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Maternal Urinary Phthalates and Phenols and Male Genital Anomalies

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To the Editor

Concerns have been raised about adverse health effects from ubiquitous exposure during pregnancy to phthalates and phenols. Toxicologic data suggest that some of these compounds can disrupt the hormonal signaling that regulates male genital organogenesis. Evidence from the epidemiologic literature assessing association between in utero exposure to these compounds and male genital anomalies is limited and inconclusive.[1–3]

We evaluated whether prenatal exposure to select phthalates and phenols was associated with occurrence of hypospadias and undescended testes in a case-control study (eTable 1, http://links.lww.com/EDE/A558) nested in the EDEN and PELAGIE mother–child cohorts (5200 pregnant women).[4] Cases of hypospadias (n = 21) and undescended testis (unilateral or bilateral, not in scrotum, n = 50) were identified during the first days after birth by pediatricians or midwives. Three controls per case were selected among male singleton live births, matched with cases for residence area, gestational age at urine sample collection, and date and day of collection (Sunday–Monday vs. other). Urinary concentrations of 11 phthalate metabolites and 9 phenols (samples collected in the morning, eTable 2, http://links.lww.com/EDE/A558), determined without knowledge of case-control status, were standardized by sampling conditions that varied among participants using a 2-step standardization method based on regression residuals as described previously.[4] As an alternative exposure metric, we used a specific job-exposure matrix (JEM).[2,3]

In all, 13 women (9%) were classified as possibly exposed to phthalates in the workplace. No correlation between occupational exposure to phthalates and the urinary concentrations of phthalate metabolites was seen (eTable3, http://links.lww.com/EDE/A558). Due to the short-lived nature of these compounds, the morning urinary biomarkers do not necessarily capture occupational exposures, such that both exposure metrics might reflect complementary exposure sources. Using conditional logistic regression, we observed slightly reduced risks of hypospadias with increasing urinary concentrations of all phthalate metabolites (Table, eTable4, http://links.lww.com/EDE/A558). Increased risk of undescended testis was observed in association with the second or third tertiles of urinary concentrations of bisphenol A (BPA), 2,4-dichlorophenol, and ethylparaben compared with the first tertile (Table); increases were more pronounced among term boys (eTable5, http://links.lww.com/EDE/A558). The odds ratio (OR) for hypospadias associated with possible maternal occupational exposure to phthalates was 4.2 (95% confidence interval [CI] 0.4–41.3; 2 exposed cases and 2 exposed matched controls), whereas the OR for undescended testes was 0.3 (0.0–3.1; 1 exposed case and 6 exposed matched controls). A possible role of co-occurring compounds in the corresponding occupations (n = 9 hairdressers in our study) cannot be discarded.

The main limitation of our study was the modest sample size, especially for results concerning phenols (available only in the EDEN cohort). Despite consistency with their estrogenic molecular activity, findings reported for phenols are subject to special caution because they are not supported by animal data. The use of a single spot urine sample may not efficiently reflect the average level of weekly or monthly exposure for compounds such as di(2-ethylhexyl) phthalate (DEHP) and BPA with an important dietary pathway,[5–7] but it

provides reliable exposure measures for low-molecular-weight phthalates and parabens, likely due to regular use of personal-care products.[5,7]

Our prospective study did not show evidence of increased risks of male genital anomalies with prenatal exposure to phthalates. We did not confirm the inverse relation between prenatal DEHP exposure and testicular descent (assessed at approximately 1 year old) previously suggested by a study relying on 12 cases[1]; both the earlier study and our study found no increased risk for other phthalates.[1] In contrast, we observed an unexpected decrease in the risk of hypospadias with increased concentrations of maternal urinary phthalate metabolites, for which we have no clear explanation. We speculate on a possible role of PPAR (peroxisome proliferator-activated receptors) ligands (known for some phthalates) and its critical role in placenta development, as previously proposed.[8]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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TABLE

ORs for Undescended Testis and Hypospadias According to Tertiles of Urinary Concentrations of Phthalate Metabolites and Phenols

