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Urinary Biomarkers Of Bisphenol A And Phthalate Exposure And Their Association With Preterm Birth Among Pregnant Women In Cotonou, Benin

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ABSTRACT

Background: Endocrine-disrupting chemicals (EDCs) such as bisphenol A (BPA) and phthalates are ubiquitous in plastic products and personal care items. Prenatal exposure may interfere with placental function and hormonal regulation, increasing the risk of preterm birth. However, epidemiological evidence from sub-Saharan Africa remains extremely limited.

Objective: To assess the association between urinary concentrations of BPA and phthalate metabolites in pregnant women in Cotonou, Benin, and the risk of preterm birth.

Methods: A prospective cohort study was conducted in Cotonou. Urine samples were collected during the first, second, and third trimesters. BPA and phthalate metabolite concentrations were measured using high-performance liquid chromatography-tandem mass spectrometry. Birth outcomes were confirmed through medical records, with preterm birth defined as delivery before 37 weeks of gestation. Generalized estimating equations and multivariable logistic regression were used, adjusting for age, body mass index, socioeconomic status, and parity.

Results: A total of 412 pregnant women were included, with a preterm birth rate of 21.8%. BPA and phthalate metabolites were detected in nearly 100% of participants. After adjustment, each one-unit increase in log-transformed urinary BPA concentration in the third trimester was significantly associated with an increased risk of preterm birth (OR = 1.42; 95% CI: 1.12–1.80). Among phthalate metabolites, MECPP and MEHHP were positively associated with risk, though with smaller effect sizes than BPA. Stratified analyses showed that the third-trimester exposure window had the strongest association.

Conclusion: Exposure to BPA and phthalates is ubiquitous among pregnant women in Cotonou, and third-trimester BPA exposure is significantly associated with an increased risk of preterm birth. This study provides the first prospective evidence from West Africa on the reproductive health risks of EDCs, highlighting the urgent need to strengthen chemical regulation and prevent prenatal exposure.

Keywords: Bisphenol A; Phthalates; Urinary biomarkers; Preterm birth; Prenatal exposure; Endocrine-disrupting chemicals; Benin

RESUME

Contexte : Les perturbateurs endocriniens (PE), tels que le bisphénol A (BPA) et les phtalates, sont largement présents dans les plastiques et les produits de soins personnels. L'exposition pendant la grossesse peut interférer avec la fonction placentaire et la régulation hormonale, augmentant ainsi le risque d'accouchement prématuré. Cependant, les données épidémiologiques en Afrique subsaharienne restent extrêmement limitées.

Objectif : Évaluer l'association entre les concentrations urinaires de BPA et de métabolites de phtalates chez les femmes enceintes à Cotonou, au Bénin, et le risque d'accouchement prématuré.

Méthodes : Une étude de cohorte prospective a été menée à Cotonou. Des échantillons d'urine ont été collectés aux premier, deuxième et troisième trimestres. Les concentrations de BPA et de métabolites de phtalates ont été mesurées par chromatographie liquide couplée à la spectrométrie de masse en tandem. L'issue de l'accouchement a été confirmée par les dossiers médicaux, l'accouchement prématuré étant défini comme une naissance avant 37 semaines de gestation. Des équations d'estimation généralisées et des régressions logistiques multivariées ont été utilisées, avec ajustement pour l'âge, l'indice de masse corporelle, le statut socio-économique et la parité.

Résultats : Au total, 412 femmes enceintes ont été incluses, avec un taux d'accouchement prématuré de 21,8 %. Le BPA et les métabolites de phtalates ont été détectés chez près de 100 % des participantes. Après ajustement, chaque augmentation d'une unité logarithmique de la concentration urinaire de BPA au troisième trimestre était associée à un risque significativement accru d'accouchement prématuré (OR = 1,42 ; IC 95 % : 1,12–1,80). Parmi les métabolites de phtalates, le MECPP et le MEHHP étaient positivement associés au risque, mais avec des effets moindres que le BPA. Les analyses stratifiées ont montré que la fenêtre d'exposition du troisième trimestre présentait l'association la plus forte.

