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Review

Effects of early exposure to phthalates and bisphenols on cardiometabolic outcomes in pregnancy and childhood

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ABSTRACT

Pregnant women are exposed to various chemicals, including endocrine-disrupting chemicals (EDCs) such as phthalates and bisphenols. Increasing evidence suggests that early life exposures to phthalates and bisphenols may contribute to cardiometabolic risks. The aim of this narrative review was to summarize current knowledge of the effects of fetal and childhood exposure to phthalates and bisphenols on child growth and child cardiometabolic outcomes and the effects on maternal outcomes. In total, 54 studies were identified and included. The majority of studies found effects of phthalates and bisphenols on maternal, child growth, and cardiometabolic outcomes. Currently results suggest that early life exposure to phthalates and bisphenols may have a substantial influence on perinatal and postnatal cardiometabolic programming. In a large part of the investigated outcomes studies show contradictory results. However, the majority of the existing evidence is based on non-cohort studies with single samples neglecting time-variant effects and complicating conclusions regarding causal inference. More studies are needed investigating the mechanisms and its potential interactions.

Contents

Abbreviations: AR, androgen receptor; BBzP, butylbenzyl phthalate; BMI, body mass index; BPA, bisphenol A; BPAG, bisphenol A monoglucuronide; BPAS, bisphenol A sulphate; BPF, bisphenol F; BPS, bisphenol S; DBP, di-*n*-butyl phthalate; DEHP, di-2-ethylhexylphthalate; DEP, di-ethyl phthalate; DiDP, di-isodecylphthalate; DiNP, di-isononylphthalate; DnOP, di-*n*-octylphthalate; DMP, di-methyl phthalate; DOHaD, Developmental Origins of Health and Disease; E2, estradiol; EDC, endocrine disrupting chemical; ER, estrogen receptor; FFA, free fatty acid; GMD, gestational diabetes mellitus; HDL, high-density lipoprotein; HMW, high molecular weight; HOMA-IR, homeostatic model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; LMW, low molecular weight; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; NHANES, National Health and Nutrition Examination Survey; PPAR, peroxisome proliterator-activated receptor; PVC, polyvinyl chloride plastics; RXR, retinoid X receptor; UGT, UDP-glucuronosyltransferase.

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1. Introduction

Pregnant women are exposed to a variety of chemicals [1,2], including endocrine-disrupting chemicals (EDCs) such as phthalates and bisphenols [3–6]. Increasing evidence suggests that early life exposures to phthalates and bisphenols may contribute to the burden of cardiovascular and metabolic disease in western countries. Recent work suggests that these exposures may be costly. Health care costs of obesity and diabetes attributable to adult phthalate and bisphenol exposure in Europe is in the order of €17 billion annually [7]. Insofar as prenatal and childhood exposures may even be more impactful, the costs of cardiometabolic conditions due to these exposures may be higher.

In this narrative review, we summarize current knowledge of the effects of fetal and childhood exposure to phthalates and bisphenols on child growth and child cardiometabolic outcomes. Additionally, we summarize the effects of phthalate and bisphenol exposure on maternal outcomes.

2. Phthalates and bisphenols

Phthalates are synthetic chemical esters of phthalic acid that are widely used in a variety of consumer products to impart flexibility, pliability and elasticity to plastics and therefore known as “plasticizers” [8]. Phthalates can be classified in two groups. Low molecular weight (LMW) phthalates (e.g. di-methyl phthalate (DMP), di-ethyl phthalate (DEP), di-*n*-butyl phthalate (DBP)) are frequently added to personal care products as aerosol delivery agents, emollients, to impart flexibility in nail polishes, and to retain scent [9]. High molecular weight (HMW) phthalates (e.g. di-2-ethylhexylphthalate (DEHP), di-isononylphthalate (DiNP), di-isodecylphthalate (DiDP), di-*n*-octylphthalate (DnOP), butylbenzyl phthalate (BBzP)) are used as plasticizers to impart flexibility in vinyl plastics (e.g. polyvinyl chloride plastics (PVC)) for diverse applications including flooring, medical devices and food packaging [10]. In the category of HMW phthalates, di-2-ethylhexylphthalate (DEHP) is of particular interest, considering many food packaging methods include the use of plastics containing DEHP [11]. However, the last few years DiNP and DiDP have replaced DEHP to a great extent, mainly due to governmental embargoes [12].

