Maternal serum bisphenol A levels and risk of pre-eclampsia: a nested case–control study

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Background: Although recent studies have indicated the potential adverse effects of maternal bisphenol A (BPA) exposure on pregnancy such as increasing the risk of pre-eclampsia, epidemiological evidence is limited. We aimed to evaluate the relationship between maternal BPA exposure and the risk of pre-eclampsia. Methods: We conducted a nested case–control study among 173 women (74 cases of pre-eclampsia and 99 controls). BPA concentrations were measured using liquid chromatography-mass spectrometry in the maternal serum samples collected during 16–20 gestational weeks. Multivariate logistic models were used to examine the relationship between maternal serum BPA concentrations and the risk of pre-eclampsia. Results: BPA was detectable (>0.1 μg/l) in 78.6% of the maternal serum samples at three levels: low (<2.24 μg/l), medium (2.24-4.44 μg/l), and high (>4.44 μg/l). BPA concentrations were significantly higher in the serum samples collected from the pre-eclampsia cases than those from controls (median: 3.40 vs. 1.50 μg/l, \(P<0.01\)). With adjustment for maternal age, primiparous and BMI, the odds of developing pre-eclampsia were significantly elevated in subjects with high serum BPA levels compared with those with low levels (adjusted OR = 16.46, 95%CI = 5.42–49.85) regardless of subcategories of pre-eclampsia including severity and onset time. Among the pre-eclampsia subjects, the maternal serum concentration of BPA was not different between the early- and late-onset subjects (median: 3.09 vs. 3.50 μg/l, \(P=0.57\)), but surprisingly higher in mild pre-eclampsia subjects compared with severe pre-eclampsia subjects (median: 5.20 vs. 1.80 μg/l, \(P<0.01\)). Conclusions: These results demonstrated that maternal exposure to high level of BPA could be associated with an increased risk of pre-eclampsia.

Introduction

Pre-eclampsia, a new-onset hypertension disorder that occurs after the 20th week of pregnancy and is characterized by proteinuria and multisystem damage, affecting 2–8% of pregnancies worldwide.\(^1\) Pre-eclampsia is one of the leading causes of maternal mortality and morbidity and accounts for 30–35% of preterm births.\(^1\) Although the aetiology of pre-eclampsia remains elusive, endocrine dysregulation is considered a possible contributor to pathogenesis of this disease\(^2,3\); thus, maternal exposure to endocrine disrupting chemicals (EDCs) can be a potential risk factor of pre-eclampsia. However, this research area is understudied.

Bisphenol A (BPA), one of the most studied EDCs, is a man-made chemical widely utilized in the production of epoxy resins and polycarbonate polymers and exists in various consumer products such as water bottles, metal coating, flooring materials and thermal papers.\(^4\) BPA can be easily released from these products, resulting in ubiquitous human exposure\(^5\) primarily through diet.\(^6,7\) Oral intake of BPA could result in elevated serum BPA levels in does–effect relationship in mice.\(^8,10\) Previous studies have demonstrated that BPA could accumulate in the placenta\(^9,11\) and induce toxic effects in placental cells\(^11–13\) which are potentially associated with abnormal placental development and subsequent pregnancy outcomes such as pre-eclampsia. However, current epidemiological evidence for the association between maternal BPA exposure and pre-eclampsia is limited.\(^14,15\) It was found that pre-eclampsia women showed increased BPA concentrations in placenta at delivery\(^15\) and in urinary samples at early pregnancy\(^15\) comparing with normotensive controls, but data of BPA exposure as an influence on maternal serum level is lacking. The objective of the present study was to examine the relationship between maternal BPA exposure and risk of pre-eclampsia. We hypothesized that maternal exposure to BPA could be associated with an increased risk of pre-eclampsia. To test our hypothesis, we designed a nested case–control study between pre-eclampsia cases and healthy term controls. Maternal serum concentrations of BPA in mid-pregnancy were compared between cases and controls. We calculated the odds ratio for having a pregnancy complicated with pre-eclampsia in subjects with high, medium levels of serum BPA compared with subjects with low levels of serum BPA.