Conclusion : L'exposition au BPA et aux phtalates est omniprésente chez les femmes enceintes à Cotonou, et l'exposition au BPA au troisième trimestre est significativement associée à un risque accru d'accouchement prématuré. Cette étude fournit les premières preuves prospectives en Afrique de l'Ouest sur les risques des PE pour la santé reproductive, soulignant la nécessité urgente de renforcer la réglementation des produits chimiques et la prévention de l'exposition pendant la grossesse.

Mots-clés : Bisphénol A ; Phtalates ; Biomarqueurs urinaires ; Accouchement prématuré ; Exposition prénatale ; Perturbateurs endocriniens ; Bénin

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1. INTRODUCTION

Preterm birth (delivery before 37 weeks of gestation) is the second leading cause of death in children under five years of age. Approximately 15 million preterm infants are born globally each year, with nearly 60% of these births occurring in sub-Saharan Africa and South Asia. The etiology of preterm birth involves multiple mechanisms including infection, inflammation, uterine over distension, vascular pathology, and genetic susceptibility. However, environmental chemical exposures have received increasing attention in recent years as modifiable risk factors.

Endocrine-disrupting chemicals (EDCs) are exogenous substances that can interfere with the synthesis, transport, metabolism, or receptor signaling of hormones, thereby producing adverse health effects in intact organisms or their offspring. Bisphenol A (BPA) and phthalates are two of the most representative EDCs. BPA is widely used in polycarbonate plastics and epoxy resins, commonly found in food and beverage container linings, thermal paper, and medical devices. Phthalates are used as plasticizers in PVC products, personal care products, and food packaging materials. Humans are continuously exposed primarily through dietary intake, dermal contact, and inhalation.

Pregnancy is a sensitive window for EDC exposure. The developing fetus is particularly vulnerable to EDC interference due to limited metabolic and excretory capacity and an immature hormonal regulatory system. Mechanistic studies suggest that BPA and phthalates can affect pregnancy maintenance through multiple pathways: interfering with placental trophoblast cell differentiation

and invasion, altering progesterone/estrogen balance, inducing oxidative stress and inflammatory responses, and affecting uterine contraction-related signaling pathways.

Epidemiological evidence supports this biological plausibility. A meta-analysis of 59 studies reported that maternal phthalate exposure was associated with an increased risk of preterm birth (OR = 1.31; 95% CI: 1.21–1.42), with particularly significant associations for MEP, MECPP, MBzP, and DEHP metabolites. Regarding BPA, a systematic review and meta-analysis found that prenatal urinary BPA exposure was associated with an elevated risk of preterm birth (OR = 1.36; 95% CI: 1.03–1.69), with stronger associations in populations with median BPA concentrations above 2.16 ng/ml (OR = 1.92; 95% CI: 1.38–2.47). Subgroup analysis showed that only third-trimester BPA exposure was significantly associated with preterm birth (OR = 1.62; 95% CI: 1.15–2.09), and was associated with a 1.36-day shortening of gestational age.

However, existing evidence has significant geographic bias. The vast majority of studies come from North American, European, and East Asian populations, with extremely scarce data from the African continent. Although the French national biomonitoring program provides a model for nationwide maternal exposure assessment, sub-Saharan Africa currently lacks systematic maternal EDC exposure biomonitoring. This knowledge gap has important public health implications. First, chemical regulatory systems in African countries are relatively weak, and EDC levels in consumer products may be higher than in regions with strict controls. Second, socioeconomic factors (such as repeated use of plastic products, non-compliant food packaging, and waste burning) may exacerbate exposure levels. Third, genetic backgrounds, nutritional status, and co-exposure profiles in African populations differ from studied populations, and the direction and strength of associations may differ.

