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Phthalate exposure from drugs during pregnancy and possible risk of preterm birth and small for gestational age

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ABSTRACT

Background: Phthalates are chemical compounds present in a wide range of consumer products and are thought to be endocrine disruptors. Though not commonly known, phthalates are present in some medication with previous studies finding up to 50-fold higher urinary metabolite concentrations among exposed compared to the general population. Previous studies on environmental phthalate exposure and pregnancy outcomes have been contradictory and inconclusive and all previous studies have assessed phthalate exposure using biomarkers despite a known rapid metabolism of phthalates.
Objective: To determine whether phthalate exposure from pharmaceutical drugs have effects on preterm birth (PTB) and small for gestational age (SGA).
Study design: We conducted a nested case-control study among women in Denmark with a recorded singleton birth and included women who conceived between January 1st, 2004 and December 31st, 2015. To mitigate drug effect and confounding by underlying disease we included pregnancies exposed to selected study drugs, and compared pregnancies exposed to phthalate containing drugs to pregnancies exposed to phthalate free generic drugs. Using Danish health registries, we identified 30,899 singleton pregnancies exposed to study drugs available in both phthalate-containing and phthalate free versions. Using conditional logistic regression, we estimated associations between phthalate exposure and the risk of PTB and SGA. Birth weight according to gestational age was defined by INTERGROWTH-21st (SGA-I) and by Marsal's equation (SGA-M) for expected birthweight.
Results: We included 1965 PTBs, 1315 SGA-Is, and 891 SGA-M cases, matched to 19,537, 12,008, and 7573 controls, respectively. Orthophthalate exposure during the third trimester was positively associated with PTB with a crude OR of 1.36 (95% CI: 1.06–1.76). The association was mainly due to diethyl phthalate. Exposure to phthalate polymers in third trimester was associated with a risk of PTB with crude ORs of 2.08 (CI: 1.16-3.71. No associations were found between orthophthalate or phthalate polymer exposure and SGA.
Conclusion: Exposure to some phthalate-containing pharmaceutical drugs during third trimester is associated with preterm birth.

Introduction

Worldwide, preterm birth (PTB) is the major cause of death and handicap in neonates [1] and has a huge impact on health care costs [2]. Previous studies suggest that environmental exposure to phthalates may increase the risk of PTB [3,4], whereas studies of phthalates and birth weight have been inconclusive [5–7]. Phthalates are used as plastic softeners in consumer products such as cosmetics, food containers, toys, and other soft plastics. Though not commonly appreciated, a range of medicinal products contain both ortho-phthalates and phthalate polymers [8], and users of these products have been shown to have up to 50-fold higher urinary phthalate metabolite concentrations than the

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general population [9]. Phthalates comprise two different subgroups of chemicals: i) ortho-phthalates, which are thought to disrupt the human reproductive system, and ii) phthalate polymers, which are thought to be inert and harmless to humans. Phthalates used in medicinal products marketed in Denmark include the ortho-compounds diethyl phthalate (DEP), dibutyl phthalate (DBP), and the polymeric compounds hypromellose phthalate (HPMCP), cellulose acetate phthalate (CAP) and polyvinyl acetate phthalate (PVAP). Of these, only DEP and DBP are thought to have negative effects on human health [10,11]. While environmental exposure to phthalates is ubiquitous, exposure from medicinal products is avoidable. We designed a nested case-control study among Danish pregnant women exposed to generic drugs with or without phthalates to assess the association between *in utero* exposure to drugs containing phthalates and the risk of PTB and small for gestational age (SGA).

Materials and methods

For this nested case-control study, we identified all Danish women with a registered singleton birth and included women who conceived between January 1st, 2004 and December 31st, 2015. To mitigate confounding by indication we restricted the study population to pregnancies exposed to at least one of our selected study drugs, regardless of the product's phthalate content.

Data sources

Using a unique personal identifier assigned to all Danish residents at birth, or following immigration [12], we linked data from several Danish nationwide registries, including the Medical Birth Registry (MBR) [13], the Danish National Patient registry (DNPR) [14], the Danish Register of Medicinal Product Statistics (RMPS) [15], and data on drug excipients from the Danish Medicines Agency. These registries are described in Appendix SI.

Baseline study population

We restricted the study population to singleton pregnancies resulting in a live birth of an infant without chromosomal abnormalities defined by 'Q90-Q99 Chromosomal abnormalities' in the 10th version of the International Statistical Classification of Diseases [16]. To maximize data coverage and accuracy, pregnancies with missing information on gestational age and women not residing in Denmark continuously for at least two years prior to their delivery were excluded. To attenuate potential confounding by active drug ingredient exposure, we restricted the study population to pregnancies exposed to one or more of our selected study drugs, comprising both phthalate-containing and phthalate free versions of each generic drug. Accordingly, all study participants were exposed to at least one drug, regardless of phthalate content.

