Environmental Pollutants Affecting Growth: A Review

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Abstract: Objectives: to perform systematic review to summarize the effects of environmental pollutants on normal aspects of growth and development. **Background:** Pollution is a huge problem for whole the world since the start of the industrial revolution**.** Several environmental pollutants have been suspected to disrupt normal growth. **Data sources**: Medline, articles in Medscape and PubMed were searched. The search was performed on November 2016. All types of publications were included. **Study selection**: The initial search presented 250 articles. 30 Articles met the inclusion criteria. Studies that addressed pollutants effects on growth, development, and reproduction were selected. **Data extraction**: Data from each study were independently abstracted in duplicate using a data collection form to capture information on study characteristics, interventions, results reported for each outcome of interest. **Data synthesis:** There was heterogeneity in the collected data. Significant data were collected. Thus, a structured review was performed. **Conclusion:** Articles were reviewed; we found that Environmental chemicals associated with growth disruption can be classified into two main groups; endocrine disruptors and heavy metals. Regarding endocrine disruptors, multiple chemicals have been identified including Phthalates, Bisphenol A, and Polychlorinated biphenyls. Phthalates have confirmed endocrine disruption effects like decreased levels of thyroid hormone andsteroids. Bisphenol A has many disruptive effects like sperm production inhibition and behavioral changes. Heavy metals include basic metal elements such as lead, cadmium, and arsenic. Lead is a common pollutant causing reduction in linear growth, pubertal maturation, and IQ deficits. Arsenic and cadmium may cause decrease birth size and delayed puberty.
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1. Introduction:

Growth is the dominant biological activity of the human being including the prenatal life. Growth includes physical growth, development and puberty. During growth, humans become taller and heavier[1]. Development refers to the process of differentiation and specialization of cells to form mature cells and organs until full differentiation and complete function of tissues and organs. Development also refers to the behavioral changes and functional maturation of neural system with acquisition of skills and adaptation to society [2]. Puberty is a dynamic period of growth anddevelopment marked by rapid changes in body size, shape, and composition [3].

Environmental pollution is a huge problem for many centuries. However, it became more deeper since the start of the industrial revolution [4]. Pollution is the introduction of contaminants into the environment that cause harm or discomfort to humans or other living organisms. It can come in the form of chemical substances or energy such as noise, heat or light. Pollutants can be naturally occurring substances or energies. However, they are considered contaminants when they are present in excess of natural levels [4]. Several environmental pollutants have been suspected of having effects on the growth of fetuses and children [5].

This study aims to perform systematic review to summarize the effects of environmental pollutants on normal aspects of growth and development.

2. Material and Method

The guideline for conducting this review according to guidance developed by the center for review and dissemination. It was used to assess the methodology and outcome of the studies.

Search strategy

Search was performed in several database. It included Medline, articles in Medscape, AAFP and PubMed. The search was performed on 1st November 2016, and included all articles published. No restriction according to language.

Study selection:

All researches were assessed to include in the review by three researchers. They were included if they fulfilled.

1- Normal Growth and Development.
2- Endocrine Disruptors.

3- Environmental Pollutants.
4- Environmental chemicals disrupting growth.

Participants: humans and animals exposed to pollution.

Intervention: prevention of exposure to pollutants.

Comparative: exposed and non-exposed.

Outcome: proper health.

Articles in no English language were translated. The article title and abstract were initially screened. Then the selected articles were read in full and further assessed for eligibility. All references from the eligible articles were reviewed in order to identify additional studies.

Data extraction:

Data from each eligible study were independently abstracted in duplicate using a data collection form to capture information on study characteristics, interventions, quantitative results reported for each outcome of interest. Conclusion and comments on each study made.

There was heterogeneity in the collected data. Significant data were collected. Thus, a structured review was performed withthe result tabulated.

3. Result:

The selected studied were 30studies. The studies were deemed eligible by fulfilling the inclusion criteria. There was a high degree of heterogeneity regarding environmental pollutants that affect normal growth and development.