Bisphenol A (BPA) is used to produce polycarbonate plastics and epoxy resins used in various consumer products, including the lining of metal cans, toys and water pipes [13]. The last few years, bisphenol A has been substituted by synthetic bisphenol analogues like bisphenol F (BPF) and bisphenol S (BPS), which has been determined in various food items [14]. BPS has been found as well in paper and paper products, including currency bills [15].

3. Routes of exposure and metabolism

Phthalates are non-covalently bound to many plastics, creating a large risk for release into the environment over time [9]. Phthalates are generally lipophilic [16] and have short biological half-lives (less than 24 h), undergoing hydrolysis and sometimes oxidation before glucuronidation or sulfation before excretion into urine of feces, but it can be measured as well in blood and breast milk [9]. A portion of the unconjugated (free) monoester and/or its secondary metabolites may also be directly excreted in urine [17]. The primary routes of exposure to phthalates are ingestion, salivary absorption, inhalation, intravenous, and transdermal. Depending on the route of exposure, the chemical is distributed into various body parts based on vascular blood supply and affinity, which in turn may lead to a difference in bioavailability. Ingested chemicals often undergo a first-pass effect, entering the liver through the hepatic portal system for metabolization, which reduces bioavailability. Following inhalation, salivary absorption, intravenous, and transdermal exposure this first-pass effect is initially bypassed, provoking a higher bioavailability [18].

Population based studies often use urine as a measurement for exposure to phthalates because it is noninvasive and notwithstanding the short biological half-life it may reasonably reflect the exposure in the last several weeks or even months [18,19]. The majority of the population based studies using urinary phthalate concentrations measured the concentration of the free plus glucuronidated species of phthalate metabolites, together being the total concentration. However, the free metabolite concentrations are less stable over time than the total metabolite concentration, suggesting free metabolite concentrations are not a useful indicator of metabolic susceptibility. Time of collection is an important factor that must be taken into account, since concentrations of metabolites vary during the day as a result of timing of exposure [17].

Various products containing polycarbonate plastics and epoxy resins have been studied to obtain more knowledge on bisphenol leaching. Regarding polycarbonate plastics, different results have been obtained on the effects of washing and heating on BPA leaching, although all studies found leaching. Several studies have been performed that found that heating temperature had a significant effect on BPA leaching from metallic coated food cans [13].

Studies investigating the metabolism of BPS and BPF are lacking. Concerning BPA it is known that after ingestion BPA undergoes a first-pass metabolism in the gastrointestinal tract and liver consisting of glucuronidation and, to a lesser extent, sulfation metabolizing BPA to bisphenol A monoglucuronide (BPAG) and bisphenol A sulphate (BPAS) for approximately 98%. In plasma, more than 90% of BPA is bound, depending on the route of exposure. Exposure through inhalation and skin absorption have been reported as important routes of exposure, as unconjugated bisphenols might circulate longer in the plasma, while ingested bisphenols undergo the first-pass metabolism [20,21]. However, it has been reported that UDP-glucuronosyltransferase (UGT) enzymes found in the airways exhibit a high activity towards bisphenols [21]. Both BPAG and BPAS are excreted in urine within 5–7 h after oral administration [20,22]. BPA penetrates and accumulates in the human placenta, with higher levels of BPA in the placenta compared to maternal and fetal plasma [23]. In a rat-study, BPF residues have been detected in the uterus, placenta, amniotic fluid, and fetuses, with comparable higher levels of BPF in the (intra)uterine compartment compared to maternal blood [24].

Biomonitoring studies have observed high plasma concentrations not consistent with the observation of an extensive first-pass metabolism of oral BPA. However, concentrations of urinary BPA tend to be much higher than serum concentrations. It has been hypothesized that these relatively high concentrations both in plasma and urine could be explained by sublingual absorption, bypassing the first-pass metabolism [25]. While another study has suggested that this hypothesis does not hold, the contradictory