Cases and controls

We defined three case sets, jointly describing adverse outcomes of pregnancy. The three case-control sets comprised PTB, and SGA defined by two different birth weight charts (*vide infra*). To minimize confounding by indication - disease or treatment - we matched 10 controls with replacement to each case on active drug substance, and timing on prescription during pregnancy, using 30-day exposure intervals (binary variables). Active drug substances were defined by the fifth level of the Anatomical Therapeutic Chemical (ATC) classification system [17].

Pregnancies with longer gestation will have a greater opportunity to become exposed, thereby causing a potential downward bias. To ensure comparable 'exposure risk-time' among cases and controls, we further matched PTB controls to each case using risk set sampling, and SGA controls using survival sampling. The risk sets were unique for each PTB case and consisted of pregnancies at risk of becoming a case at the time the case became a case. Controls were assigned an index date equal to the gestational age at birth of their corresponding case, and only exposure before the index date was considered in the analysis. SGA cases were besides active drug substance and timing of exposure, also matched to controls on completed weeks of gestation. Gestational age was calculated from the first day of the last menstrual period or from biometric measurements at the first antenatal ultrasound examination. For the majority (>93%), gestational age was determined by the first trimester dating scan.

The PTB case-control set included all pregnancies with a birth before 37 completed weeks of gestation, and matched controls. To ensure identical drug exposure between cases and controls, controls were selected from all pregnancies that had not yet had a PTB, regardless of phthalate exposure status. Pregnancies with a later PTB could therefore be sampled as a control before becoming a case. This means a pregnancy with a delivery at 36 weeks could be a control for a pregnancy with a recorded delivery at 30 weeks. Accordingly, the estimated odds ratio (OR) is an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study conducted in the same source population [18–20].

The SGA case-control sets included all pregnancies with a SGA newborn, defined as a birth weight less than the 10th centile according to either: i) the INTERGROWTH-21st newborn size (henceforth known as SGA-I) or ii) Marsal's expected birthweight charts (henceforth known as SGA-M) (*vide infra*). The SGA-I international size charts for fetuses and neonates were established following the publication of child growth standards by the World Health Organization (WHO) in 2006 [21]. These were based on multinational, multiethnic population samples, and used a strict approach to describe how growth should occur with optimal growth conditions. The strict inclusion and exclusion criteria of the INTERGROWTH-21st project are described elsewhere [22]. The alternative definition of SGA, used in Scandinavia (SGA-M), was defined as a birth weight <2 standard deviations (SD) of the expected birth weight calculated using Marsal's equation [23]. Controls were further matched on duration of completed weeks of gestation and were sampled among birth of offspring with a birth weight above the SGA cutoff.

Exposure ascertainment

The exact contents of active ingredients and excipients of all pharmaceutical products marketed in Denmark are recorded by the Danish Medicines Agency. The active ingredient for each drug product was classified according to the ATC classification system. The Nordic Product code (VNR), assigned to each specific drug product with marketing authorization in the Nordic countries, uniquely identified package size, amount and type of phthalate content per tablet, dates of market entrance and withdrawal, and any changes in ingredients. Duration of treatment was capped at 90 days with prescriptions of shorter duration assigned the stated amount of defined daily doses (DDD) prescribed.

As adverse consequences of drug exposure depend on the active drug substance and the timing of exposure relative to critical windows in embryo and fetal development, we categorized exposure into 30-day windows regardless of phthalate content. A pregnancy would be considered exposed if a prescription of a relevant study drug would overlap by one or more days with a given exposure window. Exposure during the first 14 days of pregnancy was unaccounted for due to

Table 1
Characteristics of cases and matched controls for each outcome (Preterm birth [Defined as birth before 37 completed weeks of gestation], Small for gestational age [Defined by INTERGROWTH-21st size charts and Marsal's expected birth weight chart]).