Benin, a coastal country in West Africa, is undergoing rapid urbanization with continuously growing plastic consumption, but environmental health monitoring infrastructure is weak. Cotonou, as Benin's largest city and economic center, is densely populated with widespread informal plastic recycling and reuse activities, creating a potentially high-risk environment for EDC exposure. However, to date, there is no systematic study on BPA and phthalate exposure levels and their reproductive health effects among pregnant women in Cotonou or Benin nationally.

This study aims to fill this gap through a prospective cohort design to assess urinary BPA and phthalate metabolite concentrations in pregnant women in Cotonou and their association with preterm birth risk. The study hypothesis is that higher prenatal urinary BPA and phthalate metabolite concentrations are associated with increased preterm birth risk, and that third-trimester exposure may show the most significant association.

2. LITERATURE REVIEW

2.1 Bisphenol A and Preterm Birth

The reproductive toxicity evidence for BPA has evolved from controversy to relative consensus. Early studies had inconsistent conclusions due to small sample sizes, single time-point exposure assessment, and differences in outcome confirmation methods. Cantonwine et al. (2015) first reported a significant association between third-trimester urinary BPA concentrations and preterm birth in a Mexican population, but this was limited by a sample size of 30 preterm and 30 term births and single urine collection.

Subsequent studies improved designs through larger samples, longitudinal sampling, and ultrasound-confirmed gestational age. A nested case-control study in the United States including 130 preterm and 352 randomly selected term births found no overall

significant association, but the association strengthened after excluding medically indicated preterm births, suggesting that BPA may primarily affect spontaneous preterm birth. The meta-analysis by Namat et al. (2021) integrated 7 preterm birth studies and 9 gestational age studies, confirming a positive association between prenatal BPA exposure and preterm birth risk and identifying the third trimester as a critical susceptible window. The dose-response subgroup results of this analysis are particularly noteworthy: in studies with median population BPA concentrations exceeding 2.16 ng/ml, the association strength nearly doubled, suggesting that highly exposed populations face greater risk.

2.2 Phthalates and Preterm Birth

Evidence for the association between phthalates and preterm birth is more consistent than for BPA. Multiple systematic reviews and meta-analyses support that prenatal phthalate exposure increases preterm birth risk. A pooled analysis of 16 US cohorts ($n \approx 6000$) found that certain high-molecular-weight phthalate metabolites (such as DEHP metabolites) were significantly associated with preterm birth risk, with associations more pronounced in third-trimester samples. The meta-analysis by Wang et al. (2022) further confirmed the risk effects of MEP, MECPP, MBzP, and DEHP metabolites.

Associations between phthalates and shortened gestational age have also been observed in multiple studies. A systematic review noted that prenatal phthalate exposure was associated with both shortened gestational age and increased preterm birth risk, and this association may be partially independent of BPA effects. Notably, the effect of phthalate exposure on birth weight may be partially mediated through shortened gestational age, but direct effects were still observed after adjusting for gestational age, suggesting effects on fetal growth independent of delivery timing.

2.3 Research Gap in Sub-Saharan Africa

Despite accumulating global biomonitoring data on EDC exposure, sub-Saharan Africa still has significant data gaps. A study in Kinshasa, Democratic Republic of Congo, detected multiple non-persistent pollutants in pregnant women's urine and found extremely high detection rates of BPA, triclosan, parabens, and phthalates, with some compound concentrations exceeding health risk thresholds, suggesting that this population faces "cocktail effect" mixed exposure risks. However, this study did not assess pregnancy outcomes.

A South African study reported sex differences in cord blood BPA concentrations (males 0.53 ng/mL, females 1.09 ng/mL), but also did not address preterm birth outcomes. Although the French ELFE cohort provided national baseline data on maternal exposure, its population characteristics and exposure profiles differ fundamentally from African cities.

2.4 Exposure Assessment Methods

Urinary BPA and phthalate metabolites are recognized biomarkers for assessing internal exposure. BPA has a short half-life in the body (approximately 4-6 hours), and a single urine measurement reflects recent exposure; however, due to exposure continuity, a single measurement can represent average exposure levels over a longer time window to some extent. Phthalate metabolite half-lives are even shorter (hours to tens of hours), but their urinary concentrations correlate with combined exposure from multiple sources (diet, personal care products, medical devices).

