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Bisphenol chemicals in colostrum from Shanghai, China during 2006–2019: Concentration, temporal variation, and potential influence on birth parameters

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ABSTRACT

Bisphenol A (BPA) and its alternatives bisphenol S (BPS) and bisphenol F (BPF) are identified as endocrine disruptors that have negative impacts on infant growth. Their temporal variations in human milk and potential effects on fetal growth are not well known. In this study, colostrum collecting at four time points between 2006 and 2019 and paired urine in 2019 from Shanghai, China, were analyzed for eight bisphenols. The total concentrations in colostrum in 2019 were up to 3.43 ng/mL, with BPA being dominant, followed by BPS and BPF. BPA levels in colostrum noticeably decreased from 2010 to 2013. Additionally, obvious percentage changes in bisphenols were observed in 2019. The BPA concentrations in paired colostrum and urine were not significantly correlated. High levels of BPA in colostrum were linked to a significant reduction in birth head circumference in 2019 ($p = 0.031$). BPA and BPS in colostrum might have similar negative effect on fetal growth in 2019, but these effects were generally non-significant. Further studies are needed to testify the potential impact. The hazard indexes for infants in the first week of life were below 1, suggesting no obvious health risks. However, the high contribution from BPA still warrants further attention.

1. Introduction

Bisphenol A (BPA) is a type of endocrine disruptor with a bisphenol structure (Iyigündogdu et al., 2020; Lee et al., 2016). Through several implemented regulations, its usage has been prohibited or limited in the European Union (EU), China, and other countries since 2011 (Casas et al., 2016; Ye et al., 2015). In response to the restrictions, various BPA analogs like bisphenol AF (BPAF), bisphenol S (BPS), bisphenol B (BPB), and bisphenol F (BPF), which share a similar base structure of BPA, are widely used in food packaging, thermal paper receipts, and other consumer products (Chen et al., 2016). Currently, the BPA analogs were ubiquitously detected in sediments, surface water, indoor dust, and various human fluids, indicating their extensive usage (Huang et al., 2023; Li et al., 2021; Liu et al., 2021; Lu et al., 2018; Zhang et al., 2019).

Toxicology studies have revealed that BPA analogs may exhibit similar toxic effects as BPA (Lei et al., 2019; Pelch et al., 2019; Zhang et al., 2019). For example, an increased risk of type 2 diabetes mellitus was found to be related to BPS and BPAF, and a positive correlation was observed between asthma and urinary BPF in adults (Duan et al., 2018; Mendy et al., 2020). The substitutes for BPA are not necessarily safer. BPS, BPF, and BPAF have been included in the EU's latest list of endocrine-disrupting chemicals in 2021, and BPS has been regulated by the US Environmental Protection Agency (Catenza et al., 2021). As bisphenols (BPs) can directly cross the placenta (Cantonwine et al.,

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2015; Li et al., 2019), the potential health risks to fetuses are of particular concern (Hu et al., 2019; Pelch et al., 2019; Yang et al., 2021). Some studies have linked BPA exposure during pregnancy to adverse birth outcomes and parameters (Cantonwine et al., 2015; Huo et al., 2015; Jin et al., 2020). However, the reported adverse effects of BPA in epidemiological studies were not always consistent, and the potential effects of BPA analogs have been less discussed (Hu et al., 2019; Yang et al., 2021). More epidemiological data are needed to examine the possible prenatal effects.

Human milk is an important biological matrix that directly reflects the cumulative exposure of both nursing infants and mothers. Recent studies identified BPA as the primary compound, followed by BPS or BPF in human milk. Their concentrations ranged from below the limit of detection (LOD) to several dozen nanograms per milliliter (Jin et al., 2020; Mercogliano and Santonicola, 2018; Niu et al., 2021). Regional variations in contamination levels were always suggested (Dualde et al., 2019; Zimmers et al., 2014). Colostrum is unique milk produced in the initial days after childbirth. Few studies were conducted to investigate the presence of BPA analogs in colostrum and the potential temporal variations in their levels.

Urine samples from mothers were commonly used for BPs detected. The concentrations in urine were usually 2–10 times higher than those in human milk (Hines et al., 2015; Lee et al., 2018a; Li et al., 2019). Limited evidence suggested a significant correlation between maternal urine and milk for BPA (Lee et al., 2018a). Investigation examining the differences between urine and human milk characteristics is still lacking (Arbuckle et al., 2015; Lee et al., 2018a). Temporal variations in urinary BPA concentrations among the general population were usually observed (Frederiksen et al., 2020; Gys et al., 2020). The BPA levels in male adults declined nearly 10 % per year during 2009–2017 in a Danish study (Frederiksen et al., 2020).

In previous studies, prenatal exposure has primarily estimated based on single or repeated urinary measurements (Cantonwine et al., 2015; Li et al., 2019). However, the reproducibility of urinary BPA or BPS concentrations during pregnancy has been questioned (Hu et al., 2019; Vernet et al., 2018). Alternatively, colostrum has the potential to serve as a biomonitoring matrix, reflecting the maternal body burden towards the end of pregnancy (Guo et al., 2021). The effects of colostrum exposure to BPs were seldom discussed (Jin et al., 2020). Thus, further studies are needed to assess the influence of colostrum exposure on birth outcomes.

In the present study, we hypothesized that there were temporal variations of BPs in colostrum due to the usage and prohibition of certain BP species in the past few years, and colostrum exposure to some BPA analogs may affect fetal growth. Therefore, 130 colostrum samples at four time points between 2006 and 2019 were collected, and 43 paired urine samples in 2019 were obtained simultaneously. The concentrations of BPs in colostrum were measured and compared. And the correlation between colostrum and urine was analyzed. Finally, the potential effects of colostrum exposure to BPs on neonates were preliminarily investigated and health risks for infants were assessed. This study aimed to provide insights into the temporal variation of BPs in human milk in China and the potential effects on birth outcomes.