Co-variates	Preterm Birth		Small for gestational age			
			INTERGROWTH-21st		Marsal	
	Cases	Controls	Cases	Controls	Cases	Controls
	(n = 1965)	**(n = 19,537)**	**(n = 1315)**	**(n = 12,008)**	**(n = 891)**	**(n = 7573)**
Age, mean year (SD)	29.6 ± 5.5	29.6 ± 5.2	29.4 ± 5.6	29.6 ± 5.3	29.6 ± 5.6	29.6 ± 5.3
Parity (primipara)	981 (50%)	8058 (41%)	761 (58%)	4800 (40%)	533 (60%)	3141 (41%)
Sex of offspring (boys)	1084 (55%)	10,005 (51%)	662 (50%)	6198 (52%)	462 (52%)	3900 (51%)
Mother's level of education (years)						
Low (7-10)	270 (14%)	1876 (10%)	195 (15%)	1228 (10%)	137 (15%)	791 (10%)
Medium (11-12)	335 (17%)	3603 (18%)	224 (17%)	2156 (18%)	162 (18%)	1368 (18%)
High (13+)	519 (26%)	6218 (32%)	311 (24%)	3735 (31%)	203 (23%)	2319 (31%)
Vocational training	638 (32%)	5596 (29%)	422 (32%)	3470 (29%)	281 (32%)	2241 (30%)
No information	203 (10%)	2244 (11%)	163 (12%)	1419 (12%)	108 (12%)	854 (11%)
Mother's socioeconomic status						
Un-employed	572 (29%)	4710 (24%)	407 (31%)	3026 (25%)	273 (31%)	1850 (24%)
Students	90 (5%)	945 (5%)	63 (5%)	553 (5%)	45 (5%)	348 (5%)
Employed	1,205 (61%)	13,014 (67%)	781 (59%)	7863 (65%)	533 (60%)	5023 (66%)
Self-employed	38 (2%)	278 (1%)	22 (2%)	201 (2%)	15 (2%)	119 (2%)
No information	60 (3%)	590 (3%)	42 (3%)	365 (3%)	25 (3%)	233 (3%)
Annual personal Income (DKK)						
<100.000	319 (16%)	2780 (14%)	247 (19%)	1764 (15%)	165 (19%)	1061 (14%)
100.000-200.000	1,100 (56%)	10,693 (55%)	762 (58%)	6551 (55%)	518 (58%)	4188 (55%)
200.000-400.000	470 (24%)	5311 (27%)	256 (19%)	3220 (27%)	174 (20%)	2023 (27%)
400.000+	16 (1%)	163 (1%)	8 (1%)	108 (1%)	9 (1%)	68 (1%)
No information	60 (3%)	590 (3%)	42 (3%)	365 (3%)	25 (3%)	233 (3%)
Pre-pregnancy BMI						
<18 (Underweight)	49 (2%)	290 (1%)	38 (3%)	152 (1%)	30 (3%)	114 (2%)
18-24 (Normal weight)	958 (49%)	9674 (50%)	682 (52%)	5919 (49%)	436 (49%)	3790 (50%)
25-29 (Overweight)	440 (22%)	4875 (25%)	277 (21%)	2933 (24%)	191 (21%)	1816 (24%)
30-34 (Obese class I)	223 (11%)	2203 (11%)	132 (10%)	1415 (12%)	99 (11%)	842 (11%)
35+ (Obese class II & III)	185 (9%)	1693 (9%)	112 (9%)	1106 (9%)	81 (9%)	688 (9%)
No information	110 (6%)	802 (4%)	74 (6%)	483 (4%)	54 (6%)	323 (4%)
Smoking status (cigarettes/day)						
Non-smoker	1,399 (71%)	15,141 (77%)	783 (60%)	9304 (77%)	537 (60%)	5755 (76%)
Light smoker (1-10)	325 (17%)	2685 (14%)	301 (23%)	1691 (14%)	208 (23%)	1109 (15%)
Heavy smoker (11+)	166 (8%)	1185 (6%)	198 (15%)	697 (6%)	126 (14%)	499 (7%)
No information	75 (4%)	526 (3%)	33 (3%)	316 (3%)	20 (2%)	210 (3%)

Co-variates	Preterm Birth		Small for gestational age			
			INTERGROWTH-21st		Marsal	
	Cases	Controls	Cases	Controls	Cases	Controls
	(n = 1960)	(n = 19,487)	(n = 1314)	(n = 12,002)	(n = 340)	(n = 2633)
Phthalate exposure						
Orthophthalate exposure	291 (15%)	2721 (14%)	187 (14%)	1690 (14%)	126 (14%)	1036 (14%)
Both orthophthalates and polymers	218 (11%)	2074 (11%)	148 (11%)	1348 (11%)	98 (11%)	824 (11%)
Polymers only	46 (2%)	408 (2%)	34 (3%)	257 (2%)	24 (3%)	146 (2%)
Exceeding DME for DBP No. of pregnancies		n<5				
Exceeding DME for DEP No. of pregnancies	41 (2%)	379 (2%)	17 (1%)	173 (1%)	14 (2%)	96 (1%)
Length of gestation						
Term delivery	–	18,972 (97%)	1154 (88%)	11,053 (92%)	686 (77%)	6528 (86%)
Moderate preterm	1,699 (86%)	552 (3%)	129 (10%)	872 (7%)	141 (16%)	878 (12%)
Very preterm	173 (9%)	10 (0%)	26 (2%)	71 (1%)	50 (6%)	144 (2%)
Extremely preterm	93 (5%)	n<5	6 (0%)	12 (0%)	14 (2%)	23 (0%)
Method of labor and delivery						
Induction	201 (10%)	1499 (8%)	234 (18%)	1885 (16%)	160 (18%)	1160 (15%)
Cesarean	691 (35%)	4039 (21%)	296 (23%)	2695 (22%)	247 (28%)	1763 (23%)
Elective	188 (10%)	1624 (8%)	87 (7%)	1183 (10%)	62 (7%)	678 (9%)
Emergency	557 (28%)	2876 (15%)	230 (17%)	1859 (15%)	200 (22%)	1296 (17%)
Emergency pre-labor	348 (18%)	628 (3%)	102 (8%)	457 (4%)	105 (12%)	362 (5%)
Spontaneous delivery	871 (44%)	9814 (50%)	524 (40%)	6082 (51%)	340 (38%)	3761 (50%)
Diagnoses at any point before delivery						
Diabetes	239 (12%)	1291 (7%)	63 (5%)	845 (7%)	51 (6%)	541 (7%)
Hypertension	399 (20%)	1906 (10%)	203 (15%)	1245 (10%)	167 (19%)	838 (11%)
Heart disease	18 (1%)	68 (0%)	9 (1%)	62 (1%)	6 (1%)	41 (1%)
Chronic renal disease	26 (1%)	59 (0%)	10 (1%)	43 (0%)	10 (1%)	31 (0%)
Diagnoses during current pregnancy						
Pre-eclampsia	274 (14%)	990 (5%)	122 (9%)	700 (6%)	114 (13%)	473 (6%)
Eclampsia	8 (0%)	22 (0%)	n<5	11 (0%)	n<5	5 (0%)
Infections during pregnancy	16 (1%)	108 (1%)	n<5	60 (0%)	n<5	45 (1%)
Diseases during pregnancy	1,031 (52%)	8590 (44%)	571 (43%)	5259 (44%)	394 (44%)	3270 (43%)
Previous Preterm Birth	289 (15%)	1040 (5%)	66 (5%)	718 (6%)	50 (6%)	490 (6%)