Table (1): Examples of endocrine disrupting chemicals affecting growth and development

Chemical	Sources	Mechanism	Health Effects
Diethylstilbesterol (DES)	Medication	Mimics estrogen	In humans; Female; vaginal cancer, reproductive tract abnormalities; male; abnormalities of the penis and testicles, semen abnormalities
Polycyclic aromatic hydrocarbons (PAHs)	burning of non-renewable energy sources, tobacco smoke	Inhibit thyroid hormones	Delayed neurological development and IQ deficits
Bisphenol A	Resin in dental sealants, lining of food cans, and polycarbonateplastics	Mimics estrogen	Alters prostate size, decreases sperm productionand affects behavior
Perfluoroalkyl acids (PFAAs)	Industrial applications	Inhibits testosterone Increase estrogen	In male rodents; causes feminization, nipple development0 and abnormal penis development
Polychlorinated biphenyls (PCBs)	Industrial applications	Inhibit thyroid hormones Alter sex hormones	In humans; causes adverse birth outcomes, delayed neurological development and IQ deficits and growth failure
Phthalates	Product of industrial processes,polycarbonateplastics	Decreases estrogen, decreases testosterone and alters thyroid hormone	In female rodents; delays puberty, and increases mammary cancers. In male rodents; decreases testosterone, causes penis and testicular abnormalities, and affects sexual behavior. In humans; decreases thyroid and testosterone levels and induces carcinogenicity.

Table (2): Effects of heavy metals on growth and development

Metal	Sources	Mechanism	Health Effects
Lead	Inhalation of lead-contaminated dust particles, paints	Alter bone cell function, destruct of nerve cells and decrease reproductive hormones	In humans, reductions in linear growth, pubertal maturation, delayed neurological development and IQ deficits
Arsenic	Pesticides, fungicides	Affect glucose metabolism and inhibit thyroid hormones	Decrease size at birth and cause delayed neurological development
Cadmium	Pesticides, batteries	Decrease levels of estradiol and testosterone in the blood	Decreased height and cause delayed puberty

4. Discussion:

According to Sharma and Agrawal[4], Pollution is the introduction of contaminants into the environment that cause harm to humans, other living organisms, or that damage the environment. It can come in the form of chemical substances, or energy such as noise, heat or light. Pollutants can be naturally occurring substances or energies, but are considered contaminants when in excess of natural levels. Several environmental pollutants are suspected to have many effects on the growth of fetuses and children. Due to children physiological immaturity, they are particularly vulnerable to pollutants. Trans-placental transfer that occurs during the fetal period and breast feeding are also significant sources of exposure to pollutants in children. At the early weeks of development, the fetus is very sensitive to teratogenic insults. Environmental chemicals can cause death of cells, alter normal growth of tissues, or interfere with normal cellular differentiation or other morphologic processes, which may cause fetal loss, growth restriction, birth defects or impaired neurologic performance**.** According to Bruner-Tran et al.[6], an endocrine-disrupting compound is "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of body hormones, and are responsible for growth, homeostasis, reproduction, and developmental process.". According to Calafat and Needham[7], endocrine disruptors can:

Mimic or partly mimic naturally occurring hormones in the body like estrogens (the female sex hormone), androgens (the male sex hormone), and thyroid hormones, potentially producing over stimulation.

Bind to a receptor within a cell and block the endogenous hormone from binding. The normal signal then fails to occur and the body fails to respond properly. Examples of chemicals that block or antagonize hormones are anti-estrogens and anti-androgens.

Interfere or block the way natural hormones or their receptors are made or controlled, for example, by altering their metabolism in the liver [8].

According to Dickerson and Gore, [9] endocrine disruptorsare different chemicals include synthetic materials used as industrial solvents/lubricants and their byproducts [polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs)], bisphenol A (BPA), phthalates, pesticides [methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT)], fungicides [vinclozolin], and pharmaceutical agents [diethylstilbestrol (DES)].

According to Lang et al.[10], Bisphenol A (BPA) is a monomer used to harden polycarbonate plastics, and some epoxy resins. These plastics are used in plastic bottles, and some medical devices. The BPA containing epoxy resins are used to coat metal products, such as food cans, and are also used in some dental sealants and composites. The primary route of exposure is ingestion through diet through food and beverage containers. According to Li et al.[11], concerns about health effects derive from animal studies that showed that BPA acts as a weak estrogen in the body and can impact biological systems at low doses. As an example, animal studies reported that low levels of exposure to BPA during development could cause changes in behavior, the brain, prostate gland, mammary gland, and the age at which the female animals attain maturity.