2. Materials and methods

2.1. Standards

Eight target BPs, BPA, BPF, BPAF, BPS, BPB, bisphenol AP (BPAP), bisphenol E (BPE), and bisphenol BP (BPBP) were purchased from Accu Standard (New Haven, CT, USA). Labeled BPA-d_{16}, BPF-d_{10}, BPS-d_4, and BPAF-d_4, were from Cambridge Isotope Laboratories (Andover, MA, USA) and used as recovery standards and internal standards, respectively.

2.2. Sampling and information collection

A total of 130 colostrum samples from volunteers were collected within 3–5 days after delivery at four time points between 2006 and 2019. The sample number was 20 in 2006, 19 in 2010, 20 in 2013, and 71 in 2019. In 2019, 10 mL urine samples were also collected on the same day that paired with 43 of the 71 colostrum samples. The colostrum and urine samples were stored at −20 °C before analysis. The volunteers, who had lived in Shanghai for at least 3 years, were randomly recruited by their gynecologists and midwives during the delivery period at two hospitals in the urban area of Shanghai. Mothers with potential occupational exposure were not included. All samples and data were processed blindly, although selection bias could not be excluded. This study was approved by the ethics committees of the two hospitals, and all volunteers signed informed consent forms.

During sampling, information of mothers such as age, parity, occupation, and smoking habits were recorded using a questionnaire. Infant sex, birth weight and birth length were retrieved from medical records. The number of infants participated in the survey was 72 in 2019 (including a single pair of fraternal twins), 20 in 2013, 19 in 2010, and 20 in 2006 (**Table 1**). Among the survey, little information in 2019 was lost. However, the information of infants in 2006, and the parameters on birth length and head circumference in 2010 were not collected. Maternal body mass index (BMI, kg/m^2) was calculated based on weight and height squared. Ponderal index (PI, g/cm^3) was calculated as birth weight divided by the cube of birth length.

2.3. Sample treatment protocols

The colostrum samples were extracted using a modified method described by Zimmers et al. (2014). In brief, after spiking with 1.2 ng BPA-d_{16}, 1.2 ng BPS-d_4, and 0.30 ng BPAF-d_4, 3.0 mL of colostrum was subjected to protein precipitation and extraction process using acetonitrile. The supernatants were concentrated, dissolved in a methanol/-water solution (1:8, v/v), and purified using a Poly-Sery HLB cartridge (60 mg/3 mL; CNW, Germany). The cartridge was rinsing with methanol/water (1:1, v/v), dichloromethane and methyl tert-butyl ether. And the final eluent was concentrated, added with 1.2 ng BPF-d_{10}, and reconstituted in 30 μL methanol. The resulting solution was then analyzed using UPLC-MS/MS.

The urine samples were pretreated following the method described in our previous study with some modifications (Li et al., 2021). A 2.0 mL urine sample was mixed with β-glucuronidase and incubated at 37 °C for 12 h. Afterword, combined with internal standards and adjusted to pH < 2.5, this mixture was loaded onto a Poly-Sery HLB cartridge. The cartridge was rinsed sequentially with KH_2PO_4 solution and ultrapure water, and eluted with methanol/dichloromethane (1:1, v/v). The eluent was concentrated and dissolved in 30 μL methanol, with the addition of 1.2 ng BPF-d_{10}. Finally, the samples were analyzed by UPLC-MS/MS.

2.4. Instrumental analysis

The target compounds were analyzed by an LC-Agilent Technologies 1290 Infinity UPLC-MS/MS (MS-AB SCIEX QTRAP 4500; Santa Clara, CA, USA). A Technologies Eclipse Plus C_{18} column (100 × 2.1 mm, 2.7 μm, Agilent) was used. The mobile phase, consisting of methanol (A) and water (B), was programmed accordingly with a flow rate of 0.4 mL/min. Multiple reaction monitoring mode (MRM) and electrospray ionization in the negative were used for quantification. Details of MRM transitions and instrumental conditions are listed in Table S1.

2.5. Estimated daily intake and health risk assessment of exposure to BPs

The estimated daily intake (EDI, ng/kg bw/day) for infants in the first week after birth was estimated using the following equation:

Table 1
Anthropometric and socioeconomic information of mothers and neonates [mean ± SD or N (%)].

Characteristic	2019 (n = 71)	2013 (n = 20)	2010 (n = 19)	2006 (n = 20)	All (n = 130)
Mothers					
Age (years)	29.6 ± 3.2	29.0 ± 3.3	29.4 ± 3.1	27.4 ± 3.2	29.1 ± 3.3
≤30	43 (61)	16 (80.0)	14 (74)	17 (85.0)	90
>30	28 (39)	4 (20.0)	5 (26)	3 (15.0)	40
BMI[a] (kg/m^2)	20.4 ± 6.7	21.4 ± 2.5	/	/	22.1 ± 2.6
<25	53 (74.6)	18 (90.0)	/	/	71
≥25	12 (16.9)	2 (10.0)	/	/	14
Information lost	6 (8.5)	0	/	/	45
BMI[b] (kg/m^2)	27.8 ± 2.9	27.6 ± 2.6	26.9 ± 2.7	/	27.6 ± 2.8
<25	14 (19.7)	4 (20.0)	5 (26.3)	/	23
≥25	55 (77.5)	16 (80.0)	14 (73.7)	/	85
Information lost	2 (2.8)	0	0	/	22
Parity					
Primipara	36 (50.7)	19 (95.0)	15 (78.9)	/	70
Multipara	27 (38.0)	1 (5.0)	4 (21.1)	/	32
Information lost	8 (11.3)	0	0	/	28
Education					
Under college	15 (21.1)	13 (65.0)	/	/	28
College and above	53 (74.6)	7 (35.0)	/	/	60
Information lost	3 (4.2)	0	/	/	42
Infants					
Male	38 (52.8)[c]	13 (65.0)	11 (57.9)	/	62[c]
Female	33 (45.8)[c]	7 (35.0)	8 (42.1)	/	48[c]
Information lost	1 (1.4)	0	0	/	21
Birth weight (g)	3287 ± 409	3298 ± 301	3422 ± 420	/	3306 ± 374
Infants	71 (98.6)	20 (100)	15 (78.9)	/	106
Information lost	1 (1.4)	0	4 (21.1)	/	25
Birth length (cm)	49.3 ± 1.5	50.0 ± 0.7	/	/	49.4 ± 1.6
Infants	65 (90.3)	20 (100)	/	/	85
Information lost	7 (9.7)	0	/	/	46
Head circumference (cm)	34.5 ± 1.1	33.1 ± 1.0	/	/	34.2 ± 1.3
infant	65 (90.3)	20 (100)	/	/	85
Information lost	7 (9.7)	0	/	/	46
PI[d] ($*10^{-2}$ g/cm^3)	2.73 ± 0.20	2.65 ± 0.28	/	/	2.71 ± 0.22
Infants	65 (90.3)	20 (100)	/	/	85
Information lost	7 (9.7)	0	/	/	46

