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Bisphenol and phthalate concentrations and its determinants among pregnant women in a population-based cohort in the Netherlands, 2004–5

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ABSTRACT

Background: Exposure to bisphenols and phthalates in pregnancy may lead to adverse health effects in women themselves and their offspring.
Objective: To describe first trimester bisphenol and phthalate urine concentrations, including bisphenol and phthalate replacements, and determine nutritional, socio-demographic and lifestyle related determinants.
Methods: In a population-based prospective cohort of 1396 mothers, we measured first trimester bisphenol, phthalate and creatinine urine concentrations (samples collected in 2004–2005, median gestational age 12.9 weeks [inter-quartile range (IQR) 12.1–14.4]). We examined associations of potential determinants with log-transformed bisphenol and phthalate concentrations. Outcomes were back-transformed. Nutritional analyses were performed in a subgroup of 642 Dutch participants only, as the Food Frequency Questionnaire was aimed at Dutch food patterns.
Results: Bisphenol A, bisphenol S, and bisphenol F were detected in 79.2%, 67.8% and 40.2% of the population, respectively. Mono-*n*-butylphthalate, mono-(2-ethyl-5-hydroxyhexyl)phthalate and monobenzylphthalate were detected in > 90% of the population. Nutritional intake was not associated with bisphenol and phthalate concentrations after correction for multiple testing was applied. Obesity was associated with higher high-molecular-weight phthalate concentrations and the lack of folic acid supplement use with higher di-*n*-octylphthalate concentrations (respective mean differences were 46.73 nmol/l [95% CI 14.56–93.72] and 1.03 nmol/l [0.31–2.06]).
Conclusion: Bisphenol S and F exposure was highly prevalent in pregnant women in the Netherlands as early as 2004–5. Although associations of dietary and other key factors with bisphenol and phthalate concentrations were limited, adverse lifestyle factors including obesity and the lack of folic acid supplement use seem to be associated with higher phthalate concentrations in pregnant women. The major limitation was the availability of only one urine sample per participant. However, since phthalates are reported to be quite stable over time, results concerning determinants of phthalate concentrations are expected to be robust.

Abbreviations: BMI, body mass index; BPA, bisphenol A; BPS, bisphenol S; DEHP, di-2-ethylhexylphthalate; DNOP, di-*n*-octylphthalate; EDC, endocrine-disrupting chemical; FFQ, food-frequency questionnaire; HPLC-ESI-MS/MS, high performance liquid chromatography electrospray ionization-tandem mass spectrometry; mCPP, mono(3-carboxypropyl)phthalate; mIDP, mono-(8-methyl-1-nonyl)phthalate; mINP, monoisononylphthalate; mOP, monooctylphthalate; LOD, limit of detection; LOQ, limit of quantification; LMW, low molecular weight; HMW, high molecular weight; PA, phthalic acid; SPE, solid-phase extraction

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1. Introduction

Bisphenols are used to produce polycarbonate plastics and epoxy resins used in various consumer products, including the lining of metal cans, toys, water pipes and paper products (Liao and Kannan, 2014; Liao et al., 2012b; Vandenberg et al., 2007). Phthalates are frequently added to personal care products and vinyl plastics to impart flexibility, pliability and elasticity (Braun et al., 2013; Sathyanarayana, 2008; Serrano et al., 2014). When ingested, both bisphenols and phthalates undergo a first-pass metabolism consisting of glucuronidation or sulfation and these chemicals have been shown to cross the placenta-blood barrier (Braun et al., 2013; Mattison et al., 2014; Schonfelder et al., 2002; Silva et al., 2004).

During the last few decades, concerns over human exposure and potential health effects from bisphenol A (BPA) and several phthalates including di-2-ethylhexylphthalate (DEHP) have led to regulations on its production and usage in North America and the European Union. However, these governmental embargoes apply mainly to toys and childcare products for oral exposure. In the meantime, this stimulated the use of synthetic bisphenol analogues and DEHP replacements. A shift in phthalate metabolite concentrations has been observed in the first decade of this century (Zota et al., 2014). The European Chemicals Agency (ECHA) reported that the share of phthalate replacements, such as di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP), in total phthalate sales in Europe has increased with over 40% in the years between 2001 and 2010 with concurrently a decline in the share of DEHP (European Chemicals Agency (ECHA), 2013). DEHP replacements have been introduced in the mid-20th century and have first been identified in human urinary samples from 1988 (Wittassek et al., 2007). Several studies reported the presence of bisphenol analogues in environmental compartments, foods and consumer products in the last decade (Chen et al., 2016). However, bisphenol S (BPS) has not been reported in a human biomonitoring study before 2010 (Liao et al., 2012a). Quantification of bisphenol analogues in those specimens that were collected before the governmental regulations were effective is lacking. Human biomonitoring and association studies have rarely focused on bisphenol analogues and were performed in non-pregnant subjects.

