Prenatal exposure to phthalates and phenols in relation to anogenital distance (AGD) at birth in male infants

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Introduction

- The increasing incidence of male reproductive disorders may be due to fetal exposure to putative endocrine disruptor chemicals (EDCs), such as phthalates and phenols[1].
- AGD is a biomarker of fetal androgen action in animals[2], and has recently been linked to Testicular Dysgenesis Syndrome in humans[2-4].

Objective

- To examine the relationship between prenatal phthalate and phenol exposure and birth AGD in male infants.

Method

- Serum samples were collected from pregnant women between 10-12 weeks of gestation as part of a larger prospective study (n=334).
- 27 EDCs (16 phthalate monoesters, 9 phenols) were measured using liquid chromatography/tandem mass spectrometry.
- Statistical analyses excluded EDCs detectable in <45% of mothers. EDC levels below the limit of detection (LOD) were assigned a value equal to LOD/√2 if the data were not highly skewed or LOD/2 if the data were highly skewed[5].
- Birth AGD in males (measured from centre of anus to base of scrotum) was recorded (n=151).

Results

EDC characteristics

- 6 phthalate monoesters (MEP, MiBP, MnBP, MEHP, MECPP, MCiOP) and 3 phenols (BPA, TCS, BP-3) were detectable in ≥45%; median concentrations were 1.57, 3.77, 1.30, 1.17, 0.52, 0.19, 1.78, 0.75 and 0.30 µg/l, respectively.
- Summed levels were calculated for:
  - Di(2-ethylhexyl)phthalate metabolites: ΣDEHPm
  - Dibutylphthalate isomer metabolites: $\Sigma MBP_{(i+n)}$
  - All phthalate metabolites: Σall.phth.m

Male infant characteristics (mean ± SD)

Maternal age (years)	33.0 ± 4.1
Maternal pre-pregnancy BMI (kg/m²)	24.1 ± 4.1
Gestational age (weeks)	39.9 ± 1.8
Birth weight (kg)	3.49 ± 0.55
Birth length (cm)	51.5 ± 2.6
Birth AGD (mm)	19.5 ± 5.5

Associations

- AGD was negatively correlated with ΣDEHPm (rho=-0.188, p=0.021) and Σall.phth.m (rho=-0.203, p=0.012), but no other EDCs.
- In a hierarchical multiple regression model, potential confounding factors (maternal age, BMI, gestation, birth weight, birth length) explained 4.5% of variance in birth AGD; entry of EDC levels explained an additional 7.1%. In this model, only ΣDEHPm (beta=-0.210, p=0.019) and BMI (beta=0.177, p=0.043) were significant.

	Non-parametric correlation		Multiple regression	
	Spearman's rho correlation coefficient of EDC concentration	P value	Beta correlation coefficient of log-transformed EDC concentration	P value
MEP	-0.060	0.463	-0.090	0.304
$\Sigma MBP_{(i+n)}$	0.018	0.831	0.043	0.624
ΣDEHPm	**-0.188**	**0.021**	**-0.210**	**0.019**
MCiOP	-0.011	0.897	0.014	0.871
BPA	0.029	0.726	0.072	0.410
TCS	0.013	0.872	0.026	0.768
BP-3	-0.084	0.308	-0.128	0.147

- In a separate analysis, Σall.phth.m explained an additional 4.5% of variance in AGD when potential confounders were controlled for (beta=-0.213, p=0.014).

Conclusion

- These results suggest that exposure to phthalates during the first trimester (specifically DEHP and possibly others in combination), but not phenols, may adversely affect male reproductive development.

References

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Acknowledgements

We are very grateful to Professor Anders Juul, Dr Anna-Maria Andersson and Dr Hanne Frederiksen - Department of Growth and Reproduction, Copenhagen University Hospital, Denmark for undertaking the analysis of serum EDC levels and for their support and advice with this project.