[a] Pre-pregnancy body mass index.
[b] Pregnancy body mass index before deliveries.
[c] Including a single pair of fraternal twins.
[d] Ponderal index;/: not available.

$$EDI = C \times MCR \quad (1)$$

where C (ng/mL) is the median or 95th percentile concentration of target species in colostrum from 2019; MCR (mL/kg bw/day) was the mean value of milk intake rate in age of first week, which was 150 mL/kg bw/day (Gao et al., 2021).

To assess the potential health risks of the BPs, a hazard quotient (HQ, dimensionless) was calculated as follows:

$$HQ = \frac{EDI}{TDI} \quad (2)$$

$$HI = \Sigma HQ \quad (3)$$

Where TDI (μg/kg bw/day) is the tolerable daily intake. The temporary tolerable daily intake (*t*-TDI) of BPA (4 μg/kg bw/day) recommended by European Food Safety Authority (EFSA) in 2015 was used. The *t*-TDI was mainly based on the renal toxic effects observed in multiple generations of mice reproductive toxicity studies following oral exposure of BPA (EFSA, 2015). The TDI values for BPA analogs, such as BPS and BPF, were set at the same molar levels as the *t*-TDI of BPA, which were 4.4 and 3.5 μg/kg bw/day, respectively (Lyu et al., 2023). In addition, a hazard index (HI) was used to estimate the total risks of the chemicals and calculated as the sum of HQ values of each BP species. If the HQ or HI value exceeds 1, it indicates potential health risk associated with the exposures to BPs.

To quantify uncertainty and variability in the assessment, a Monte Carlo simulation was conducted. The health risk cumulative frequency distribution from BP exposure was calculated by repeated sampling in the fitted distribution function of the exposure variable (Qu et al., 2015). In the simulation, the milk concentrations of all BPs, or BPA, BPS, or BPF, were used as the variables. The 95 % confidence intervals (CI) for health risks were calculated using 50,000 trials in Crystal Ball (Oracle, Redwood City, CA, USA). A sensitivity analysis was also performed using Crystal Ball software. The probability distributions of colostrum concentrations of BPs were set as lognormal distributions, and MCR was set as uniform distribution.

2.6. Quality assurance and quality control

The laboratory took several measures to avoid potential contamination. To monitor potential contamination, procedural blanks were run for every batch of 12–15 samples. The average spiked recoveries were 69.4 ± 17.7 %. The concentrations were not corrected on the basis of recoveries. The concentrations of BPA, BPAP, and BPAF were determined by subtracting the background levels. The linear regression coefficients were higher than 0.99 for the calibration curves (**Table S2**). The LODs of BPs were 0.001–0.06 ng/mL, and the limits of quantification (LOQs) were assumed to be two times of LODs.

2.7. Statistical analysis

IBM SPSS Statistics 23.0 software was used for data analysis. Spearman's correlation test was conducted to determine the concentration correlation. The differences among samples were analyzed using ANOVA, Mann–Whitney *U* test, or Kruskal-Wallis H test, depending on the specific circumstances. A statistical significance threshold was set as $p < 0.05$. When the measured concentration was below LOD, it was set as 0 in concentration calculation and composition analysis. However, when calculating concentration ratios and performing statistical analysis, the concentration below LOD was set as $LOD/\sqrt{2}$ as a denominator. If the concentration was below LOQ, it was treated as 1/2 LOQ in the analysis.

Based on the colostrum concentrations in 2019, three groups for BPA or BPA analogs were categorized. The first group, referred to as the low exposure group, consisted of mothers whose milk BPA or BPA analog concentrations fell within the lower quartile (0–25th percentile). The second group, known as the high exposure group, included mothers whose concentrations were within the upper quartile (75th–100th percentile). The remaining mothers were assigned to the medium exposure group. For BPS, three exposure groups were also categorized. Women with milk BPS concentrations below or equal to LOD were classified as no exposure group. Those with milk BPS concentrations in the upper quartile were categorized as the high exposure group. Mothers with milk BPS concentrations below the 75th percentile but above the LOD were placed in the medium exposure group. As for mothers in 2013, two exposure groups were established. The first group referred to as the no exposure group, included mothers with colostrum concentrations below or equal to LOD. The second group known as the exposure group, consisted of mothers with colostrum concentrations above LOD.

3. Results and discussions

3.1. Characteristics of study populations

The detailed anthropometric data of the survey are shown in Table 1. The mean ages in each sampling period were close, 27.4 years in 2006, 29.4 years in 2010, 29.0 years in 2013, and 29.6 years in 2019. The overall average age was 29.1 years. The BMI values before pregnancy were 17.6–29.3 kg/m^2, and the BMIs before delivery were 22.5–35.5 kg/m^2. The male to female ratio of neonates was 62:48, and there was a single pair of fraternal twins and a loss of gender information in 2019. The averaged birth weight and birth height were 3306 ± 374 g and 49.4 ± 1.6 cm, respectively. The averaged PI of neonates was (2.71 ± 0.22) × 10^{-2} g/cm^3 (**Table 1**).