According to the report of United States Department of Health and Human Services National Toxicology Program (NTP)[12] about the effects of BPA on human growth and reproduction; BPA has "some concern" for neural and behavioral effects in fetuses, infants, and children. According to Silva et al.[13], phthalates are class of chemicals has recently received considerable attention due to its widespread use and reported endocrine disruption activities. They are used as plasticizers in polyvinyl chloride (PVC) plastics to impart flexibility. They are also used as emulsifying agents, surfactants, and lubricants in numerous industrial, medical, and cosmetic products. Detectable levels of various phthalate metabolites have been observed in the urine of the general population by the United States Centers for Disease Control and Prevention.

Early work on the endocrine-disrupting activities of phthalates by the National Toxicology Program (NTP)[14]demonstrated alterations to reproductive tract structure, seminiferous tubule degeneration, and lowered sperm counts in male pups exposed to di-(n-butyl) phthalate (DBP) during mid to late gestation. According to Hallmark et al.[15], the effects of in utero exposure to phthalates have been well characterized, demonstrating clear antiandrogenic effects on the rat male reproductive tract. The antiandrogenic mode of action was confirmed when it was shown that DBP and its active monoester metabolite, mono-(n-butyl) phthalate (MBP), could lower both the expression of steroidogenic genes and intratesticular testosterone content without interacting with the AR. According to Jönsson et al.[16], phthalates Decrease estrogen, decrease testosterone and alterthyroid hormone; the suppression of fetal steroidogenesis has resulted in an expression of "serious concern" for human phthalate exposure.

Airborne polycyclic aromatic hydrocarbons (PAHs) are discharged into the air from fragmented burning of non-renewable energy sources, tobacco smoke, and other natural material. Air contamination and ecological tobacco smoke are the most widely

recognized wellsprings of PAH introduction. This may antagonistically influence kids' IQ. According to Perera et al.[17], PAH introduction through individual air examining in non-smoking dark or Dominican-American ladies amid the third trimester of pregnancy. Afterward, they tested their 249 youngsters with neurobehavioral testing (Wechsler Preschool and Essential Size of Knowledge Reconsidered) at age 5 years. Multivariate relapse models were utilized to test relationship between pre-birth PAH introduction and IQ. After alterations for different variables, high PAH levels (over the middle of 2.26 ng/m^3) were contrarily connected with decrements in full-scale IQ and verbal IQ scores. Youngsters in the high introduction aggregate had full-scale and verbal IQ scores that were 4.31 and 4.67 focuses lower, separately, than those of less-uncovered kids. According to Cocchi et al.[5], Polychlorinated biphenyls (PCBs) are persistent, lipophilic chemicals which have been used as heat transfer fluids in transformers until 1970s. Till now, they are detected in children's blood at low levels, and have been identified as endocrine disruptors that could interfere with fetal and postnatal growth and development. Some of chlorophenols, as 2,4,6-trichlorophenol (2,4,6-TCP), 2,4-dichlorophenol (2,4-DCP), and pentachlorophenol (PCP), have been considered as poisons and pollutants by the US Environmental Protection Agency (EPA), European Commission (EC) Environmental Directive and China because of their high danger, industriousness, and bioaccumulation potential. Children are powerless against these contaminants due to their physiological adolescence. These chemicals can be transferred to them from their mothers during pregnancy and lactation. Numerous growth and neurobehavioral impacts of pre- and post-natal PCB introduction have been accounted among children.

According to Xu et al.[18], exposure to CPs has attracted growing public concern because certain CPs have been suspected to disrupt the endocrine function and thus affect reproduction and development in human. For example, paternal PCP exposure was associated with spontaneous abortion in humans, and obesity and pubertal development in adolescent girls were found in associations with exposure to 2.5-DCP due to its potential endocrine disrupting activity. Moreover, exposure to high levels (>3.58 mg/g) of urinary 2,4,6-TCP may increase the risk of attention deficit hyperactivity disorder among US school-aged children. According to Chen et al.[19], Zheng et al.[20], it was found that paternal exposure to chlorophenates in the sawmill industry was associated with the certain developing congenital anomalies of their offspring. It was reported that maternal occupational exposure to CPs might be associated with small for gestational age infants at birth. However, few studies have focused on associations between prenatal multiple CPs exposure in the general pregnant population and adverse birth outcomes including weight, length and head circumference at birth.

According to Wolff et al.[21], the study observed that maternal higher exposure to 2,5-DCP, not 2,4-DCP during pregnancy predicted lower birth weight and length in boys.

According to Yin et al.[22], in experimental animal studies, exposure to 2,4,6-TCP during pregnancy was related to reproductive toxicity as reduction in litter weights at birth on rat and developmental toxicity on aquatic organisms. Similarly, a significantly reduced birth weight and length between PCP exposed and non-exposed pregnant women has been examined.