Methods

Study design and data source

Eligible subjects were women with singleton pregnancies who had records of serum samples collected during 16–20 gestational weeks.
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Statistical analysis

Statistical analyses were performed using SPSS 20.0, and the statistical threshold for significance was set as 0.05. Data of maternal characteristics were analysed using basic descriptive statistics, such as the Student’s t-test for continuous variables and then χ² or Fisher’s exact test for categorical variables. The distribution of serum BPA concentrations was tested by the Kolmogorov-Smirnov normality test, and it was found to be skewed and log-transform did not change this status. A Mann–Whitney U test was used to compare the differences in serum BPA concentrations between cases and controls. To examine the association between serum BPA concentration and the risk of developing pre-eclampsia, multivariate logistic regression models were performed by calculating the unadjusted (Model 1) and adjusted odd ratios (ORs) (Model 2) and their 95% CI. In the adjusted model, variables including maternal age, parity and BMI were retained in the model, regardless of statistical significance, because they have been reported to be associated with pre-eclampsia; other variables were included in the adjusted model if they altered the association between BPA concentration and pre-eclampsia by >10%. Similar regressions were conducted to examine the association between maternal serum BPA concentrations and the risk of developing each subcategory of pre-eclampsia including mild, severe, early- and late-onset pre-eclampsia. For the sensitivity analysis, additional models were run when superimposed pre-eclampsia was excluded.

To explore the effects of BPA on pre-eclampsia at different exposure levels, and the potential for non-linear relationships, we grouped the study subjects into low, medium, and high level based on the optimal point of the ROC analysis where optimal consistency (sensitivity + specificity–1) was met at this point. Unadjusted and adjusted ORs of pre-eclampsia were calculated by comparing subjects with medium or high BPA levels respectively with subjects with low BPA levels in logistic regression models. Additionally, we conducted a Log-rank survival analysis to explore the cumulative incidences of pre-eclampsia among different BPA levels with the progress of pregnancy. The research period ranged through pregnancy. The occurrence of pre-eclampsia was considered an end event. Complete data included the pregnancy age of women in whom pre-eclampsia occurred, and censored data included the pregnancy age of those who did not develop pre-eclampsia.

Results

General characteristics

Table 1 summarized the general characteristics of all participants. Maternal age ranged from 19 to 39 years with a mean of 29.20 (SD =3.52 years). The majority had a normal BMI (n = 113; 68.48%),
Maternal serum BPA concentrations

Maternal serum concentrations of BPA were below LOD in 37 samples (21.4%; 30 controls and 7 cases). The median (25th, 75th) maternal serum BPA concentration in all subjects was 2.30 μg/l (0.05–3.93 μg/l; data not showed).

Associations between maternal BPA exposure and pre-eclampsia

Significantly higher maternal serum BPA concentrations were observed in pre-eclampsia cases compared with controls (median: 3.40 vs. 1.50 μg/l; P < 0.01) (table 2). Significantly elevated odds of pre-eclampsia with each unit increase in BPA concentrations (unadjusted OR = 1.43; 95% CI = 1.24, 1.67) was observed and this effect was slightly attenuated after adjusted for maternal age, BMI and parity (adjusted OR = 1.19; 95% CI = 1.19, 1.63) (table 2). In the subset analysis, all subsets of pre-eclampsia had significantly higher serum BPA concentrations than controls (P < 0.01) (table 2).

Interestingly, among pre-eclampsia subjects, significantly higher BPA concentrations were observed in mild-pre-eclampsia cases compared with severe-pre-eclampsia cases (median: 5.20 vs. 1.80 μg/l; P < 0.01) (Supplementary table S1). No significant difference was observed in BPA concentrations between early- and late-onset pre-eclampsia cases (median: 3.09 vs. 3.50 μg/l; P = 0.57) (Supplementary table S1).