3.2. Concentrations and composition profiles of BPs in colostrum

The examined compounds with >50 % detection frequencies were BPA (86.2 %) and BPS (62.3 %). BPF, BPAF, and BPAP were found in 29, 27, and 18 of all colostrum samples, respectively. BPB and BPE were sporadically detected, while BPBP was not found in any samples (Table S3). At least two target compounds were detected in 53 of 71 in 2019. The concentrations of total BPs (ΣBPs) ranged from <LOD to 67.82 ng/mL (Table S3). BPA (<LOD to 67.77 ng/mL, median: 0.16 ng/mL) and BPS (<LOD to 0.43 ng/mL, median: 0.03 ng/mL) usually had higher concentrations compared with the others. In addition, high detectable concentrations of BPF (0.05−0.55 ng/mL) were also observed in some colostrum samples. Variable median BPA concentrations (0.10−1.47 ng/mL) were reported in human milk from Europe, Canada, South Korea, Japan, and China (Table S4). The present results were lower than those in the previous studies. On the contrary, the present BPS levels were higher than those in Spain (from <LOQ to 0.37 ng/mL) (Dualde et al., 2019), and in China (from <LOD to 1.3 ng/mL, median: <LOQ) (Jin et al., 2020; Luo et al., 2020; Niu et al., 2021). However, the present BPF concentrations were comparable to those in previous studies, despite limited data on BPF in human milk. As reported by Niu et al. (2021), the median BPF concentration in human milk from China in 2014 was 0.051 ng/mL. In a study conducted in Spain, the milk concentration of BPF ranged from <LOQ to 0.46 ng/mL (Dualde et al., 2019). China and EU have banned the use of BPA in the production of baby bottles since 2011, and set a specific migration limit for BPA in food contact materials since 2016. The EU also categorized BPA as a Substance of Very High Concern under the REACH regulation, and restricted the use of BPA in other food contact materials (ECHA, 2017). The different regulations and usage patterns (Chi et al., 2023) may account for much of this regional variation.

Among the target substances, BPA was the most dominant species, accounting for 68.1 % of the ΣBPs. BPS and BPF were the second most important species, accounting for 23.6 % of the total BPs. Although the application for BPA has been forbidden in many products (Chen et al., 2016; Liao and Kannan, 2013), it was still the predominant BP observed in global human milk (Dualde et al., 2019; Jin et al., 2020). Following the prohibition of BPA in certain products, BPS and BPF became widely used as alternatives in various industrial and consumer products (Pelch et al., 2019). These alternatives can be detected in food, indoor dust, drinking water, serum, human milk, and urine (Gao et al., 2021; Liu et al., 2021; Zhang et al., 2019). Dietary sources are usually identified as the highest contributor to human exposure (Liu et al., 2018), and inhalation intake remains important (Sasso et al., 2020). Although the concentrations of BPF and BPS were lower compared with BPA in the present study, they still represented a significant proportion of the BPs. This highlights the presence of BPs in human milk and the importance for continually monitoring.

3.3. Temporal variations of BPs in colostrum

There were noticeable changes in colostrum around 2010–2013. Obvious decrease in BPA concentrations and ΣBPs between 2006–2010 and 2013–2019 were observed (Fig. 1). The median BPA concentrations were nearly 16−29 times lower in 2013 and 2019 (0.11−0.12 ng/mL) than in 2006 and 2010 (1.94−3.18 ng/mL), and the highest ΣBPs was found in a colostrum sample from 2006. A significant decline in the percentage of BPA was also identified, with a decrease from 90.3 % to 93.1 % (in 2006 and 2010) to 47.7 %–53.6 % (in 2013 and 2019) (Fig. 2A). The median values of concentration ratios of BPS + BPF to BPA ($R_{(BPS + BPF)/BPA}$) were 0.60 and 0.46 in 2013 and 2019, respectively; while in 2006 and 2010 were 0.01–0.02 (Fig. 2B). There was a significant change in $R_{(BPS + BPF)/BPA}$ from 2010 to 2013 (Mann–Whitney U test, $p < 0.01$).

To our knowledge, no longitudinal study has been carried out to understand the time trends of BP contamination in milk. However, urinary BPA levels have been reported to decrease significantly over time. The concentrations of BPA in urine from Japanese school children (n = 396) showed a significant decrease of 6.5 % annually from 2012 to 2017 (Gys et al., 2020). Similarly, in the general population of European countries (n = 300), Frederiksen et al. (2020) observed a progressive decline in BPA concentration over the past decade. The decline in urine levels of BPA is consistent with the present result in colostrum. This phenomenon would be attributed to the growing concerns about the harmful effects of BPA, and resulting in reduced usage and legislative restrictions in some regions (Gyllenhammar et al., 2017). A Chinese study detected BPs in human milk in 2014, and a value of 0.30 for $R_{(BPS + BPF)/BPA}$ was proposed based on average concentrations (Niu et al., 2021). In other Chinese studies conducted around 2018, the calculated concentration ratio of BPS to BPA in human milk ranged from 0.076 to 0.13 (Jin et al., 2020; Luo et al., 2020). A slight low level of BPS derivative was found (Luo et al., 2020). The increase in $R_{(BPS + BPF)/BPA}$ after 2013 could be attributed to the regulation of BPA since 2011 and the widespread use of BPA alternatives. The production and use of BPS and BPF have significantly increased in recent decades, leading to high concentrations of these alternatives in the environment (Catenza et al., 2021). BPS and BPF have similar toxic effects on infants as BPA (Hu et al., 2019). The temporal variation in BPS and BPF levels in colostrum and the associated exposure through breastfeeding should be a cause for concern.