Table 1 (*Continued*)

Co-variates	Preterm Birth		Small for gestational age			
			INTERGROWTH-21st		Marsal	
	Cases	Controls	Cases	Controls	Cases	Controls
Procedures						
Cervical cerclage	24 (1%)	355 (2%)	34 (3%)	281 (2%)	20 (2%)	172 (2%)
Progesterone treatment	101 (5%)	502 (3%)	43 (3%)	313 (3%)	40 (4%)	211 (3%)
Cervical surgery	9 (0%)	49 (0%)	n<5	30 (0%)	n<5	24 (0%)

SD, Standard Deviation; DKK, Danish Kroner; BMI, Body Mass Index.
DME, Daily Maximum Exposure; DBP, Dibutyl Phthalate; IQR, Interquartile Range; DEP, Diethyl Phthalate.
Moderate preterm (32–36 completed weeks of gestation).
Very preterm (28–31 completed weeks of gestation).
Extremely preterm (<28 completed weeks of gestation).

uncertainty of the date of conception. After exposure to phthalate containing drugs, we calculated the risk ratios for PTB and SGA by trimester.

Study drugs were grouped according to phthalate content and were categorized into: i) products containing ortho-phthalates (DEP or DBP); ii) products containing phthalate polymers, but no ortho-phthalates, and iii) phthalate-free formulations.

Covariates

Candidate confounders included risk factors for PTB and SGA, including age at conception, calendar year of conception, sex of offspring, parity, smoking status, pre-pregnancy body mass index (BMI) measured at the first antenatal visit, level of mother's education at delivery, socio-economic status, and annual income. Pregnancy related factors included are listed in Table 1.

Statistical analyses

We fitted conditional logistic regression models to estimate ORs with 95% confidence intervals (CI) associating phthalate exposure from drugs to PTB and SGA. In all analyses, pregnancies exposed to phthalate-free drug products were used as a comparator. To examine dose-response relationships, we estimated associations of cumulated amount of phthalate divided into four quartiles of exposure according to type of phthalate and grouped into ortho-phthalates and polymers. Unexposed pregnancies of any type of phthalate were used as the reference category for calculating associations.

Demographic characteristics and pregnancy related factors were tabulated for cases and controls for the three different case-control sets. To verify that phthalate containing versions of a drug were not associated with risk factors for the outcome, we tested the balance of risk factors among exposed and unexposed controls. Exploratory analyses were performed for each specific phthalate.

Other

Stata Version 15.1 (StataCorp, College Station, USA) was used for all analyses. The study was approved by the Danish Data Protection Agency (Jour. No 2015-57-0008 & 2015-54-0993), and ethical approval was not required.

Results

We identified a baseline cohort comprising 30,899 pregnancies with a registered date of conception between January 1st, 2004 and December 31st, 2015. Excluded pregnancies are illustrated in Fig. 1. From the baseline cohort, we identified 1965 PTB cases, 1315 SGA-I cases, and 891 SGA-M cases, that were matched to 19,537, 12,008, and 7573 controls, respectively. As expected, risk factors for the outcomes, such as primiparity, unemployed status and smoking, were more prevalent among cases than controls (Table 1). Furthermore, for all outcomes, cases were more often diagnosed with hypertension and pre-eclampsia. Diabetes, maternal disease complicating pregnancy, and previous PTB were more prevalent among cases of PTB. No differences were found between unexposed and exposed controls (Table SI).

