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Semen quality and insulin-like factor 3: Associations with urinary and seminal levels of phthalate metabolites in adult males

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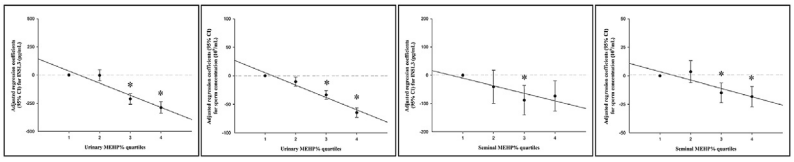
HIGHLIGHTS

- Few studies simultaneously examine phthalate metabolites in urine and semen.
- Urinary BBzP and DEHP metabolites adversely associated with testicular function.
- Seminal DEP and DEHP metabolites adversely associated with testicular function.
- Sperm concentration associated with increasing quartiles of Plasma INSL3 levels.
- First human study linking phthalates, testosterone, INSL3 and low sperm production.
- Adds evidence on mechanisms of phthalates' effects on male reproductive health.

GRAPHICAL ABSTRACT



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ABSTRACT

Certain phthalates have adverse effects on male reproductive functions in animals, and potentially affect human testicular function and spermatogenesis, but little is known about the active mechanisms. We measured the urinary and seminal phthalate metabolites and explored their associations on insulin-like factor 3 (INSL3) and semen quality. Urine, blood, and semen samples were collected from the male partners of subfertile (n = 253) and fertile (n = 37) couples in a reproductive center in southern Taiwan. INSL3, reproductive hormones, semen-quality, and 11 phthalate metabolites in urine and semen were measured. There were significant correlations in the distribution pattern of metabolites, such as the relative contribution of low or high molecular weight phthalate metabolites. The significantly monotonic trends in semen volume, sperm concentration and motility were associated with increasing quartiles of INSL3 (all p-trend < 0.001). In adjusted regression models, increases in urinary phthalate metabolites levels were adversely associated with sperm concentration (monobenzyl phthalate [MBzP], mono-2-

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ethylhexyl phthalate [MEHP] and MEHP%), motility (MBzP and MEHP) and INSL3 (MBzP, MEHP and MEHP%) (all $p < 0.01$). Higher seminal phthalate metabolite levels were associated with decreases in sperm concentration (MEHP and mono-2-ethyl-5-hydroxyhexyl phthalate), motility (mono-ethyl phthalate [MEP] and di-(2-ethylhexyl) phthalate [DEHP] metabolites), normal morphology (MEP), and INSL3 (monomethyl phthalate and MEP) (all $p < 0.05$). Our data suggest that INSL3 secretion, reproductive hormone balance, and sperm production and quality might be simultaneously adversely affected for individuals excreting increasing levels of phthalates metabolites (especially di-ethyl phthalate, butylbenzyl phthalate, and DEHP) in urine and semen samples.

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1. Introduction

A worldwide decline in human sperm quality has become a growing public health concern in recent years (Carlsen et al., 1992; Jørgensen et al., 2011; Rolland et al., 2013). This decline seems to be related to the status of human fertility (Bonde et al., 1998; Zinaman et al., 2000). Exposure to environmental factors such as endocrine disrupting chemicals (EDCs) has been hypothesized to be a risk, and the hypothesis has been strengthened by increasing evidence over the past decade (Jeng, 2014; Kay et al., 2014; WHO/UNEP, 2013). This suggests that male reproduction might be fundamentally changed in the future by continued exposure to EDCs. Phthalates are a family of chemicals whose structure varies only in the length of their ortho-positioned hydrocarbon chain 'arms'. Alkyl-chain length varies from 3 to 10 carbons, in linear or branched format. Phthalates are widely used as solvents, additives, and plasticizers for commercial goods (plastic products, paint, glues, personal care products, pharmaceutical products and cosmetics) and industrial processes (Kelley et al., 2012; Koniecki et al., 2011; Wittassek et al., 2011). Humans are exposed to phthalates via multiple routes (oral, dermal, respiratory, and parenteral), and the pathways vary with the individual phthalates (Koch et al., 2013; Wittassek et al., 2011). Diester phthalates are rapidly cleaved into their hydrolytic monoesters, some of which could be further oxidized (Koch et al., 2006; Wittassek et al., 2011). Consequently, phthalates and their metabolites have been detected in human biological samples, including urine, serum, and semen (Frederiksen et al., 2010; Nakazawa et al., 2014).