Additionally, the distribution patterns of BPA analogs in 2019 were

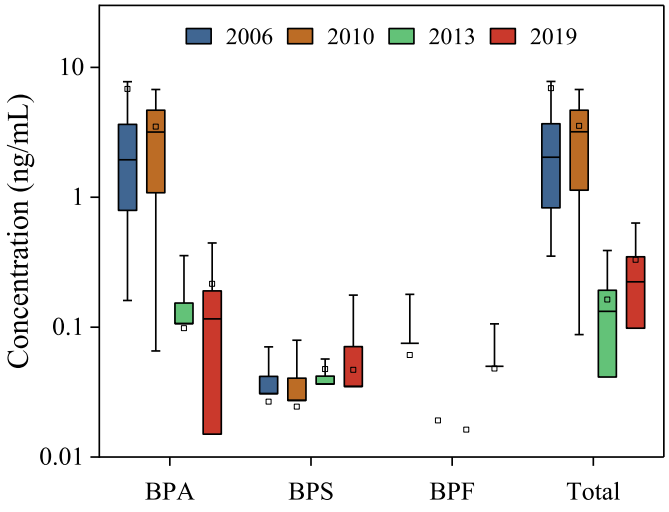

Fig. 1. Concentrations of bisphenol A and its main analogs in colostrum samples. Boxes show the interquartile ranges; the square and center line in the boxes show the median and mean levels, respectively; and upper and lower whiskers show the 95th and 5th percentiles, respectively.

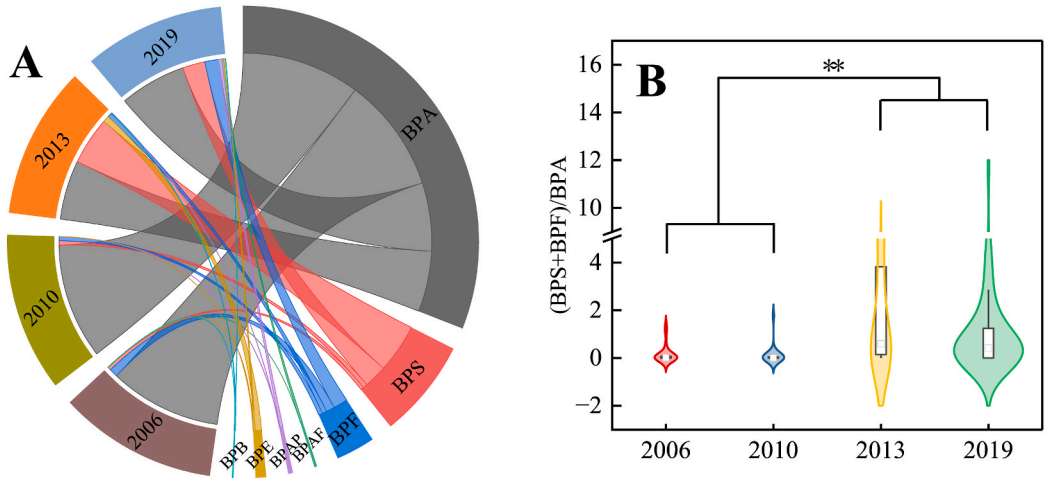

Fig. 2. Time variations on concentration percentages (A) and concentration ratios (B) in colostrum samples. **Mann–Whitney *U* test, $p < 0.01$. The boxes show the interquartile ranges, and the upper and lower whiskers show the 95th and 5th percentiles, respectively.

significantly different from those in 2013. In 2019, out of 71 samples, 33 (46.5 %) were found to contain two or more BPA analogs, which was higher compared with 2013, where only two of 20 samples (10 %) showed their presence (**Table S3**). Several detectable BPAF and BPAP were additionally identified in 2019. The averaged percentages for BPF, BPAF, and BPAP in 2019 were also increased, which were 11.3 %, 1.6 %, and 2.4 %, respectively (Fig. 2). This phenomenon suggested that the distribution of BPA analogs in colostrum were variable during 2013–2019. There was a concentration increase in urinary BPE in Japan during 2009–2016 (Lyu et al., 2023). And Ye et al. (2015) reported a significant increase in BPS exposure but no change in BPF exposure among U.S. adults from 2000 to 2014. The composition of BPs in human exposure has become increasing complex in recent years (Luo et al., 2020). These alternatives may exhibit similar or even more potent estrogenic activities than BPA. Research had linked these compounds to various health issues, including cardiovascular diseases, diabetes, obesity, and childhood asthma (Ji et al., 2022; Rochester and Bolden, 2015). More research is needed to determine if the changing trends over time continue.

3.4. Levels of BPs in paired colostrum and urine and associated correlations

A total of 43 urine samples paired with partial colostrum samples in 2019 were collected and analyzed. The frequently detected species in urine were BPA, BPF, BPS, and BPAF, with detection frequencies exceeding 60 %. Among these, BPA remained the most predominant compound, followed by BPS and BPF. The median levels declined as BPA, BPS, BPF, and BPAF, with concentrations of 2.12, 1.09, 0.81, and 0.01 ng/mL (corresponding to 4.49, 1.80, 0.88, and 0.02 μg/g creatinine), respectively (**Table S5**), while the median concentration in related colostrum samples was 0.09 ng/mL for BPA, 0.01 ng/mL for BPS, and <LOD for BPF. Compared with the levels found in colostrum samples, the presence and concentrations of these compounds in urine were obviously higher (Fig. 3). The urine BPs concentrations were approximately 4–610 times higher than those in colostrum. And the relative order of the top three BPs in urine was similar with that in colostrum samples.

