (129), and psychiatric disorders (130) in childhood have been more noticed.

3-16. Ambient air pollution during pregnancy

The effects of ambient air pollution on human health is widely accepted previously (131). Exposure with air pollutions has increased dramatically in recent years and evidence indicating increase in the rate of adverse respiratory outcomes following increase exposure to particulate matter (132). Nonetheless, developing organ systems of the fetuses, due to their exposure pattern and physiologic immaturity are more susceptible to a variety of toxicants and air pollution. Therefore, maternal exposure with environmental pollution can result in some adverse reproductive outcomes. One of the plausible biologic mechanisms for the effect of air pollution on infants is that Polycyclic Aromatic Hydrocarbon (PAH) and their metabolites could bind to the aryl hydrocarbon receptor (AhR) and store in the nucleus of cells, therefore can cause the increase rates of mutagenesis. Since PAHs bind to the AhR, it may result in anti-estrogenic action through increased metabolism and the reduction of endogenous estrogens, therefore disrupting the endocrine system by changing steroid function (133). Furthermore, exposure with air pollutants during pregnancy are associated with significant increase in pregnancy complications, such as hypertensive disorders of pregnancy, GDM and placental abruption , and therefore indirectly through this pathway can affects on the fetus and neonates health (134).

3-17. Ambient air pollution during pregnancy and birth outcome

Birth outcomes are used as an important indicators of pregnancy, infant and newborn health and through this indicators we can have a better judged about quality of pregnancy and neonates care. Evidence shows that fetuses and neonates are the vulnerable groups to the toxic effects of pollutants such as suspended particles and PAH (135). Many studies have examined the relation between air pollution exposure during pregnancy with IUGR, premature births and birth weight. The significant effect of some air pollutants including SO_2, TSP, NO_x, CO, NO_2 and PM_{10} on low birth weight has been shown previously (136-138). Moreover, the association between the above mentioned air pollutant and preterm births has been proven in studies in this regard (137, 138). Also, the relationship between IUGR and air pollution were assessed previously. Dejmek et al. showed that exposure during pregnancy with PM_{10} and $PM_{2.5}$ are associated with increased risk of IUGR (139). Vassilev et al. found that POM in outdoor air increased the risks of SGA (140). However, Hansen et al. did not see a relation between birth length and head circumference with PM_{10}, black smoke, ozone and NO_2 (141). It should be noted that air pollution exposure in the first and third trimester has more side effects compared to the second trimester of pregnancy (142).

3-18. Ambient air pollution during pregnancy and long term effects on Childs

The effect of air pollution during pregnancy on neurodevelopmental impairment leading to ADHD and autism has been reviewed and confirmed in previous studies (143, 144). Moreover, has the undeniable role in developing long-term inflammatory diseases including asthma (145). Some burden of infant eczema also can be attributable to exposure to air pollution during pregnancy (146). Studies have revealed that exposure to PM during pregnancy, are associated with increased risk of many health issues in offspring including reduced lung function, increased risk of lower respiratory infections and cardiovascular diseases (147).

5- CONCLUSION

Maternal exposure to environmental risk factors causing an enormous burden of adverse health outcomes in the offspring. Our evaluation of the literature showed that the effects of a variety of environmental risk factors including smoking, infections, alcohol consumption and air pollution during pregnancy are associated with many offspring externalizing problems, including: developmental, neurological and psychological disorders and their long-term effects are associated with the increased risk of some long term chronic conditions such as childhood cancers, COPD and cardiovascular diseases. Therefore, it is recommend that recommend that pregnant women should avoid exposure to environmental risk factors as much as possible in order to protect them and their fetus against the adverse effects of environmental risk factors.

6- CONFLICT OF INTEREST: None.

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