An increasing body of evidence suggests that early life exposure to bisphenols and phthalates may lead to several adverse short and long term health effects (Philips et al., 2016). Diet is considered an important source of bisphenol and phthalate exposure (Lorber et al., 2015; Schecter et al., 2013; Schettler, 2006). Certain food groups such as canned food, fish, meat and poultry have been associated with bisphenol and phthalate levels (Braun et al., 2011; Cantonwine et al., 2014; Trasande et al., 2013b; Watkins et al., 2014). Previous studies among pregnant women generally reported higher levels of bisphenols and phthalates to be associated with lower socio-economic status, younger maternal age and smoking (Arbuckle et al., 2014, 2015; Casas et al., 2013; Valvi et al., 2015), but results are inconsistent (Arbuckle et al., 2014; Berman et al., 2014). Overweight has also been suggested as a determinant of bisphenol and phthalate levels (Valvi et al., 2015). Detailed information on nutritional, socio-demographic and lifestyle related determinants of bisphenol and phthalate concentrations in pregnant women might improve identification of women at risk for higher exposure to these chemicals.

We performed a population-based prospective cohort study among 1396 pregnant women in 2004–2005 to describe first trimester bisphenol and phthalate urinary concentrations and determine nutritional, socio-demographic and lifestyle related determinants.

2. Methods

2.1. Study design and population for analysis

The present study was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onwards (Kooijman et al., 2016). In total, 8879 women were enrolled in pregnancy, of which 76% before a gestational age of 18 weeks. The study has been approved by the Medical Ethical Committee of the Erasmus Medical Centre in Rotterdam. Written consent was obtained from all participating women (World Medical Association, 2013). Bisphenol and phthalate concentrations were measured in a subgroup study among 1431 mothers whose children also participated in postnatal studies. This subgroup included singleton pregnancies only. Thirty-five women without a first trimester urinary sample were excluded, which led to 1396 women included in the analysis. Dietary intake assessment in the Generation R study was aimed at Dutch dietary intake patterns. Therefore, information on maternal dietary intake was only included for Dutch participants, leading to 642 women included in the analysis for nutrition related factors (**Flow chart is given in** Fig. 1).

2.2. Bisphenol and phthalate measurements in urine

Bisphenol and phthalate concentrations were measured in a spot urine sample obtained from each subject during the first trimester measurement (median gestational age 12.9 weeks, inter-quartile range 12.1–14.4 weeks). All urine samples were collected between February 2004 and July 2005. Urine samples were collected between 8 a.m. and 8 p.m. in 100-ml polypropylene urine collection containers, stored at 4 °C and transported within 24 h of receipt to the STAR-MDC laboratory before being distributed manually in 25-ml polypropylene vials to be

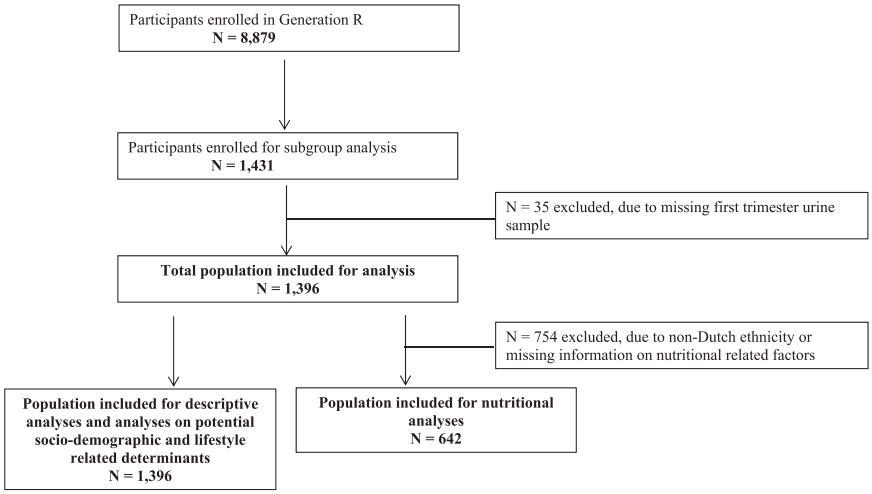

Fig. 1. Flowchart.