As a sensitivity analysis, we ran additional models after excluding cases of superimposed pre-eclampsia (n = 12) (Supplementary table S2). Intriguingly, greater ORs for pre-eclampsia associated with each unit increase of BPA were observed (adjusted OR = 1.48; 95% CI = 1.25, 1.75) (Supplementary table S2).

In the ROC analysis (Supplementary figure S1), BPA exposure showed good performance as a predictor of pre-eclampsia (AUC = 0.73; 95% CI = 0.65–0.81). When the BPA concentrations were divided into three levels, 2.24 and 4.44 were selected as the intercept points because they had an optimal consistency (0.34 = sensitivity + specificity – 1) in the ROC curve, resulting in low (<2.24 μg/l), medium (2.24–4.44 μg/l), and high (≥4.44 μg/l) BPA level. At high BPA level, there was significantly higher proportion of pre-eclampsia than the control (39.2 vs. 5.1%; P < 0.01) (table 3). The odds of pre-eclampsia were significantly elevated in subjects with high serum BPA level compared with those with low levels (unadjusted OR = 17.12; 95% CI = 5.87–49.94) (table 3) and this positive trend retained after adjusting for maternal age, parity and maternal BMI (adjusted OR = 16.46; 95% CI = 5.42–49.95) (table 3). No significant relationship was found between subjects with medium BPA level and those with low BPA level in adjusted model (adjusted OR = 2.15; 95% CI = 0.98–4.75) (table 3).

In the survival analysis, both subjects with medium and high serum BPA levels tended to significantly have a higher cumulative incidence and an earlier onset time of pre-eclampsia compared with

Figure 1 Study profile. "GMD was excluded, because it was reported to be associated with insulin resistance."
Discussion

Key findings and significance

To the best of our knowledge, this is the first study to investigate maternal serum BPA in mid-pregnancy in relation to pre-eclampsia. We found that women who developed pre-eclampsia experienced significantly higher levels of BPA exposure during 16–20 gestational weeks regardless of its subcategories including severity and onset time. Among the subjects with pre-eclampsia, the maternal serum BPA concentrations were not different between the early- and late-onset groups, and were significantly higher in the mild subjects compared with the severe subjects. Our study provided new evidence for the potential risk of maternal BPA exposure on pre-eclampsia. The major path of exposure to BPA is through diet, and behavioural changes, such as using BPA-free products, could potentially reduce the degree of exposure. Thus behaviour interventions to reduce maternal BPA exposure might reduce the risk of pre-eclampsia. Understanding the role of maternal BPA exposure in pregnancy outcomes is essential to answering important public health questions about the reproductive toxicities of this emerging