According to D'Eon et al.[23], Chang et al.[24], Perfluorinated compounds (perfluoroalkyl acids (PFAAs) and their derivatives) are essential man-made chemicals that have wide consumer and industrial applications. They are relatively newly used chemicals, being in use only since the 1950s. They have been considered as biologically inactive for long time. However, during the past few years, their wide distribution, environmental persistence, presence in humans and wildlife, and adverse health effects in laboratory animals have been proved, generating scientific, regulatory, and public interest. Exposure to PFAAs can induce decrease of thyroid hormones. In addition, it can induce changes in biosynthesis of sex steroid. Briefly, (PFAAs) has been shown to decrease serum and testicular testosterone and to increase serum estradiol in male rats, presumably via induction of hepatic aromatase. Exposure to (PFAAs) during pregnancy in rats produced obvious anatomical defects in their offspring (such as cleft palate) only at high doses, while other morphological defects reported in fetuses chiefly reflected developmental delays. Early pregnancy loss was also reported with (PFAAs) introduction to pregnant mothers but only at very high doses, and the etiology of this effect is not clear yet.

According to Newbold et al.[25], obesity is consideredhuge health problem. The estrogenic chemicals e.g Diethylstilbesterol (DES) illuminates the relationship between perinatal exposures and latent development of high body weight and obesity. Moreover, there is a complex relationship between the concentration of estrogen to which pregnant animals are exposed and the weight of the offspring in adulthood. Specifically, mice neonatally exposed to DES developed increased body weight in adulthood associated with excess abdominal body fat.

Heavy metals are basic metal elements such as lead, mercury, cadmium silver nickel, vanadium, chromium and manganese. They are natural components of the earth's crust; they cannot be

degraded or destroyed, and can be transported by air, and enter water and human food supply. In addition, they enter the environment through a wide variety of sources, including combustion, waste water discharges and manufacturing facilities. To a small extent they enter human bodies where, as trace elements, they are essential to maintain the normal metabolic reactions. However, at higher (although relatively low) concentrations they can become toxic. Most heavy metals are dangerous because they tend to bio-accumulate in the human body. Bioaccumulation means an increase in the concentration of a chemical in a biological organism over time, compared to the chemical's concentration in the environment[26].

According to Bellinger[27], Grandjean and Landrigan[28], Lead is a naturally occurring bluish-gray metal present in little amounts in the earth's crust. Despite the fact that lead happens actually in nature, anthropogenic activities, for example petroleum products consuming, mining, and manufacturing, contribute to the release of high concentrations. Lead has a wide range of modern, rural, and household applications. Exposure to lead occurs mainly via inhalation of lead-contaminated dust particles or aerosols and ingestion of food or water contaminated with lead. Paints also is considered as source of lead presented to humans. Adults absorb 35–50% of lead through drinking contaminated water, and the absorption rate for children may be greater than 50%. Lead ingestion is affected by age and physiological status. In the human body, the best rate of lead is taken into the kidney, trailed by the liver and the other delicate tissues, for example, heart and brain. Lead in the skeleton represents significant body percentage.

According to Ignasiak et al.[29], Elevated blood lead levels adversely affect prenatal growth and development. A frequent finding among children is reduced stature in association with increased blood lead levels. Many studies have discussed the association between lead exposure and children's growth. Most of these studies focused on postnatal exposure and found some evidence of associations between lead exposure during childhood and children's growth. Lead is especially unsafe for the baby because it crosses the placenta and may cause unfavorable birth results, including low birth weight and preterm birth. There are numerous routes by which lead may interfere with growth and development in early life. Lead may alter bone cell function directly (through changes in circulating hormones or by impairing their ability to synthesize or secrete other components of the bone matrix) or indirectly (by perturbing the ability of bone cells to respond to hormonal regulation, or by effecting or replacing calcium in the active sites of its messenger system. Greater reductions in linear growth were observed at higher blood lead levels. The observations were consistent with experimental data suggesting a major influence of lead on linear bone growth, specifically proliferation of chondrocytes, hypertrophy and matrix calcification at the growth plates of long bones. Other potential targets for lead are reduced osteoblast activity and bone remodeling.