Nonetheless, no significant correlation was found between the concentrations of BPA and ∑BPs in paired urine and milk samples (Spearman's test, $p > 0.05$), with an exception of BPS (Spearman's test, $p < 0.01$). Studies conducted in Korea and the USA also reported no significant correlation between urine and human milk concentrations of BPA (Hines et al., 2015; Lee et al., 2018a). BPs is rapidly excreted through the urinary route, and the elimination of conjugates, such as

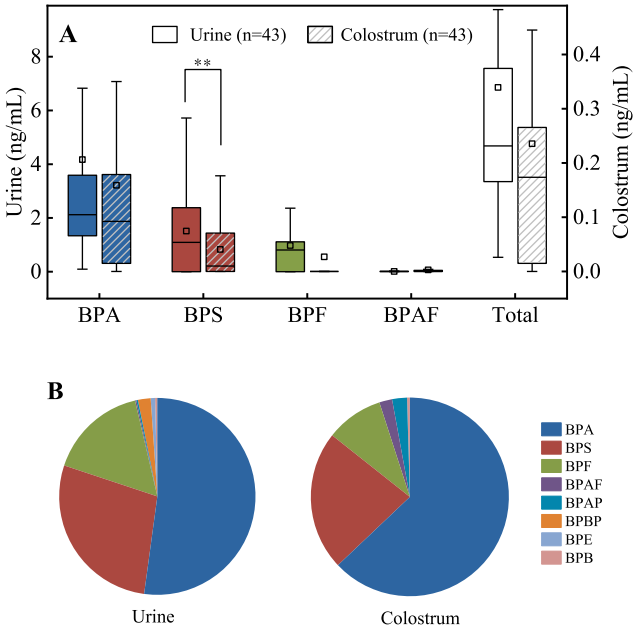

Fig. 3. Comparisons of concentrations (A) and distributions (B) in paired urine and milk samples. The boxes show the interquartile ranges; the square and center line in the boxes show the median and mean levels, respectively; and the upper and lower whiskers show the 95th and 5th percentiles, respectively. **: Spearman's test, $p < 0.01$).

BPA-glucuronide or BPA-sulfate, largely occurs within 24 h (Thayer et al., 2015). The half-life of BPA in urine typically ranges from a few hours to one day (Thayer et al., 2015). However, the estimated half-life of BPA in milk is generally long, ranging from several hours to days or even weeks (Sasso et al., 2020; Stahlhut et al., 2009). BPs in paired colostrum and urine samples in this study may provide insights into maternal exposure at different time points. The concentrations of BPs in urine collected after delivery are more closely related to maternal postpartum exposure. The colostrum, which is produced from mid-pregnancy to the first few days after giving birth, would provide an indication of maternal exposure during the last month of pregnancy (Gao et al., 2021; Migeot et al., 2013). In addition, individual variability may also impact the lack of BPA concentration correlation.

The concentration ratios between paired human milk and urine (M:U

ratios) were analyzed. In sample pairs with both detectable concentrations, the concentration ratios (M:U ratios) ranged from 0.003 to 0.85 (median: 0.056) for BPA and from 0.004 to 0.078 (median: 0.042) for BPS (Table S6). The ratios fluctuated over a large range. Previous reports provided limited data on M:U ratio. In an epidemiological study with a small sample size (n = 10), the ratios of BPA ranged from 0.125 to 1. In a Korean study with 160 mother-fetus pairs, the geometric mean ratios of human milk-to-maternal serum and maternal urine-to-maternal serum for BPA were 0.51 and 2.23, respectively (Lee et al., 2018a). Thus, the M:U ratio was calculated as 0.23 in that study, which was higher than the present results. Higher ratios of BPA were observed compared with BPS in the present study, suggesting that BPS is more readily excreted in urine and less likely to accumulate in human milk. The higher hydrophilicity of BPS compared to BPA may explain the observed findings, as it enables BPS to be more easily eliminated from the body through urine.

3.5. Influence of colostrum exposure to BPs on birth parameter

Colostrum could reflect the body burden of pregnant women during the latter half of the third trimester of pregnancy (Migeot et al., 2013). A negative correlation between the concentration of PCB 77 in colostrum and birth head circumference was suggested (Guo et al., 2021). Thus, an exploratory analysis to investigate the possible relationship between colostrum BPs concentration and birth parameters was conducted in the present study. The effects of BPA, BPS, and BPA analogs on birth parameters were observed, either significantly or marginally (Fig. 4). For instance, the high colostrum exposure group to BPA exhibited low levels of birth head circumference in 2019 (Kruskal-Wallis test, $p = 0.031$). The average birth weight and PI in 2013 tended to increase (ANOVA test, $p = 0.028$–0.049), when mothers had certain concentrations of BPS in colostrum (>LOD). The overall impacts of colostrum BPS and BPA on birth parameters were generally similar in 2019, as well as in 2013 (Fig. 4). This was consistent with the result of previous animal studies (Siracusa et al., 2018). A study conducted on rodents showed that exposure to BPA during prenatal and early postnatal stages could result in fat accumulation and increased offspring body weight (Miyawaki et al., 2007). Animal studies also suggested that BPA analogs may negatively impact fetal intrauterine growth by disrupting the endocrine system (Rochester and Bolden, 2015). BPS, exhibiting similar endocrine-disrupting effects and hormonal activities as BPA, may also affect fetal growth (Siracusa et al., 2018; Yang et al., 2021).