Table 1 General characteristics of 173 mothers

| Variables                        | Total (n = 173) | Controls (n = 99) | Cases (n = 74) | P-valuea |
|----------------------------------|----------------|------------------|---------------|----------|
|                                  | Mean ± SD or n (%) | Mean ± SD or n (%) | Mean ± SD or n (%) |           |
| Maternal age (years)             | 29.20 ± 3.52 | 28.92 ± 3.73 | 29.57 ± 3.20 | 0.23     |
| BMI at first visit (kg/m²)       |                |                  |               | <0.01    |
| <18.5 (underweight)              | 24 (14.55) | 20 (20.20) | 4 (5.72) |          |
| 18.5–24.99 (normal weight)       | 113 (68.48) | 66 (66.67) | 47 (67.14) |          |
| >25 (overweight)                 | 28 (16.97) | 10 (10.10) | 19 (27.14) |          |
| Education                        |                |                  |               | 0.54     |
| <College                         | 21 (12.28) | 11 (11.22) | 10 (13.70) |          |
| College                          | 142 (83.04) | 81 (81.67) | 61 (83.56) |          |
| >College                         | 8 (4.68) | 6 (6.12) | 2 (2.74) |          |
| Primiparous (%)                  | 155 (89.60) | 87 (87.88) | 68 (91.89) | 0.39     |
| Gestational age at delivery (weeks) | 38.53 ± 2.30 | 39.13 ± 1.23 | 37.73 ± 3.05 | <0.01   |
| Infant sex                       |                |                  |               | 0.54     |
| Female                           | 82 (47.95) | 45 (45.45) | 37 (50.68) |          |
| Male                             | 89 (52.05) | 53 (53.54) | 36 (49.32) |          |
| Gestational weeks at serum collection | 16.79 ± 1.71 | 16.77 ± 1.52 | 16.83 ± 1.94 | 0.81 |
| Season of blood collection       |                |                  |               | 0.51     |
| Spring                           | 45 (26.01) | 23 (23.23) | 22 (29.73) |          |
| Summer                           | 40 (23.12) | 26 (26.26) | 14 (18.92) |          |
| Fall                             | 49 (28.32) | 26 (26.26) | 23 (30.08) |          |
| Winter                           | 39 (22.54) | 24 (24.24) | 15 (20.27) |          |
| Storage time of samples (day)    | 639.41 ± 140.04 | 651.00 ± 151.61 | 623 ± 121.89 | 0.21 |

a: Cases were compared with controls.

Table 2 ORs (95% CIs) of pre-eclampsia subcategories associated with serum BPA concentrations

| BPA concentration (µg/l) median (25th, 75th) | Unadjusted OR (95% CI) | P-value | Adjusted OR (95% CI)b | P-value |
|--------------------------------------------|------------------------|---------|-----------------------|---------|
| Controls                                   | 1.50 (0.05, 1.98)      | 1       | 1.39 (1.19, 1.63)     | <0.01   |
| Cases                                      | 3.40 (1.85, 6.73)      | 1.43 (1.24, 1.67) | <0.01 | 1.42 (1.21-1.67) | <0.01 |
| Severity Mild                              | 5.20 (2.96, 7.17)      | 1.47 (1.25-1.73) | <0.01 | 1.35 (1.14-1.60) | <0.01 |
| Severe                                     | 1.80 (0.48, 2.94)      | 1.38 (1.17-1.64) | <0.01 | 1.33 (1.07-1.66) | <0.01 |
| Onset time Early onset                     | 3.09 (2.28, 4.94)      | 1.35 (1.08, 1.70) | <0.01 | 1.41 (1.20-1.66) | <0.01 |
| Late onset                                 | 3.50 (1.70, 6.80)      | 1.48 (1.26, 1.73) | <0.01 |                 |       |

a: Pre-eclampsia subsets were separately compared with controls by logistic regression.
b: Adjusted for maternal age, parity and BMI.
c: One case of severe pre-eclampsia lacked information regarding the gestational week in which pre-eclampsia was diagnosed and was therefore considered missing; two cases of pre-eclampsia superimposed on chronic hypertension were excluded.

Table 3 ORs (95% CIs) for the onset of pre-eclampsia associated with BPA levels

| BPA levela (µg/l) | Controls n (%) | Pre-eclampsia n (%) | Unadjusted OR (95% CI)b,c | P-value | Adjusted OR (95% CI)b,c | P-value |
|-------------------|----------------|---------------------|--------------------------|---------|-------------------------|---------|
| Low (<2.24)       | 62 (62.6)      | 21 (28.4)           | 1.00                     | 1.00    |                         |         |
| Medium (2.24–4.44)| 32 (32.3)      | 24 (32.4)           | 2.21 (1.07–4.57)         | 0.03    | 2.15 (0.98–4.75)        | 0.06    |
| High (≥4.44)      | 5 (5.1)        | 29 (39.2)           | 17.12 (5.87-49.94)       | <0.01   | 16.46 (5.42-49.95)      | <0.01   |

a: BPA level was determined according to the cut-off point for optimal consistency (0.34) of the ROC curve.
b: When compared with the lowest BPA level by logistic regression.
c: Adjusted for maternal age, primiparous and BMI.

those with low BPA level (P < 0.05 for medium level; P < 0.01 for high level) (Supplementary figure S2).
environment pollutant, thus providing scientific basis for exposure reduction policies.