Exposure to ortho-phthalates and phthalate polymers

We found that exposure to ortho-phthalates or phthalate polymers from drugs during third trimester was associated with PTB with ORs of 1.36 (95% CI: 1.06–1.76) and 2.08 (CI: 1.16–3.71), respectively. Adjusting for covariates only marginally changed the risk (Fig. 2 Ortho-phthalates, Fig. 3 Phthalate polymers). Exposure to phthalate polymers in first trimester was negatively associated with SGA-I and SGA-M with ORs as low as 0.55 (CI: 0.29–1.05) and 0.48 (CI: 0.20–1.15) in first trimester (Fig. 3). Adjusted estimates (aOR) were largely unchanged. The associations varied with timing of exposure during gestation.

Exposure to individual ortho-phthalates

We found that exposure to the orthophthalate DEP from drugs during third trimester was positively associated with PTB; aOR 1.41 (CI: 1.03–1.95), and weakly associated with SGA (aOR 1.22, 95% CI: 0.86–1.74), depending on timing of exposure and definition of SGA (Fig. S1). No associations were found between exposure to orthophthalate DBP, and PTB or SGA (Fig. S2).

Exposure to individual phthalate polymers

Exposure to HPMCP from drugs during third trimester was associated with PTB; aOR 2.87 (CI: 1.16–7.12) (Fig. S3). Exposure to CAP containing drugs was negatively associated with SGA-I throughout pregnancy with aORs ranging from 0.61 (CI: 0.31–1.22) to 0.77 (CI: 0.37–1.62) depending on timing in pregnancy. No association was seen between CAP exposure and PTB (Fig. S4). Exposure to PVAP from drugs throughout pregnancy was associated with PTB with aORs ranging from 2.15 (CI: 0.78–5.80) to 4.82 (CI: 1.42–16.40), however the CIs were very wide (Fig. S5). Analysis of cumulated exposure showed no relationship between dose of exposure and risk of outcomes (data not shown).

Comment

Overall, our results provide evidence that exposure to orthophthalates from drugs during third trimester is associated with PTB. Somewhat surprisingly, we found that phthalate polymers from drugs appear to have similar effects. Some studies

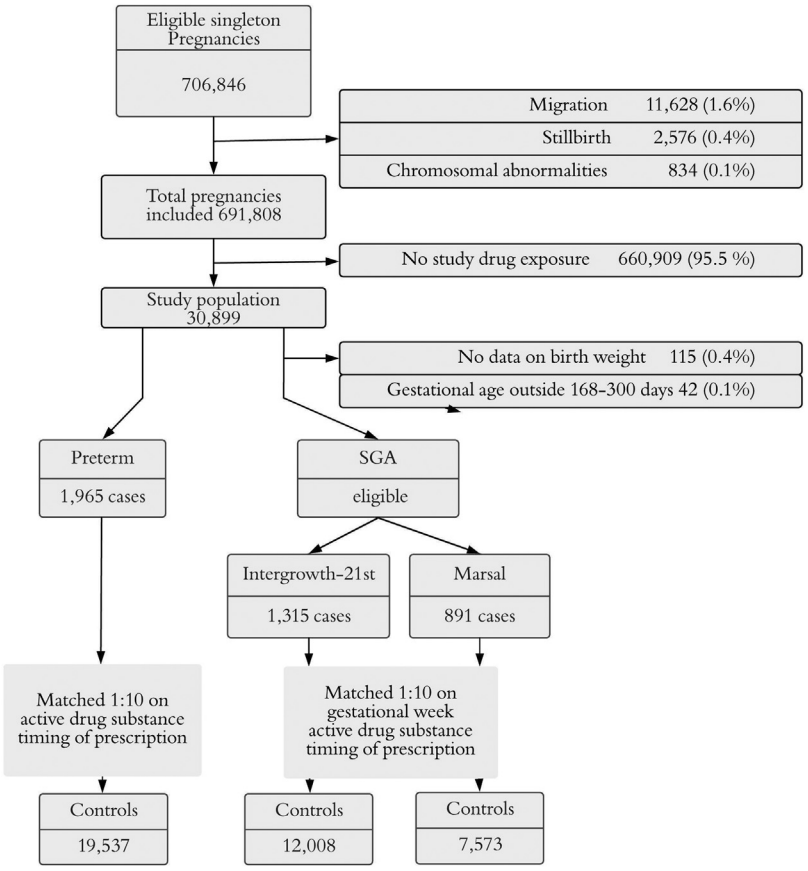

Fig. 1. Flowchart of exclusions and identification of cases and controls.