When comparing the influence of different levels of colostrum BPA, inconsistent results were sometimes found (Table S7). Exposure to BPA was linked to a positive impact on averaged birth weight and PI in 2013, while in 2019, a negative effect was observed on high colostrum BPA group. Additionally, the medium BPA colostrum group in 2019 had the

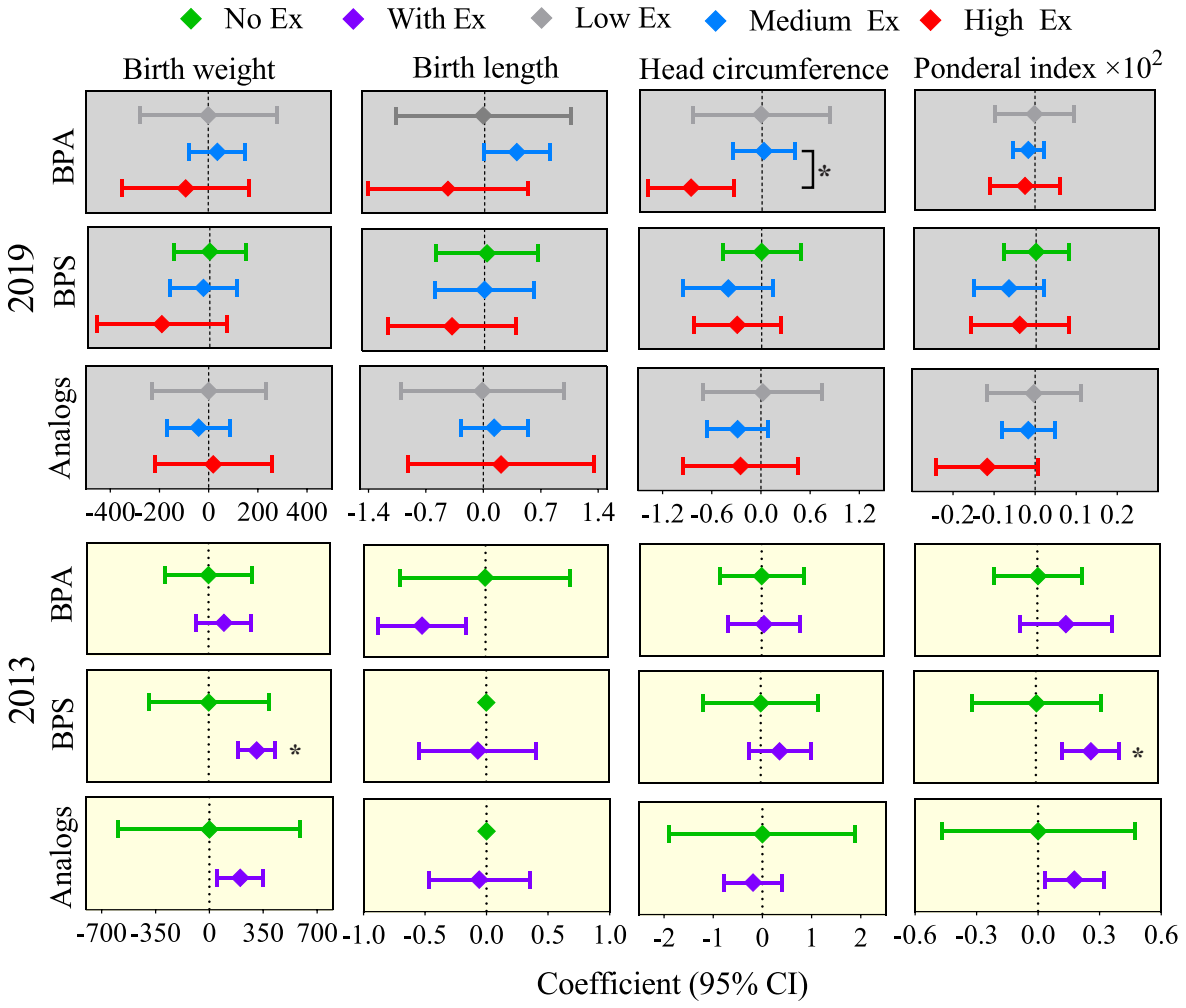

Fig. 4. Associations between colostrum bisphenol concentrations (in 2013 and 2019) and birth parameters. No Ex: no exposure group, colostrum concentration below or equal to LOD; With Ex: exposure group, colostrum concentration above LOD; Low Ex: low exposure group, colostrum concentration within the lower quartile (0–25th percentile); Medium Ex: medium exposure group, colostrum concentration below the 75th percentile but above the 25th percentile (or above the LOD for BPS); Upper Ex: upper exposure groups, colostrum concentration within the upper quartile (75th–100th percentile); *: Kruskal-Wallis test or ANOVA test, $p < 0.05$.

highest average birth length and birth weight (49.6 cm and 3324 g, respectively), compared with the others. It appeared that the influence of BPA on birth parameters does not consistently exhibit a similar pattern or a monotonic changing pattern.

The literature also provided data on the impact of prenatal BPA exposure, in which maternal urine concentrations in different pregnancy periods were used (Huo et al., 2015; Lee et al., 2014; Snijder et al., 2013). In a study in China (n = 452), higher exposure to BPA was associated with an elevated risk of infants having low birth weight (Huo et al., 2015). A cohort study in the Netherlands (n = 219) found that pregnant women exposed to high levels of BPA had slower fetal weight and head circumference growth throughout pregnancy (Snijder et al., 2013). However, a study in Korea (n = 757) reported contrasting results, showing that higher maternal BPA levels were linked to increased birth weight (Lee et al., 2018b). The epidemiological evidence was often inconsistent. The explanations for this discrepancy may be attributed to variations in the range of exposure levels and the possible presence of a nonlinear non-monotonic dose–response effect (Chang et al., 2019; Yang et al., 2021). Other possible reasons for the inconsistent findings could be variations in sampling timing and sample size.

The potential relationship between colostrum BPs concentration and birth parameters was preliminarily discussed in the present study, and some interesting data was obtained. The urine BPs would indicate recent or short-term exposure levels, while colostrum could serve as a reflection of the overall exposure of the mother during the later stages of pregnancy (Guo et al., 2021; Migeot et al., 2013). It was a challenging to try to find a direct relationship between colostrum contaminants and birth parameters (Jin et al., 2020; Yin et al., 2019). To fully understand prenatal exposure effects (Hu et al., 2019), analyzing of multiple human fluids including maternal blood, urine, and colostrum was necessary in our opinion.

