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Review

Maternal exposure to di-2-ethylhexylphthalate and adverse delivery outcomes: A systematic review

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ABSTRACT

Adverse pregnancy outcomes, including preterm delivery, short gestational age, and abnormal birth weight, remain a public health concern. The evidence on the association of the most common phthalate, di-2-ethylhexyl phthalate (DEHP) with adverse pregnancy outcomes remains equivocal. This systematic review summarizes published studies that investigated the association of DEHP with preterm delivery, gestational age, and birthweight. A comprehensive literature search found 15 relevant studies, most of which evaluated more than one outcome (four studies for preterm delivery, nine studies for gestational age, and ten studies for birthweight). Studies varied greatly with respect to study design, exposure assessment, analytical methods, and direction of the associations. We identified important methodological concerns which could have resulted in selection bias and exposure misclassification and contributed to null findings and biased associations. Given limitations of the previous studies discussed in this review, more thorough investigation of these associations is warranted to advance our scientific knowledge.

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1. Introduction

Phthalates are industrial chemicals extensively used in a variety of consumer products, including plastic food containers, cosmetics/beauty products, toys, and certain medical products such as blood bags and pharmaceutical coatings [1]. Because of their widespread use and biological effects in animals, phthalates were included in the list of regulated (priority) pollutants by the US Environmental Protection Agency and the European Union [2]. Humans are exposed to phthalates through ingestion, inhalation, and dermal contact as well as via parenteral route when using medical devices [1]. Phthalates have short biological half-lives (6–12 h), metabolize quickly, do not bioaccumulate, and are primarily excreted in urine [1,3]. Secondary phthalate metabolites are detected in 100% of the samples from general US population with wide variation [4,5]. Further, higher levels of phthalates in younger women as compared to men of the same age have been also reported possibly reflective of their potential exposure from cosmetic products [6].

Di-2-ethylhexyl phthalate (DEHP) is the most common phthalate that the general population is exposed to ubiquitously mainly through ingestion [7,8]. DEHP is rapidly hydrolyzed in the intestine to the corresponding monoesters (mono-(2-ethylhexyl)phthalate, MEHP) [7,9,10]. These monoesters are considered the biologically active metabolites and their use as biomarkers of DEHP exposure minimizes accidental contamination from parent compound [11–13]. In addition, urinary concentrations integrate exposures from multiple routes thus accounting for the total exposure [14]. Upon absorption, these monoesters undergo further hydroxylation and oxidation (Fig. 1) [7]. A greater proportion of the dose of DEHP is represented by the more downstream metabolites, including mono-(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl)phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl)phthalate (MECPP) [15,16]. In addition, it has been previously shown that a higher ratio of MEHP to MEHHP or MEHP to MEOHP is associated with potentially greater endocrine disrupting capacity [7].

Animal studies have found a variety of adverse effects from exposure to phthalates, including DEHP. Most severe of these effects were noted for reproductive system and normal development. In animal studies, reduction in testosterone levels following administration of DEHP in male animals resulted in underdevelopment of various androgen-dependent tissues and testicular abnormalities including reduced anogenital distance, agenesis of the gubernacular cords and sex accessory tissues, undescended testis, epididymal agenesis, testicular atrophy, and others [13,17,18]. Some of these effects resemble testicular dysgenesis syndrome in humans [14]. In female animals, reproductive effects from phthalates included altered serum estradiol levels, advanced or delayed onset of puberty, increased ovarian and uterine weights, and deficits in growing follicles and corpora lutea [14]. Other effects observed in one or more animal species included changes in hepatic structure and function, including liver cancer, changes in kidney function, and disruption of thyroid signaling, immune functions, and metabolic homeostasis [13,14,19–25].

The evidence on the association of phthalates with adverse effects in humans is limited. Previous studies suggested an association of exposure to phthalates with the risk of premature thelarche [26,27], higher risk of endometriosis [14,28,29], low sperm quality [11,30,31], reduced testosterone levels [32–34], obesity, diabetes, and possibly breast cancer [12,35–41]. Given the variety of these effects and ubiquitous exposure, phthalates were included on the list of endocrine-disrupting compounds with high exposure concern, evidence of endocrine disruption, and highest priority for research [42]. Moreover, phthalates have been recently classified by the International Agency for Research on Cancer as possible carcinogens to humans [43].

Several biological mechanisms were suggested for reproductive and developmental toxicity of DEHP. The primary metabolite of DEHP, MEHP, is a well-known ligand for the peroxisome proliferator-activated receptor (PPAR) family [14,44], is a mitochondrial toxicant and disruptor of lipid and glucose metabolism [14,44–46], and is the most potent DEHP metabolite in its toxicity [14,47,48]. Even though some studies suggested differences in susceptibility to the toxic effects of peroxisome proliferators across species with lower potential in humans, the basis for species differences in peroxisome proliferation and carcinogenesis by phthalate esters has not been fully described [13,48]. In addition, phthalates were also found to reduce the expression of insulin-like factor 3 (insl3) gene involved in the initial stages of testicular descent [14]. In females, DEHP-induced activation of PPAR resulted in dysregulation of aromatase activity and decreased estradiol production in rat granulosa cells [14]. Finally, a growing body of evidence suggests that, in addition to endocrine-disrupting effects on reproductive system, DEHP exhibits pro-inflammatory properties [49–53] and is associated with thyroid dysfunction [54–57]. Importantly, inflammation, oxidative stress, and hypothyroidism, all have been associated with adverse pregnancy outcomes in previous studies in humans [58–61].

The role of prenatal exposures with endocrine disrupting potential, including phthalates, on pregnancy outcomes is poorly understood. Adverse pregnancy outcomes, including preterm delivery, short gestational age, and abnormal birth weight, remain a public health concern [62,63]. These outcomes are associated with an increased risk of morbidity and mortality in the first year of life [64] as well as long-term health consequences in childhood and adulthood, such as neurodevelopmental disability, an increased risk of behavioral problems, hypertension, type 2 diabetes, cardiovascular disease, obesity, psychiatric disorders, and cancer [65–70].

The purpose of this systematic review was to summarize published studies on the association of exposure to DEHP, the most common phthalate, with preterm delivery, gestational age, and birthweight in humans and to identify methodological gaps that need to be addressed in future studies.

2. Materials and methods

2.1. Literature search, study selection, and data extraction

An electronic search was performed using PubMed Central (U.S. National Institutes of Health [NIH]), BioMed Central, and Toxnet with the cutoff date of July 31, 2015. Bibliographies of the articles identified in the electronic searches were then searched manually for additional relevant references. We used any combination of the key words/terms “DEHP” ‘MEHP’; ‘MEHHP’; ‘MEOHP’; “MECPP”; ‘DEHP metabolites’ with “gestational age”; “preterm delivery”; “birth weight”; and “birthweight” to identify relevant publications.

Study selection was accomplished by first applying the following inclusion criteria: (1) accessible in full-text manuscript and (2) published in English. We then excluded studies that did not measure DEHP metabolites in biological specimens to objectively characterize the exposure (referred to as exposure biomarkers or direct exposure assessment method). Our search yielded 117 manuscripts, from which 17 studies were relevant to the topic and met the eligibility criteria (Fig. 2). Two studies were further excluded due to the absence of objective exposure assessment (biomarkers of exposure) [71,72]. Two articles reported the results on the exactly same study population [73,74] and thus only one was included in the review [73]. From each selected article, we extracted the data on epidemiologic design features including study type,