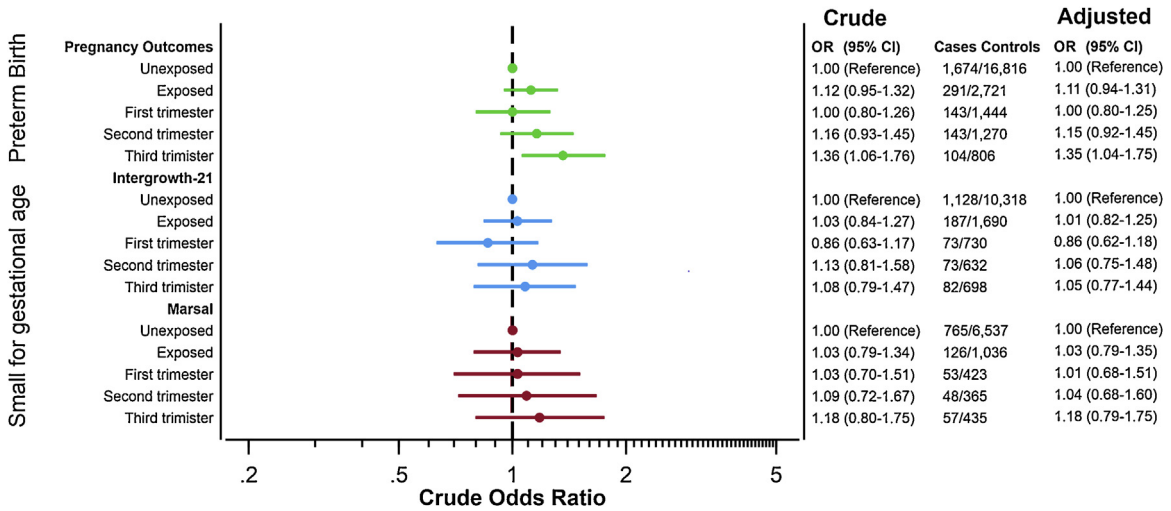

Fig. 2. Exposure to phthalate containing drugs and risk of preterm birth, small for gestational age as defined by INTERGROWTH-21 and Marsal.

have addressed the potential association between environmental phthalate exposure (assessed by biomarkers) and PTB or differences in gestational age [3,24–31]. Studies that focus on gestational age are less conclusive, whereas studies that address the risk of PTB, support an association. Several studies have explored the association between DEP and DBP metabolites and birth weight [6,24–26,32–34] with conflicting results. DBP metabolites measured at birth are associated with increased birth weight [24]. Two studies found no associations with DBP metabolites but an association between DEP metabolites and reduced birth weight [25,26]. In contrast, an association between DBP metabolites and low birthweight among preterm infants was found [32]. Three studies found no such association [6,33,34]. These different results might simply reflect study heterogeneity in levels of exposure between nations, study design, method of exposure assessment, and covariate considerations.

Our study has several strengths, one of which was that we were able to quantify the amount and timing of phthalate exposure from drugs. In addition, while we could not exclude the potential misclassification of exposure due to environmental and occupational exposure, individuals exposed to prescription drugs would be expected to have significantly higher exposure levels. By

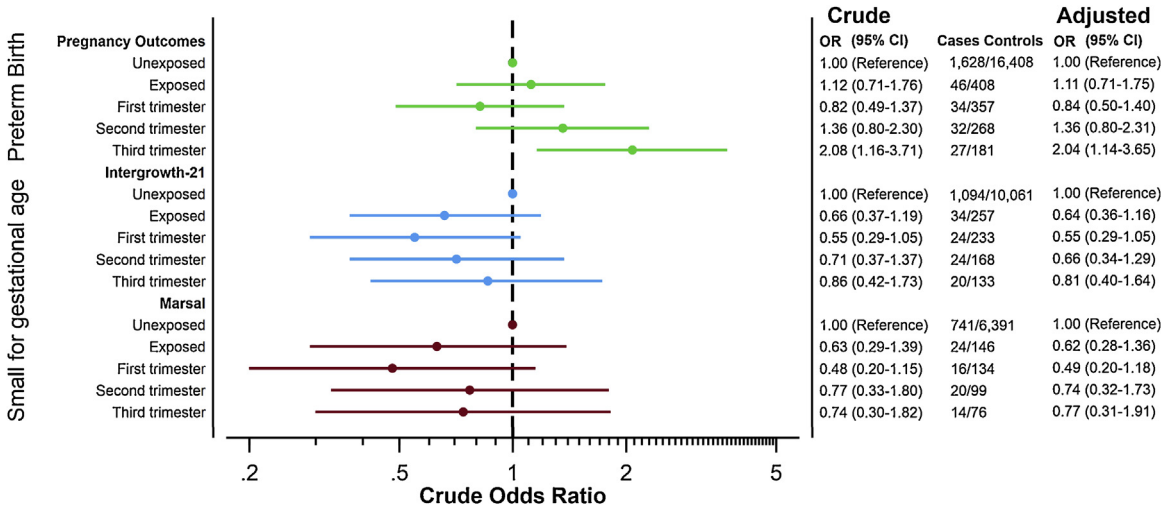

Fig. 3. Exposure to phthalate polymer containing drugs and risk of preterm birth, small for gestational age as defined by INTERGROWTH-21 and Marsal.

matching cases and controls according to active drug group, we ensured a high degree of comparability between phthalate exposed and unexposed pregnancies. Our interest was in phthalate exposure from pharmaceutical drugs, and pregnancies that were not exposed to prescription drugs were more likely to have been healthier than exposed pregnancies and not comparable.