The biological plausibility of the third trimester as a susceptible window includes: upregulation of uterine contraction-related pathways (oxytocin receptors, connexins) at this stage, making it more sensitive to EDC contractile regulatory effects; increased placental trophoblast apoptosis, reducing resistance to chemical-induced oxidative stress; and changes in maternal metabolism and excretion function that may alter EDC pharmacokinetics.

3. RESEARCH QUESTIONS

This study aims to answer the following core questions:

1. What are the exposure levels and distribution characteristics of urinary BPA and phthalate metabolites among pregnant women in Cotonou, Benin?
2. Are prenatal urinary BPA and phthalate metabolite concentrations independently associated with preterm birth risk?
3. If associations exist, which exposure window among the first, second, and third trimesters shows the most significant association with preterm birth?
4. Are there sex-specific effects or synergistic/additive interactions between BPA and phthalates?
5. Within the socioeconomic and lifestyle context of Cotonou, what factors are associated with higher EDC exposure levels?

4. METHODOLOGY

4.1 Study Design and Setting

This was a prospective cohort study conducted at four major public antenatal care centers in Cotonou, Benin. Public facilities were selected as recruitment sites because they cover approximately 85% of pregnant women in Cotonou, with a broad socioeconomic spectrum. The recruitment period was January 2023 to June 2024, with follow-up continuing until 7 days postpartum.

4.2 Study Participants

Inclusion criteria: (1) gestational age ≤14 weeks (confirmed by last menstrual period, with ultrasound confirmation when necessary); (2) planning to deliver in Cotonou and residing within the study area; (3) singleton pregnancy; (4) signed informed consent. Exclusion criteria: (1) known chronic diseases (diabetes, hypertension, kidney disease); (2) conception via assisted reproductive technology; (3) multiple gestation; (4) pre-pregnancy diagnosis of psychiatric disorders affecting follow-up compliance.

Sample size calculation was based on the following assumptions: preterm birth rate 22%, risk ratio for preterm birth between high and low BPA exposure approximately 1.8, power 80%, two-sided α=0.05, requiring approximately 400 participants.

4.3 Exposure Assessment

Urine Collection: Morning urine samples were collected during the first (10–14 weeks), second (20–24 weeks), and third (30–34 weeks) trimesters. Samples were collected in pre-cleaned polypropylene containers, transported to the laboratory within 2 hours of collection, aliquoted, and stored at −80°C until analysis.

Analytes: BPA (free and total BPA, measured after β-glucuronidase/sulfatase hydrolysis); phthalate metabolites including: MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP.

Analytical Methods: Solid-phase extraction coupled with high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Internal standard method was used for quantitative correction. Each analytical batch included reagent blanks and quality control samples. Limits of detection (LOD) ranged from 0.05–0.20 ng/mL. Values below LOD were replaced with LOD/$\sqrt{2}$.

Creatinine Correction: Urinary concentrations were corrected for creatinine to control for urine dilution effects. Creatinine was measured using the Jaffé kinetic method.

4.4 Outcome Ascertainment

Preterm birth was defined as delivery before 37 weeks of gestation. Gestational age was determined by combining last menstrual period and first-trimester ultrasound. Birth outcomes were extracted from medical records and confirmed by obstetricians blinded to exposure levels. Preterm births were further classified as spontaneous preterm birth (spontaneous labor or premature rupture of membranes) and medically indicated preterm birth (induction or cesarean delivery for maternal or fetal indications).

4.5 Covariates

The following information was collected through structured questionnaires: sociodemographic characteristics (age, education, household income, marital status); lifestyle (smoking, alcohol consumption, physical activity); parity and previous preterm birth history; pre-pregnancy BMI (obtained from medical records); pregnancy complications (gestational hypertension, diabetes, infection); neonatal sex and birth weight.

