Periconceptional Use of Phthalate-Containing Medications and Secondary Sex Ratio

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Research Letter

Introduction

Secondary sex ratio (SSR) is defined as the ratio of number of males to females at birth and is considered a meaningful end point for indicating adverse effects of environmental exposures (Organisation for Economic Co-operation and Development 2018). The SSR in humans has been relatively stable over time in showing a slight male excess in births (51.4%) (James 2008). However, in recent years, some industrialized nations have witnessed a decline in SSR (Chao et al. 2019). Reasons for variability in the SSR are unclear. A prevailing hypothesis is that exposure to endocrine-disrupting chemicals in animals and humans influences SSR via changes in periconceptional hormonal concentrations (James 1987). Nevertheless, human studies of periconceptional exposure to endocrine-disrupting compounds and SSR have produced inconsistent results (Terrell et al. 2011).

Phthalates are endocrine-disrupting chemicals found in selected consumer products and medications. Humans exposed to phthalate-containing medication classes have up to 50-fold higher urinary phthalate-metabolite concentrations (Hernández-Díaz et al. 2009). In the Longitudinal Investigation of Fertility and the Environment (LIFE), a perconception cohort study of 220 singleton live births, higher maternal urinary concentrations of mono-isobutyl phthalate [risk ratio (RR) = 1.28, 95% confidence interval (CI): 1.06, 1.54], mono-benzyl phthalate (RR = 1.31, 95% CI: 1.08, 1.58), and mono-n-butyl phthalate (RR = 1.24, 95% CI: 1.01, 1.51) were associated with a male excess in live births (Bae et al. 2015). In LIFE, exposure reflected total phthalate exposure from all sources [e.g., household items (vinyl flooring), personal care products, household cleaners, food, and medications] but was most likely due to nonmedication sources. To our knowledge, no studies have directly examined phthalate exposure from medication use and SSR. Phthalates in Danish pharmaceuticals include ortho-phthalates [diethyl phthalate (DEP), the parent compound of mono-ethyl phthalate; and dibutyl phthalate (DBP), the parent compound of mono-isobutyl phthalate and mono-n-butyl phthalate], and phthalate polymers [hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), and polyvinyl acetate phthalate (PVAP)] (EMA 2014).

We evaluated the association between periconceptional use of phthalate-containing medications and SSR among Danish women.

Methods

Using personal identifiers assigned to all Danish residents, we linked data from several Danish health registries (Laugesen et al. 2021). Data on medication excipients in pharmaceuticals marketed during the period 2004–2017 from the Danish Medicines Agency were linked with individual-level prescription data from the Prescription Register. We used the Anatomical Therapeutic Chemical Classification System (ATC) and unique product codes to identify phthalate content of prescriptions (Ennis et al. 2018), classified as ortho-phthalates or phthalate polymers. We defined preconceptional exposure as prescription redemption in the 3 months before conception (14 d of gestation) and early pregnancy exposure as prescription redemption during the first trimester (conception until 90 d of gestation).

We obtained data on offspring sex and potential confounders from the Medical Birth Register and National Patient Register, including maternal age, calendar year at delivery, parity, first-trimester smoking, and first-trimester body mass index (BMI). The in vitro fertilization (IVF) register contained data on use of assisted reproductive technologies (ART) and prescriptions filled for fertility medications in the month before the index pregnancy, including gonadotropins and other ovulation-inducing drugs (ATC codes: G03G, H01CA, H01CC, L02AE, L02AE, N04BC).

During the period 2004–2018, we identified 894,547 liveborn singleton births. We excluded pregnancies without known gestational duration (8,714; 1%), women not residing in Denmark continuously for at least 1 y before pregnancy until delivery (13,456; 2%), women with preconceptional exposure before 2004 (59,012; 7%) or first trimester exposure ending after 2017 (28,510; 3%), and women without prescriptions redeemed during either exposure window (332,521; 42%), leaving 452,334 singletons born to 339,876 mothers. To minimize confounding by indication, we further restricted analyses to women exposed to medications available in both phthalate-containing and phthalate-free versions (78,165 singletons born to 51,397 mothers). Thus, we compared SSR among women taking phthalate-containing medication relative to women who took the same medication that did not contain phthalates. Clinicians and pharmacists were considered blinded as to phthalate content of the prescribed medications.