	Undescended Testis				Hypospadias			
	No. Controls	**No. Cases**	**OR (95% CI)[a]**	**Test for Trend**	**No. Controls**	**No. Cases**	**OR (95% CI)[a]**	**Test for Trend**
Phthalate sums (nmol/L)								
Low-MWP[b]								
<1426[c]	48	19	1.00	*P* = 0.43	19	12	1.00	*P* = 0.06
1426–3276	44	12	0.74 (0.3–1.9)		25	3	0.15 (0.02–0.9)	
≥3276	57	19	0.67 (0.2–1.9)		13	4	0.19 (0.02–2.3)	
ΣDEHP metabolites[d]								
<433	49	20	1.00	*P* = 0.35	18	8	1.00	*P* = 0.20
433–986	51	17	0.72 (0.3–1.8)		19	8	0.60 (0.2–2.2)	
≥986	49	13	0.60 (0.2–1.7)		20	3	0.21 (0.04–2.1)	
High-MWP[e]								
<676	49	19	1.00	*P* = 0.98	18	10	1.00	*P* = 0.07
676–1591	50	15	0.78 (0.3–2.1)		20	6	0.22 (0.02–1.4)	
≥1591	50	16	1.01 (0.3–2.9)		19	3	0.05 (0.00–1.5)	
Phenols (μg/L)								
Bisphenol A								
<2.2	42	12	1.00	*P* = 0.97	6	4	NA	
2.2–4.7	36	17	2.54 (0.8–7.9)		11	4		
≥4.7	35	9	1.03 (0.3–3.2)		13	2		
Benzophenone 3								
<0.7	43	19	1.00	*P* = 0.24	5	4	NA	
0.7–2.7	30	12	0.87 (0.3–2.5)		17	4		
≥2.7	40	7	0.51 (0.2–1.5)		8	2		
Triclosan								
<4	33	12	1.00	*P* = 0.64	15	3	NA	
4–51	39	10	0.59 (0.2–1.7)		9	3		
≥51	41	16	0.74 (0.3–2.1)		6	4		

	Undescended Testis				Hypospadias			
	No. Controls	No. Cases	OR (95% CI)[a]	Test for Trend	No. Controls	No. Cases	OR (95% CI)[a]	Test for Trend
2,4-dichlorophenol								
<0.6	33	7	1.00	*P* = 0.63	14	4	NA	
0.6–1.4	39	20	2.41 (0.7–8.6)		10	3		
≥1.4	41	11	0.93 (0.2–3.5)		6	3		
2,5-dichlorophenol								
<4.1	33	14	1.00	*P* = 0.54	14	6	NA	
4.1–14.2	38	9	0.44 (0.1–1.5)		11	1		
≥14.2	42	15	0.61 (0.2–1.8)		5	3		
Methylparaben								
<66	37	14	1.00	*P* = 0.32	10	3	NA	
66–213	37	8	0.79 (0.3–2.4)		11	6		
≥213	39	16	1.64 (0.6–4.5)		9	1		
Ethylparaben								
<0.6	38	12	1.00	*P* = 0.14	9	5	NA	
0.6–4.0	37	9	0.72 (0.2–2.7)		12	5		
≥4.0	38	17	2.12 (0.7–6.2)		9	0		
Propylparaben								
<5	37	16	1.00	*P* = 0.62	10	2	NA	
5–25s	38	11	1.13 (0.4–3.4)		10	4		
≥25	38	11	1.34 (0.4–4.2)		10	4		
Butylparaben								
<0.7	36	13	1.00	*P* = 0.98	11	4	NA	
0.7–7.3	35	13	1.01 (0.3–2.9)		13	3		
≥7.3	42	12	1.01 (0.3–3.0)		6	3		
Paraben sum[f] (nmol/L)								
<500	37	14	1.00	*P* = 0.39	11	3	NA	
500–1636	38	10	0.90 (0.3–2.6)		10	6		
≥1636	38	14	1.60 (0.6–4.6)		9	1		

[a]Conditional logistic model adjusted for maternal age (categories), parity (categories), educational level, gestational duration (continuous), creatinine (continous).

[b] Comprises MEP, MBP, MiBP.

[c] Reference category.

[d] Comprises the 4 metabolites of DEHP measured (ie, MEHP, MEOHP, MEHHP, MECPP).

[e] Comprises MCNP, MCOP, MECPP, MEHHP, MEOHP, MEHP, MBzP, MCPP.

[f] Comprises methylparaben, ethylparaben, propylparaben, butylparaben.

MWP indicates molecular weight phthalates; Σ, sum; NA, not available because of limited sample size.