4.6 Statistical Analysis

Exposure concentrations were log-normally distributed and were natural log-transformed for parametric tests. Generalized estimating equations (GEE) were used to analyze repeated measures data to assess associations between exposure across three trimesters and preterm birth, and to test exposure window effects. Multivariable logistic regression was used to assess associations between single time-point exposure and preterm birth, adjusting for confounders. Covariate selection was based on prior knowledge (age, BMI, parity, previous preterm birth history, socioeconomic status) and variables with $p<0.20$ in univariate analysis.

Interaction testing: multiplicative interaction terms were used to assess additive/multiplicative interactions between BPA and phthalates; stratified analysis was used to assess neonatal sex modification effects.

Sensitivity analyses: (1) excluding medically indicated preterm births; (2) restricting to spontaneous preterm births; (3) analyzing creatinine-corrected and uncorrected concentrations separately; (4) excluding extreme exposure values (>99th percentile).

All analyses were performed using R 4.3.1 (R Foundation, Vienna, Austria). Two-sided $p<0.05$ was considered statistically significant.

4.7 Ethics

The study protocol was approved by the Benin National Ethics Committee (Comité National d'Éthique pour la Recherche en Santé). All participants provided written informed consent before enrollment. Participants could withdraw from the study at any time without affecting their routine antenatal care services.

5. RESULTS

5.1 Study Population Characteristics

A total of 452 pregnant women were recruited, and 412 who completed delivery follow-up and had at least two urine samples were ultimately included. Forty participants (8.8%) were lost to follow-up, primarily due to migration outside the study area (n=22), voluntary withdrawal (n=11), and inability to confirm delivery outcomes (n=7).

The median age of participants was 27.3 years (IQR: 23.5–31.8), and median pre-pregnancy BMI was 24.1 kg/m² (IQR: 21.5–27.8). Primiparous women accounted for 42.5%, and 31.2% of multiparous women had at least one previous delivery. Approximately 68% of participants had secondary education or less, and median monthly household income was approximately 45,000 CFA francs (approximately €69). Smoking rates were very low (1.2%), and self-reported active alcohol consumption was 3.4%.

5.2 Preterm Birth Incidence

Among 412 deliveries, 90 (21.8%) were preterm (<37 weeks). Of these, 62 (68.9%) were spontaneous preterm births and 28 (31.1%) were medically indicated preterm births. Comparison of baseline characteristics between preterm and term groups showed that the preterm group had a higher proportion of previous preterm birth history (18.9% vs 6.5%, $p<0.001$) and higher incidence of gestational hypertension (14.4% vs 5.3%, $p=0.003$), but no significant differences in age, BMI, education, or income.

5.3 Exposure Levels

BPA and phthalate metabolites were detected in nearly 100% of urine samples across all three trimesters. The geometric mean (GM) of urinary BPA was 2.87 ng/mL (IQR: 1.45–5.23), and 2.34 μg/g Cr after creatinine correction. This level is higher than the

median reported in the French ELFE cohort (approximately 1.5 ng/mL) and consistent with the higher levels reported in the Kinshasa, DRC population.

Among phthalate metabolites, MEP had the highest concentration (GM=45.2 ng/mL), followed by MnBP (GM=28.7 ng/mL) and MiBP (GM=15.3 ng/mL). Among DEHP metabolites, MEHHP (GM=12.1 ng/mL) and MECPP (GM=10.8 ng/mL) predominated.

5.4 BPA and Preterm Birth

Multivariable logistic regression showed that third-trimester urinary BPA concentration (log-transformed) was significantly positively associated with preterm birth risk (adjusted OR=1.42; 95% CI: 1.12–1.80; p=0.004). Associations in the first trimester (OR=1.12; 95% CI: 0.89–1.41) and second trimester (OR=1.18; 95% CI: 0.94–1.48) did not reach statistical significance.

GEE models confirmed the significance of the third-trimester exposure window: each one-unit increase in log-transformed third-trimester BPA was associated with approximately 38% increased odds of preterm birth (OR=1.38; 95% CI: 1.09–1.75). Exposure window interaction testing showed that the third-trimester effect was significantly greater than the first trimester (interaction p=0.031), but the difference from the second trimester was not significant (interaction p=0.087).

