Environment International 111 (2018) 23–31

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes

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ARTICLE INFO

Keywords:
IVF
Phthalates
Phthalate alternatives
Oocytes
Implantation
Live birth

ABSTRACT

Phthalates are a class of chemicals found in a large variety of consumer products. Available experimental and limited human data show adverse effects of some phthalates on ovarian function, which has raised concerns regarding potential effects on fertility. The aim of the current study was to determine whether urinary concentrations of metabolites of phthalates and phthalate alternatives are associated with intermediate and clinical in vitro fertilization (IVF) outcomes. We enrolled 136 women undergoing IVF in a Tertiary University Affiliated Hospital. Participants provided one to two urine samples per cycle during ovarian stimulation and before oocyte retrieval. IVF outcomes were abstracted from medical records. Concentrations of 17 phthalate metabolites and two metabolites of the phthalate alternative di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH) were measured. Multivariable Poisson regression models with log link were used to analyze associations between tertiles of specific gravity adjusted phthalate or DINCH metabolites and number of total oocytes, mature oocytes, fertilized oocytes, and top quality embryos. Multivariable logistic regression models were applied to evaluate the association between tertiles of specific gravity adjusted phthalate or DINCH metabolites and probability of live birth. Urinary concentrations of the sum of di-2-ethylhexyl phthalate metabolites (ΣDEHP) and the individual metabolites mono-2-ethyl-5-hydroxyhexyl phthalate, mono-2-ethyl-5-oxohexyl phthalate, and mono-2-ethyl-5-carboxypentyl phthalate were negatively associated with the number of total oocytes, mature oocytes, fertilized oocytes, and top quality embryos. Of the low molecular weight phthalates, higher monoethyl phthalate and mono-*n*-butyl phthalate concentrations were associated with significantly fewer total, mature, and fertilized oocytes. None of the urinary phthalate metabolite concentrations were associated with a reduced probability implantation, clinical pregnancy or live birth. Metabolites of DINCH were not associated with intermediate or clinical IVF outcomes. Our results suggest that DEHP may impair early IVF outcomes, specifically oocyte parameters. Additional research is needed to elucidate the potential effect of DEHP on female fertility in the general population.

1. Introduction

Diester ortho-phthalates are synthetic chemicals widely used in personal care, consumer, and industrial products. Exposure to phthalates is ubiquitous and may occur through dermal absorption, inhalation, or ingestion (Lyche et al., 2009). After exposure, phthalates are metabolized to monoesters and oxidative products, some of which are biologically active and exert anti-estrogenic, anti-androgenic or anti-thyroid activity (Caserta et al., 2008; Lyche et al., 2009).

Phthalates can be classified into two groups based on their molecular weight. Low molecular weight phthalates include diethyl phthalate (DEP), di-*n*-butyl phthalate (DnBP), and di-iso-butyl phthalate

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https://doi.org/10.1016/j.envint.2017.11.011
Received 29 August 2017; Received in revised form 11 November 2017; Accepted 13 November 2017
0160-4120/ © 2017 Published by Elsevier Ltd.

(DiBP) and are used in personal-care products (e.g., cosmetics, hair spray, shampoos, deodorants, perfumes, nail polish, body lotions) but also in medication coatings (Hauser and Calafat, 2005; Just et al., 2010; Meeker et al., 2009). High molecular weight phthalates include di(2-ethylhexyl) phthalate (DEHP), benzylbutyl phthalate (BzBP), and di (isononyl) phthalate (DiNP) and are mainly used in the manufacturing of flooring, carpet backings, adhesives, wallpaper and polyvinyl chloride (Hauser and Calafat, 2005; Just et al., 2010; Meeker et al., 2009). Because phthalates are not covalently bound to the products in which they are incorporated, they can therefore leach into foods or into the environment during use (Koch et al., 2006).

Animal data indicate that exposure to some phthalates and their metabolites can alter folliculogenesis, steroidogenesis, oocyte maturation, and even impair embryo development (Grossman et al., 2012; Hannon et al., 2015). Although the data are limited (Minguez-Alarcon and Gaskins, 2017), several epidemiology studies suggest that background low level exposure to some phthalates are associated with lower ovarian reserve parameters and increased pregnancy loss (Messerlian et al., 2016a, b).

For over a decade, some phthalates including DiNP, and non-phthalate plasticizers such as di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH) have been used in specific countries (e.g., the United States, Germany, Switzerland, Austria) as alternatives to DEHP (Bui et al., 2016; Lessmann et al., 2016; Silva et al., 2017; Silva et al., 2013) because they were expected to have lower toxicity than DEHP. However, any potential adverse effects from these phthalates and phthalates alternatives on human reproduction including on IVF outcomes, remain largely unexplored.

Given the animal data on the toxic effects of phthalates on the female reproductive system we conducted the present investigation to expand on the limited studies in humans. Specifically, we undertook a prospective cohort study of women that were followed for a single IVF cycle to explore the associations between a panel of 17 metabolites of phthalates, including DEHP, di(2-ethylhexyl) terephthalate (DEHTP), and DiNP, and two metabolites of DINCH and in-vitro fertilization (IVF) outcomes.