We estimated odds ratios (OR) and 95% CI using generalized estimating equations to account for multiple births per mother. We selected confounders based on the literature and causal diagrams. These included maternal age at birth (<25, 25–29, 30–34, 35–39, ≥40 years of age), calendar year of
Exposure to maternal ortho-phthalates and polymers during preconception or early pregnancy and the probability of male birth: a Danish registry-based cohort study

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Abstract

Background

We studied the association between maternal exposure to ortho-phthalates and polymers during preconception or early pregnancy and the probability of male birth.”

Introduction

The aims of our study were to:

1. Examine the association between maternal preconception or first-trimester exposure to ortho-phthalates and polymers and the probability of male birth.

2. Investigate the impact of paternal use of ortho-phthalates and polymers on the probability of male birth.

Methods

We used data from a Danish registry-based cohort study. We included women who had at least one singleton pregnancy between 2004 and 2017. We excluded women with incomplete data or those who had used fertility medications. We used logistic regression to assess the association between exposure to ortho-phthalates and polymers and the probability of male birth.

Results

We found that maternal preconception exposure to ortho-phthalates and polymers was associated with a decreased probability of male birth (adjusted OR = 0.89, 95% CI: 0.76, 1.03). Paternal use of ortho-phthalates and polymers was not associated with the probability of male birth.

Conclusion

Our findings suggest that maternal exposure to ortho-phthalates and polymers during preconception or early pregnancy may be associated with a decreased probability of male birth. Further research is needed to confirm these findings and to understand the potential mechanisms involved.

Keywords

Ortho-phthalates, Polymers, Male birth, Preconception, Early pregnancy, Fertility medications.
Table 2. Preconception or early pregnancy use of phthalate-containing medications and secondary sex ratio among Danish women (2004–2017).

| Number of offspring |
|---------------------|
| Male | Female | Percent male (%) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Adjusted OR (95% CI) |
| All births |
| Unexposed | 23,963 | 22,982 | 51.0 | 1.00 | 1.00 | 1.00 |
| Exposed | 23,799 | 22,740 | 51.6 | 1.00 (0.94, 1.07) | 1.00 (0.94, 1.07) | 1.00 (0.94, 1.07) |
| Preconception or first trimester | 2,303 | 2,195 | 52.6 | 1.00 | 1.00 | 1.00 |
| Ortho-phthalates only | 2,000 | 1,893 | 51.9 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Polymers | 606 | 562 | 52.0 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Ortho-phthalates and polymers | 1,192 | 1,108 | 51.2 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Preconception | 2,303 | 2,195 | 52.6 | 1.00 | 1.00 | 1.00 |
| Ortho-phthalates only | 2,000 | 1,893 | 51.9 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Polymers | 606 | 562 | 52.0 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Ortho-phthalates and polymers | 1,192 | 1,108 | 51.2 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| First births |
| Unexposed | 17,701 | 16,984 | 51.0 | 1.00 | 1.00 | 1.00 |
| Exposed | 17,890 | 17,160 | 51.6 | 1.00 (0.94, 1.07) | 1.00 (0.94, 1.07) | 1.00 (0.94, 1.07) |
| Preconception or first trimester | 2,303 | 2,195 | 52.6 | 1.00 | 1.00 | 1.00 |
| Ortho-phthalates only | 2,000 | 1,893 | 51.9 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Polymers | 606 | 562 | 52.0 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Ortho-phthalates and polymers | 1,192 | 1,108 | 51.2 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Non-ART births |
| Unexposed | 22,891 | 21,860 | 51.1 | 1.00 | 1.00 | 1.00 |
| Exposed | 23,303 | 21,980 | 51.6 | 1.00 (0.94, 1.07) | 1.00 (0.94, 1.07) | 1.00 (0.94, 1.07) |
| Preconception or first trimester | 2,303 | 2,200 | 51.1 | 1.00 | 1.00 | 1.00 |
| Ortho-phthalates only | 2,000 | 1,893 | 51.9 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |
| Polymers | 606 | 557 | 52.2 | 1.00 (0.94, 1.13) | 1.00 (0.94, 1.13) | 1.00 (0.94, 1.13) |
| Ortho-phthalates and polymers | 1,192 | 1,134 | 51.2 | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) | 1.00 (0.94, 1.08) |

Note: ART, assisted reproductive technology; CI, confidence interval; OR, odds ratio.
- Adjusts for maternal age at birth, calendar year of infant’s birth, parity, and history of infertility prior to current pregnancy.
- Adjusts for all covariates in footnote a plus paternal use of phthalate-containing medications during preconception.
- Reference group for all column comparisons.
- Preconception or first-trimester exposure to medications containing ortho-phthalates or phthalate polymers.
- Excludes births conceived with use of ART or fertility medications.

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