By using risk set sampling to identify PTB controls among all pregnancies not yet (at the time of corresponding case diagnosis) diagnosed with a PTB from the same study population, we eliminated immortal time bias, which would have occurred had we compared cases to term-only controls. By comparing exposure to the same drug during the same time in pregnancy, we maximized the comparability between cases and controls.

We minimized selection bias by using high quality population-based registries to identify births in Denmark. All Danish citizens have access to government-funded healthcare, and consequently, nearly all contacts with the health system, are centrally recorded. As the data were recorded prior to knowledge of the outcome, any recall bias was eliminated.

The main limitation of our study is the use of prescription redemption as a proxy for drug exposure. However, it was our assumption that if individuals redeem and pay for a prescription, they will partially or fully complete the course. In addition, since most doctors and patients are unaware of the phthalate content in drugs, there is no reason to believe that there are any differences in treatment compliance between those exposed or unexposed to phthalates. Our matching did not account for polypharmacy. Despite the use of national registries and a significantly longer study period than previous studies, our study is hampered by limited numbers of exposed cases and controls.

Our findings add valuable knowledge to the existing literature however more research is needed before the information can be used in a clinical setting. Despite finding no increased risk of preterm birth after exposure during the first two trimester or of small for gestational age after exposure at any point during pregnancy, the risk of other adverse outcomes like risk of miscarriage, congenital malformations, childhood development or adult fertility, have not been assessed in this current study. While regulatory agencies have encouraged the industry to limit the use of phthalates [10,11], legislations are inadequate and phthalates remain widely used.

We found an increased risk of PTB with exposure to DEP and phthalate polymers from drugs. While environmental phthalate exposure is ubiquitous, the exposure to phthalates from pharmaceuticals is easily avoidable.

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Declaration of Competing Interest

The authors report no conflicts of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.07.023.

References

[1] WHO | Preterm birth. 2017. . Published 2017. Accessed August 24, 2017 http://www.who.int/mediacentre/factsheets/fs363/en/.
[2] Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes. In: Behrman RE, Butler AS, editors. Preterm birth: causes, consequences, and prevention. Washington (DC): National Academies Press (US); 2007. . Accessed January 24, 2018 http://www.ncbi.nlm.nih.gov/books/NBK11362/.
[3] Ferguson KK, McElrath TF, Meeker JD. Environmental phthalate exposure and preterm birth. JAMA Pediatr 2014;168(1):61–7, doi:http://dx.doi.org/10.1001/jamapediatrics.2013.3699.
[4] Marie C, Vendittelli F, Sauvant-Rochat M-P. Obstetrical outcomes and biomarkers to assess exposure to phthalates: a review. Environ Int 2015;83:116–36, doi:http://dx.doi.org/10.1016/j.envint.2015.06.003.
[5] Zhang Y, Lin L, Cao Y, Chen B, Zheng L, Ge R-S. Phthalate levels and low birth weight: a nested case-control study of Chinese newborns. J Pediatr 2009;155(4):500–4, doi:http://dx.doi.org/10.1016/j.jpeds.2009.04.007.
[6] Philippat C, Mortamais M, Chevrier C, et al. Exposure to phthalates and phenols during pregnancy and offspring size at birth. Environ Health Perspect 2012;120(3):464–70, doi:http://dx.doi.org/10.1289/ehp.1103634.
[7] Wolff MS, Engel SM, Berkowitz GS, et al. Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect 2008;116(8):1092–7, doi:http://dx.doi.org/10.1289/ehp.11007.
[8] Hauser R, Duty S, Godfrey-Bailey L, Calafat AM. Medications as a source of human exposure to phthalates. Environ Health Perspect 2004;112(6):751–3.
[9] Hernández-Díaz S, Mitchell AA, Kelley KE, Calafat AM, Hauser R. Medications as a potential source of exposure to phthalates in the U.S. Population. Environ Health Perspect 2009;117(2):185–9, doi:http://dx.doi.org/10.1289/ehp.11766.
[10] European Medicines Agency. Guideline on the use of phthalates as excipients in human medicinal products. 2016. . Published November 20, 2014. Accessed November 21, 2016 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177736.pdf.