3.6. Health risk assessment of BPs in colostrum

To assess the potential health risks of infant exposure to BPs through breastfeeding, the median and 95th percentile concentrations of BPs in 2019 were utilized to calculate normal and high daily intake levels, considering the specific consumption habits (Table S8). The EDI values of infants through colostrum intake during the first week of birth ranged from 0 for BPF to 106.2 ng/kg bw/day for BPA. The HQ values under high exposure scenarios were 0.027, 0.006, and 0.012 for BPA, BPS, and BPF, respectively, while HI was as high as 0.045. BPA, among the various BPs, accounted for 80 % of the total risk, highlighting the significance and need for further attention towards BPA. BPS contributed nearly 20 % under median exposure scenarios, while BPF contributed 27 % under high exposure scenarios.

A Monte Carlo simulation was conducted, which indicated that no potential health risks for infants through colostrum intake (Fig. 5A). A sensitivity analysis was performed to elucidate the contribution of factors to health risks (Fig. 5B). For the two exposure scenarios, the concentration of BPA (53.2 %–53.5 %) was the predominant factor that increased the health risk of BPs, followed by MCR (41.0 %–41.9 %). Positive contributions from BPS and BPF concentration were also suggested, approximately around 3.0 %.

There were some limitations in the present study. Firstly, the sample sizes were small, particularly during the period from 2006 to 2013. When analyzing temporal variations with a small sample size, there could be several uncertainties. Then, some of the relationships between colostrum BPs concentration and birth parameters were not statistically significant, which would lead to biased or incomplete results. When interpreting the effects of exposure based on these findings, it should be cautious. Additionally, breastfeeding health risks from BPs might be underestimated or overestimated when relying solely on the mathematical addition of HQs. More complex BPA analogs were found in colostrum samples, and the combined effects needed to be carefully considered since.

4. Conclusions

In the present study, temporal trends in BPs in colostrum and the potential impacts were investigated. There was a noticeable decrease in BPA colostrum levels, but BPA still had the highest concentration. The observed composition changes between 2013 and 2019 indicated a complex usage pattern of BPA analog in recent years. The BPA concentrations, as well as the total concentrations of BPs, were not significantly correlated in paired samples. This phenomenon may due to their different half-lives in human milk and urine, and individual difference. High levels of BPA in colostrum were associated with a significant reduction in birth head circumference in 2019. BPA and BPS generally showed a similar negative effect on fetal growth in 2019. However, those impacts usually do not have statistical significance and were variable in different years in present study. Thus, special caution is required to draw certain conclusions about their potential impact, and further epidemiological studies are needed to gather more information regarding the potential effects of BPs on fetal growth. To gain a comprehensive understanding of prenatal exposure profiles, combined analysis on multiple human matrices, such as human milk, blood, placenta, and urine of mothers and infants, was helpful. And the

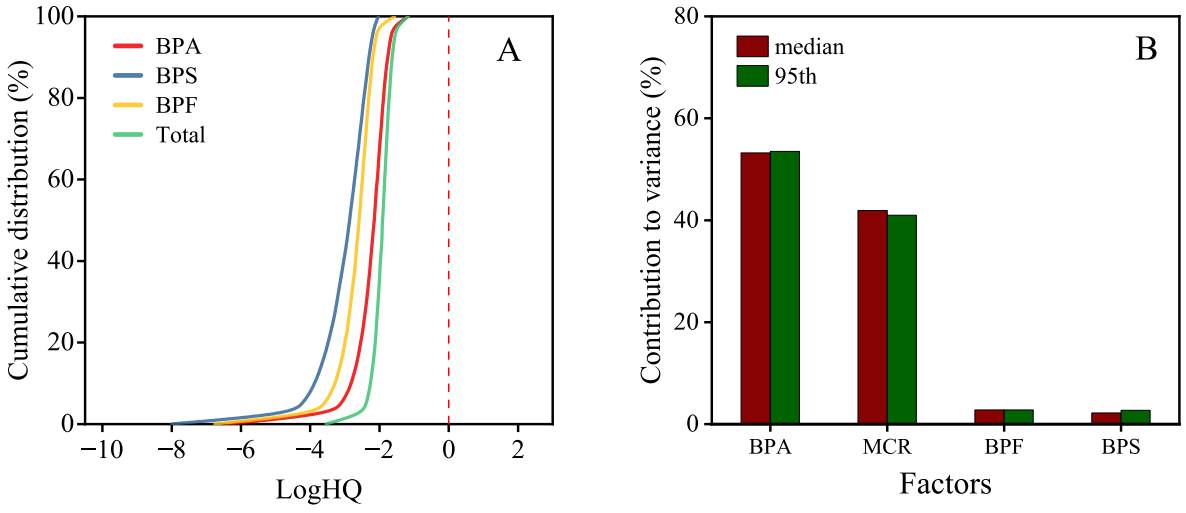

Fig. 5. A Monte Carlo simulation of health risk from breastfeeding exposure of bisphenols based on temporary tolerable daily intake (A) and the contribution of factors to hazard index (B). MCR: the mean value of milk intake rate in age of first week.

conclusion drawing from cohort studies need to be testified with other studies, including case-control and cross-sectional studies. A large sample size can help reducing uncertainty and increasing the statistical power of the studies. Conducting a sample size calculation before and developing a standardized data collection protocol to ensure consistency are still necessary.

Consent to participate

All donors involved in this study signed an informed consent form before sample collection.

Ethics approval

This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained from human subjects in this study, while their privacy rights were fully respected. The study was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, and the Ethics Committee of Shanghai Luwan Maternity & Infant Health Hospital.

CRediT authorship contribution statement

Xiaolan Zhang: Writing – original draft, Methodology. **Minghui Fu:** Writing – original draft, Formal analysis. **Kexin Li:** Methodology. **Xiaomeng Cheng:** Methodology. **Xinyu Zhang:** Methodology. **Xiuhua Shen:** Methodology. **Bingli Lei:** Writing – review & editing, Supervision. **Yingxin Yu:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.114485.

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