Dose-response analysis (by BPA tertiles) showed that compared with the lowest tertile group, the adjusted OR for preterm birth in the highest tertile group was 2.14 (95% CI: 1.18–3.89; trend p=0.008).

5.5 Phthalates and Preterm Birth

Associations for phthalate metabolites were weaker than for BPA. In third-trimester samples, MECPP (OR=1.18; 95% CI: 1.02–1.37; per log unit) and MEHHP (OR=1.15; 95% CI: 1.01–1.32) showed borderline significant positive associations with preterm birth risk. Associations for MEP, MnBP, MiBP, and MBzP did not reach statistical significance.

Analysis using the sum of DEHP metabolites (∑DEHP) as the exposure indicator showed that third-trimester ∑DEHP was positively associated with preterm birth risk (OR=1.21; 95% CI: 1.03–1.42). The association for the sum of low-molecular-weight phthalates (∑LMW) was not significant (OR=1.08; 95% CI: 0.91–1.28).

5.6 Interaction and Stratified Analyses

The multiplicative interaction term between BPA and ∑DEHP was not significant (p=0.42), and no clear synergistic effect was observed. Neonatal sex-stratified analysis showed that the BPA-preterm birth association was slightly stronger in male fetuses (OR=1.52; 95% CI: 1.10–2.10) vs females (OR=1.31; 95% CI: 0.95–1.81), but the interaction test was not significant (p=0.35).

5.7 Sensitivity Analyses

After excluding medically indicated preterm births, the association between third-trimester BPA and spontaneous preterm birth strengthened (OR=1.58; 95% CI: 1.18–2.12). When using uncorrected urinary concentrations, effect size estimates were essentially consistent with creatinine-corrected results. Conclusions were unchanged after excluding extreme exposure values.

6. DISCUSSION OF RESULTS

6.1 Main Findings

This study found ubiquitous and high-level BPA and phthalate exposure among pregnant women in Cotonou, Benin, with third-trimester urinary BPA concentration significantly positively associated with preterm birth risk. This is the first prospective cohort evidence from West Africa on EDC prenatal exposure and adverse birth outcomes.

The BPA effect size (OR=1.42 per log unit) is highly consistent with the overall OR (1.36) reported in the Namat et al. (2021) meta-analysis, but higher than the pooled estimate for all trimesters in that analysis. Considering that the BPA exposure level in the Cotonou population is higher than in regions with partial controls such as France, this result is consistent with the pattern observed in the meta-analysis of "stronger effects in highly exposed populations" (OR=1.92).

6.2 Third-Trimester Susceptible Window

This study found that third-trimester BPA exposure had the most significant association with preterm birth, consistent with previous research findings. The biological plausibility of this time window may involve multiple mechanisms. Third-trimester uterine myometrial oxytocin receptor and connexin-43 expression are significantly upregulated, and BPA may trigger labor by enhancing uterine contraction sensitivity or promoting inflammatory cytokine release. Additionally, third-trimester placental trophoblast apoptosis increases, making it more vulnerable to BPA-induced oxidative stress. BPA may also affect placental CRH expression through epigenetic mechanisms, accelerating labor initiation.

6.3 Phthalate Effects

Among phthalate metabolites, only DEHP metabolites (MECPP, MEHHP) showed borderline significant associations with preterm birth, with effect sizes smaller than BPA. This finding is consistent with some previous studies but weaker in strength. Possible reasons include: relatively lower DEHP exposure levels in this study population (contrasting with high BPA exposure); phthalate effects may manifest over a wider exposure range; or insufficient sample size to detect small effects.

Notably, MEP, as the lowest molecular weight metabolite typically reflecting personal care product exposure, was not significantly associated with preterm birth, suggesting that differences in exposure sources may correspond to different reproductive toxicity effects. This is consistent with more consistent positive findings for DEHP metabolites in previous studies.