2. Methods

2.1. Institutional review board approval

The study was approved by the Sheba Medical Center IRB and all patients signed informed consents. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subject research.

2.2. Study population

From January 2014 through August 2016, 136 women undergoing a fresh IVF cycle at Sheba Medical Center, a tertiary university affiliated hospital in the center of Israel, and one of the largest infertility centers in Israel (1100 fresh cycles a year, of them 30% PGD), were enrolled into our prospective cohort study. Approximately 95% of those contacted by the research staff agreed to participate in the study. Participants were enrolled during ovarian stimulation and followed through one fresh IVF cycle. To avoid potential confounding by infertility diagnosis, we approached only women undergoing treatment because of male factor or unexplained infertility, who were oocyte donors, or couples undergoing preimplantation genetic diagnosis (PGD) of autosomal recessive diseases. Exclusion criteria for recruitment were age > 38 years, BMI > 30 kg/m^2, a diagnosis of polycystic ovary syndrome, endometriosis, social oocyte cryopreservation, poor responders according to Bologna criteria (Ferraretti et al., 2011) (which might affect oocyte quality) and frozen IVF cycles. To avoid potential confounding by the stimulation regimen on IVF outcomes (Orvieto and Patrizio, 2013), only women using GnRH antagonist (first line protocol used in our division) were included. For the analysis of clinical IVF outcomes, we excluded 15 women that were not supposed to undergo fresh embryo transfer, i.e. "freeze all" cycles.

2.3. Exposure assessment

In the majority of women (n = 99/136; 73%), a spot urine was collected in a sterile polypropylene cup during ovarian stimulation (days 1–7 of gonadotropin injection) and on the day of oocyte retrieval, and the two specimens were pooled before further analysis. A minority of women contributed only one spot urine sample either during ovarian stimulation (n = 1; 0.7%) or on the day of oocyte retrieval (n = 36; 26%). After measuring specific gravity (SG) (Comber test strips, Roche, Switzerland), the urine was divided into aliquots and frozen at − 80 °C. Samples were shipped on dry ice to the CDC (Atlanta, GA, USA) for the quantification of concentrations of 17 phthalate metabolites and two metabolites of DINCH. The analytical approach, based on solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry, followed standard quality assurance/quality control procedures as previously described (Silva et al., 2013; Silva et al., 2017). We calculated the molar sum of DEHP metabolites (ΣDEHP) by dividing each DEHP metabolite concentration by its molecular weight and then summing: [(mono-2-ethylhexyl phthalate (MEHP) ∗ (1 / 278.34)) + (mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) ∗ (1 / 294.34)) + (mono-2-ethyl-5-oxohexyl phthalate (MEOHP) ∗ (1 / 292.33)) + (mono-2-ethyl-5-carboxypentyl phthalate (MECPP) ∗ (1 / 308.33))].

2.4. Outcome assessment

To reduce possible confounding by treatment protocol, all enrolled patients were treated with controlled ovarian stimulation using GnRH antagonist. For ovarian stimulation, a daily SC dose of recombinant FSH (Gonal-F, Merck-Serono or Puregon, Merck Sharp & Dohme) followed by hMG (Menopur; Ferring) was used starting on the third day of the menstrual cycle. The first dose administered was 150 IU, however the amount of the initial dose depended on the age, body mass index (BMI), and treatment history (Haas et al., 2014). Patients were monitored during gonadotropin stimulation for serum estradiol, follicle size measurements and counts, and endometrial thickness. Human chorionic gonadotropin (hCG) (Ovidrelle, Merck Serono) or GnRH agonist (Decapeptyl 0.2 mg, Ferring) was administered approximately 36 h before the scheduled oocyte retrieval to induce oocyte maturation. According to the policy of our department, the regimen of choice for ovulation induction was hCG. In cases that were scheduled for freezing of all the embryos (i.e., PGD in which embryos were frozen for further diagnosis or in cases with increased risk for ovarian hyper-stimulation syndrome), GnRH agonist was used to induce ovulation. Luteal phase support in cases of hCG were Crinone gel 8% (Merck-Serono) once a day or Crinone gel 8% bid and Progynova (Estradiol) 2 mg (Zydus Cadila Healthcare) when GnRH agonist was used. Ovarian sensitivity index (OSI) was calculated by dividing the total administered FSH dose (IU) by the number of oocytes retrieved (Biasoni et al., 2011). Women received conventional insemination or intracytoplasmic sperm injection (ICSI) as clinically indicated. Embryologists classified oocytes as germinal vesicle, metaphase I, metaphase II (MII), or degenerated. In ICSI, oocyte maturation was assessed during fertilization check. Oocyte maturity in conventional IVF was assessed as follows after removal of the cumulus/corona radiata cells at the fertilization check. The total number of mature oocytes in a conventional IVF cycle was determined by summing the number of oocytes exhibiting one or more pronucleus combined with those without a pronucleus but exhibiting a polar body. Embryologists determined normal fertilization 16 to 18 h after insemination or ICSI as the number of oocytes with two pronuclei. Embryos were further assessed on day 2 for cell number and on day 3 for cell number, symmetry, and fragmentation. Top quality embryos were classified as those with 7–8 cells on day 3 (or in cases of day 2 transfer,

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