Animal and toxicological studies have reported that some phthalates, most notably di-(2-ethylhexyl) phthalat (DEHP) and di-n-butyl phthalate (DBP) directly affect testicular Sertoli cells (S. Chen et al., 2013; Howdeshell et al., 2008; Sobarzo et al., 2015) and Leydig cells (Ge et al., 2007; Hu et al., 2009; Svechnikov et al., 2016), which subsequently might affect steroidogenesis (Desdoits-Lethimonier et al., 2012; Lee et al., 2009; Svechnikov et al., 2016), germ cell maturation (Erkekoglu et al., 2012; Lin et al., 2010; Yang et al., 2012), and spermatogenesis (Aly et al., 2015; Parmar et al., 1986; Zhang et al., 2013) in adulthood. Moreover, human epidemiological studies report that the evidence is inconsistent and that the mechanisms of how phthalate affect hormone imbalance and semen quality are still unknown. Moreover, surveys of the associations between diester phthalates or their metabolites with semen and semen quality are rare and contradictory (Pant et al., 2014, 2008; You et al., 2015). Although urinary metabolites have been used primarily to reflect the levels of individual exposure to phthalate, given their short half-lives, they cannot effectively account for the actual levels of testicular toxicity. Therefore, additional investigation and interpretation are needed to refine the associations between exposure and toxicity of the target reproductive organs.

Insulin-like factor 3 (INSL3) is a Leydig cell-specific peptide hormone responsible for testicular descent during fetal life; it is also a survival and anti-apoptotic factor that synergizes with androgen-dependent Sertoli cell products to support sperm production during adulthood (Ivell et al., 2014; Sagata et al., 2015). Not only toxicological studies (X. Chen et al., 2013; Lague and Tremblay, 2008; Pathirana et al., 2011) but also human studies (Chang et al., 2015; Pan et al., 2015) have reported that higher levels of exposure to mono-2-ethylhexyl phthalate (MEHP) and mono-butyl phthalate or DBP adversely affect *INSL3* expression levels in adult males. However, the effects of phthalate exposure on INSL3 are still underexplored.

In the present study, to explore the associations between internal phthalate metabolites on INSL3 and reproductive function parameters (reproductive hormones and semen quality) in adult males, we measured 11 phthalate metabolites in human urine and semen as exposure biomarkers. We also investigated whether INSL3 was associated with semen parameters, and, if so, whether internal levels of phthalate exposures would simultaneously disrupt INSL3 and reproductive hormones, and subsequently affect semen quality.

2. Methods

2.1. Study population

We conducted a cross-sectional study at the center for Reproductive Medicine of National Cheng Kung University Hospital (NCKUH) and at An-An Women and Children's Clinic, Tainan, Taiwan, from November 2010 to March 2014. We included 253 male partners of subfertile couples, defined as men whose wives did not become pregnant after having regular unprotected sexual intercourse for at least one year (WHO, 2000), who presented for investigation and treatment at an infertility clinic; 37 male partners of fertile couples who had normal semen parameters, and whose wives were spontaneously conceived and had delivered within 1 week at the time of the study. After we had excluded men with self-reported genetic, reproductive system, urologic diseases, hormonal therapy, vasectomy, and occupational exposure to reproductive toxicants (Jurewicz et al., 2009; Wang et al., 2013), the remaining men were given a physical examination. A standardized questionnaire was used to interview the men who passed a physical examination. They were asked to provide spot morning urine and semen samples, and then had a blood sample drawn between 08:00 a.m. and 11:00 a.m. The research protocol was approved by the Human Experiment and Ethics Committee of NCKUH, Tainan, Taiwan. Participants provided written informed consent before the study began. Based on the reference values (semen volume< 2 mL; sperm concentration< 20 million per mL; total motile sperm< 50%; morphologically normal forms< 14%) recommended by the World Health Organization (WHO, 1999), the male partners of subfertile couples from infertility clinics were divided into two subgroups:

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