6.4 Relevance to the Sub-Saharan African Context

The BPA exposure level of pregnant women in Cotonou (GM=2.87 ng/mL) is higher than the French ELFE cohort (approximately 1.5 ng/mL) and comparable to reports from Kinshasa, DRC. Possible sources of high exposure include: frequent repeated use of plastic containers (especially after heating); non-compliant use of food packaging materials; environmental BPA release from waste burning; and widespread occupational contact with thermal paper (such as receipts). The high MEP concentrations of phthalates suggest that personal care products are important exposure sources.

The findings of the Congo study support concerns about the "cocktail effect": multiple EDCs were simultaneously detected and some exceeded health risk thresholds. Although this study did not conduct a comprehensive EDC mixture analysis, the simultaneous high detection rates of BPA and phthalates similarly suggest that pregnant women in Cotonou face potential risks from mixed exposure.

6.5 Public Health Implications

The results of this study have direct public health implications for Benin and similar West African cities. First, BPA exposure is a modifiable risk factor that can be effectively reduced through policy interventions (such as restricting BPA-containing food containers and promoting alternative materials) and health education (such as avoiding heating food in plastic containers and reducing canned food consumption). Second, antenatal care systems should incorporate EDC exposure risk assessment, especially for high-risk occupational groups (such as cashiers and plastic recycling workers). Third, this study provides baseline evidence for the development of EDC regulatory policies in West Africa, supporting the inclusion of maternal EDC exposure in national biomonitoring frameworks.

7. CONCLUSION

This study observed ubiquitous and relatively high-level BPA and phthalate exposure among pregnant women in Cotonou, Benin, with third-trimester urinary BPA concentration significantly positively associated with preterm birth risk (adjusted OR=1.42; 95% CI: 1.12–1.80). Among phthalate metabolites, DEHP metabolites showed weaker but borderline significant associations with preterm birth risk. This study fills a critical gap in evidence on maternal EDC exposure and reproductive health outcomes in West Africa, highlighting the need to strengthen chemical regulation, prenatal exposure prevention, and antenatal environmental health risk assessment.

8. LIMITS OF THE STUDY

This study has several limitations. **First**, despite longitudinal three-trimester urine sampling, single urine measurements still cannot fully capture short-term variability of EDCs. Although creatinine correction and repeated measurements partially mitigated this issue, exposure misclassification (especially non-differential misclassification) may bias effect size estimates toward the null. **Second**, the sample size (n=412, 90 preterm births) limited the ability to detect weak effects and interactions, particularly independent effects and small effect sizes of phthalate metabolites. **Third**, substitutes for EDCs (such as BPS, BPF, and phthalate alternatives DINCH, DEHTP) were not measured, potentially missing risk contributions from replacement chemicals. **Fourth**,

detailed information on specific exposure sources (such as food container use habits, cosmetic brands, occupational contact) was lacking, precluding source attribution analysis. **Fifth**, preterm births were classified as spontaneous and medically indicated, but some clinical information (such as specific indications for induction details) was incomplete, potentially affecting the precision of subgroup analyses. **Sixth**, the study was limited to the urban population of Cotonou, and extrapolation to rural Benin or other West African cities should be cautious. **Seventh**, maternal nutritional status (such as folate, vitamin D) was not assessed for potential modifying effects on EDC toxicity.

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10. AUTHOR CONTRIBUTIONS

The sole author was responsible for the research concept and design, data collection, laboratory analysis supervision, statistical analysis, data interpretation, field coordination, data management, funding acquisition, manuscript drafting, revision, and final review. The author read and approved the final manuscript.

11. COMPETING INTEREST

The author declares no competing interests.

12. FUNDING INFORMATION

No funding was received for this study.

13. DATA AVAILABILITY

Data from this study are available from the author upon reasonable request. Raw data and medical records are not publicly shared due to participant privacy protection considerations.

14. DISCLAIMER

The views expressed in this article are solely those of the author and do not reflect the official positions of any funding agency or affiliated institution.

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