According to Grantham-McGregor et al.[30], age at exposure, duration and season of exposure, and nutritional status are related to the degree of growth stunting, with younger, chronically exposed, undernourished children at greatest risk. The stunting effect of blood lead on linear growth follows a dose-related pattern of reduction in height by about 1 to 3 cm for each 10.0 μg/dL increase in blood lead level Reduced height was associated with elevated blood lead levels in school children of the Copper Basin observed in 1995. The negative effects of elevated blood lead were more apparent in growth of the extremities (arms, estimated leg length) than in growth of the trunk.

According to Denham et al.[31], the nervous system is the most vulnerable target of lead poisoning. Headache, poor attention spam, irritability, loss of memory, and dullness are the early manifestations of the impacts of lead introduction on the central nervous system. Elevated blood lead levels had a negative influence on visual- motor control, bilateral coordination, upper limb speed of movement, dexterity and fine motor coordination, and on finger tapping speed. Visual-motor integration, eye-hand coordination and spatial relations were reduced among 8–10-year-old children with elevated blood lead. Thus, neurobehavioral effects of lead seemingly persist and perhaps the deficits may be irreversible, i.e. they do not diminish or disappear as the child grows. According to Hauser et al.[32], Williams et al.[33], data on the impact of elevated blood lead levels on markers of biological maturation commonly used in growth studies is limited largely to age at menarche and to a lesser extent to stages of puberty (breast and pubic hair development in girls, genital and pubic hair development in boys) using criteria described by Tanner. Data relating blood lead to skeletal maturation, the only maturity indicator that spans childhood through adolescence, are apparently not available. Information and data for height that span adolescence are required for estimates of the timing and magnitude of the adolescent growth spurt associated with elevated blood lead. Blood lead levels 3 μg/dL were related with later estimated attainment of stages of breast and pubic hair maturation in American girls from the Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III). Later attainment of stages of puberty was most apparent in American Black girls and to a lesser extent in Mexican

American girls with 3.0 µg/dL of blood lead compared to those with 1.0 µg/dL. Later pubertal maturation was noted in American White girls with 3.0 µg/dL of blood lead, but the effect was not statistically significant. Corresponding data for lead and sexual maturation of boys are limited to a prospective study of testicular volume and stages of pubic hair and genital maturation in Russian boys. Delayed puberty was associated with blood lead levels 5.0 µg/dL compared to boys with 5.0 µg/dL in two separate analyses of the same data base.

According to Rahman et al.[34], Henson and Chedrese[35], both arsenic exposure and cadmium exposure are inversely associated with infant size at birth, and this relationship may vary between boys and girls. Cadmium and arsenic have endocrine disrupting properties, which may disrupt growth in young children especially reproductive system. Evidence in humans and experimental animals suggests that cadmium disrupts steroidogenesis, particularly in the placenta, and acts as an endocrine-disrupting chemical, capable of inhibiting the functions of endogenous estradiol.

According to Dhooge et al.[36], Cadmium exposure in adolescents was associated with decreased height and body mass index, as well as lower circulating levels of estradiol and testosterone in the blood. Furthermore, in experimental animals, high levels of cadmium have been found to lower concentrations of insulin-like growth factor1 in plasma, which is critical hormone for childhood growth. Arsenic may affect insulin signaling and glucose metabolism, eventually leading to glucose intolerance and diabetes in exposed populations. Early disruption of glucose uptake by tissues may plausibly lead to impaired growth. This mechanism may be more pronounced in children with better overall nutrition, potentially explaining our observations of arsenic's effects after stratification by SES. Shortly, it is proved that environmental exposures to cadmium and arsenic during early life may contribute to poor growth.

Conclusion:

Several environmental pollutants have been proved to have several disruptive effects on the growth and development. Further studies are needed to advance the prevention methods and set practice guidelines to haw to deal with these environmental pollutants because of the growing evidence of their hazards and toxicity.

Table 1 summarizes the main features and effects of endocrine disruptors on growth and development.

Table 2 summarizes the features and effects of heavy metals on growth and development.

Recommendations:

There are some personal choices individuals can make, if they wish to avoid exposure to chemicals.

Not microwaving polycarbonate plastic food containers.

Avoiding use of containers that have the #7 on the bottom, since some of these are polycarbonate and might contain endocrine disruptors.

Reducing use of canned food.

Using baby bottles that are plastic free.

When possible, opting for glass, porcelain, stainless steel, or safer types of plastics for hot food or liquids.

Using lead free paints.

Avoid exposure to smoking and partially burning of plastics.

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