[11] US food and drug administration. Guidance for industry on limiting the use of certain phthalates as excipients in center for drug evaluation and research-regulated products; availability. December. 2012. . Accessed January 3, 2018 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM294086.pdf.
[12] Pedersen CB. The danish civil registration system. *Scand J Public Health* 2011;39 (7 Suppl):22–5, doi:http://dx.doi.org/10.1177/1403494810387965.
[13] Bliddal M, Broe A, Pottegård A, Olsen J, Langhoff-Roos J. The danish medical birth register. Eur J Epidemiol 2018(January), doi:http://dx.doi.org/10.1007/s10654-018-0356-1.
[14] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90, doi:http://dx.doi.org/10.2147/CLEP.S91125.
[15] Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the danish national prescription registry. Int J Epidemiol 2016(October), doi:http://dx.doi.org/10.1093/ije/dyw213.
[16] ICD-10 Version: 2016. https://icd.who.int/browse10/2016/en. Accessed July 15, 2019.
[17] WHOCC - Structure and principles. 2018. . Accessed January 30, 2019.Published https://www.whocc.no/atc/structure_and_principles/.
[18] Hanley JA, Foster BJ. Avoiding blunders involving "immortal time. Int J Epidemiol 2014;43(3):949–61, doi:http://dx.doi.org/10.1093/ije/dyu105.
[19] Matok I, Azoulay L, Yin H, Suissa S. Immortal time bias in observational studies of drug effects in pregnancy. Birt Defects Res A Clin Mol Teratol 2014;100 (9):658–62, doi:http://dx.doi.org/10.1002/bdra.23271.
[20] Rothman KJ, Greenland S, Lash TL. Study design and conduct. Case-control studies. Control selection.. Modern epidemiology. 3rd ed. Wolters Kluwer; 2008.
[21] WHO multicentre growth reference study group. WHO child growth standards based on length/height, weight and age. Acta Paediatr Oslo Nor 1992;2006 (Suppl. 450):76–85.
[22] Villar J, Altman DG, Purwar M, et al. The objectives, design and implementation of the INTERGROWTH-21st Project. BJOG Int J Obstet Gynaecol 2013;120 (Suppl. 2)9–26, doi:http://dx.doi.org/10.1111/1471-0528.12047 v..
[23] Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr Suppl 1996;85(7):843–8.
[24] Watkins DJ, Milewski S, Domino SE, Meeker JD, Padmanabhan V. Maternal phthalate exposure during early pregnancy and at delivery in relation to gestational age and size at birth: a preliminary analysis. Reprod Toxicol Elmsford N 2016;65:59–66, doi:http://dx.doi.org/10.1016/j.reprotox.2016.06.021.
[25] Shoaff JR, Romano ME, Yolton K, Lanphear BP, Calafat AM, Braun JM. Prenatal phthalate exposure and infant size at birth and gestational duration. Environ Res 2016;150:52–8, doi:http://dx.doi.org/10.1016/j.envres.2016.05.033.
[26] Smarr MM, Grantz KL, Sundaram R, Maisog JM, Kannan K, Louis GMB. Parental urinary biomarkers of preconception exposure to bisphenol A and phthalates in relation to birth outcomes. Environ Health Glob Access Sci Source 2015;14:73, doi:http://dx.doi.org/10.1186/s12940-015-0060-5.
[27] Ferguson KK, McElrath TF, Ko Y-A, Mukherjee B, Meeker JD. Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. Environ Int 2014;70:118–24, doi:http://dx.doi.org/10.1016/j.envint.2014.05.016.
[28] Meeker JD, Hu H, Cantonwine DE, et al. Urinary phthalate metabolites in relation to preterm birth in Mexico city. Environ Health Perspect 2009;117 (10):1587–92, doi:http://dx.doi.org/10.1289/ehp.0800522.
[29] Boss J, Zhai J, Aung MT, et al. Associations between mixtures of urinary phthalate metabolites with gestational age at delivery: a time to event analysis using summative phthalate risk scores. Environ Health Glob Access Sci Source 2018;17(1):56, doi:http://dx.doi.org/10.1186/s12940-018-0400-3.
[30] Weinberger B, Vetrano AM, Archer FE, et al. Effects of maternal exposure to phthalates and bisphenol A during pregnancy on gestational age. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet 2014;27 (4):323–7, doi:http://dx.doi.org/10.3109/14767058.2013.815718.
[31] Polańska K, Ligocka D, Sobala W, Hanke W. Effect of environmental phthalate exposure on pregnancy duration and birth outcomes. Int J Occup Med Environ Health 2016;29(4):683–97, doi:http://dx.doi.org/10.13075/ijomeh.1896.00691.
[32] Sathyanarayana S, Barrett E, Nguyen R, Redmon B, Haaland W, Swan SH. First trimester phthalate exposure and infant birth weight in the infant development and environment study. Int J Environ Res Public Health 2016;13(10), doi:http://dx.doi.org/10.3390/ijerph13100945.
[33] Zhao Y, Chen L, Li L-X, et al. Gender-specific relationship between prenatal exposure to phthalates and intrauterine growth restriction. Pediatr Res 2014;76(4):401–8, doi:http://dx.doi.org/10.1038/pr.2014.103.
[34] Woods MM, Lanphear BP, Braun JM, McCandless LC. Gestational exposure to endocrine disrupting chemicals in relation to infant birth weight: a Bayesian analysis of the HOME Study. Environ Health Glob Access Sci Source 2017;16 (1):115, doi:http://dx.doi.org/10.1186/s12940-017-0332-3.