**Comparisons**

Our results underscore the previously identified relationship between BPA exposure and increased risk of pre-eclampsia. A case–control study of women reported elevated BPA concentrations in placentas of pre-eclampsia women, but not maternal or cord serum at delivery, compared with normotensive controls. Other researchers revealed significantly increased odds of pre-eclampsia in association with urinary BPA concentrations at 10 weeks gestation, while urinary BPA was assessed several times during pregnancy. In our current study, BPA concentrations were measured in serum samples collected during the first half of pregnancy, a window coincides with placental development. Results from all three studies strongly suggested that maternal exposure to BPA is a risk factor for developing pre-eclampsia. We further speculated that timing of exposure to BPA is critical for its adverse effects on pre-eclampsia and maternal exposure at the first half pregnancy is riskier than the second half of pregnancy. Further evidences are needed to confirm this assumption.

**Interpretations**

Although the specific pathophysiology of pre-eclampsia is unclear, poor placentation plays a crucial role in the development of pre-eclampsia. In humans, placentation occurs during the first half of pregnancy as trophoblastic invasion remodels the narrow-lumen, muscle spiral arteries into dilated, low-resistance utero-placental vessels. Any factors that cause defective trophoblastic remodelling during early pregnancy could result in placental dysfunction following dysregulating angiogenic profiles, which play crucial roles in the development of pre-eclampsia. Free BPA can pass through the placental barrier and accumulate in the placenta, and BPA exposure can result in the degeneration and necrosis of placental cells and disturb angiogenesis both in vitro and in vivo. BPA was also reported to be associated with increased circulating sFLT–1/PLGF ratio during pregnancy, an antiangiogenic status in pre-eclampsia. Additionally, the Comparative Toxicogenomics Database shows top 10 BPA interacting genes, many of which were reported to affect trophoblastic migration, invasion and apoptosis abilities, including MAPK, caspases and BCL2. In our current study, we found an increased risk of pre-eclampsia related to BPA exposure during 16–20 gestational weeks (mean = 16.8), a window that is susceptible to various factors that may result in defective placental development. To our surprise, we found that mild-pre-eclampsia women had significantly higher serum BPA concentrations than severe-pre-eclampsia women. Although we do not have a definitive explanation for this observation, we think it is because of the complexity of pathogenesis of pre-eclampsia. For instance, severe pre-eclampsia subjects may be more susceptible to BPA exposure because of existing pre-dispositions for pre-eclampsia such as genetic predisposition. Or other risk factors appeared to play much more prominent roles in the development of severe pre-eclampsia than BPA exposure. Nevertheless, further in vivo experiments are necessary to determine the causal relationship of maternal exposure of BPA and pre-eclampsia and to investigate its possible pathological mechanisms.

**Strengths and limitations**

Strengths of our study are that BPA exposure was determined before the onset of pre-eclampsia and that serum samples were used to directly reflect the exposure levels. There were some limitations in our study. First, there were some shortages in blood sample collection and storage. In this study, all the blood samples were collected from women who underwent regular prenatal visit with the same laboratory consumables under conventional processes. Though we could not dismiss completely the possibilities of contamination during the processes of sample collection and processing, we tried our best to eliminate the difference of contamination degree between the case and controls as much as possible. In this way, we chose controls among whose sample was collected from the similar season in the same year compared with the case group to eliminate different effects of temperature and storage time on container BPA release status. Furthermore, in later analysis process, all the samples were set blindly to the laboratories and to be treated in standard procedures. Finally, serum BPA concentrations reported in our study is similar to previous reports. Therefore, the BPA levels in our study, to a great extent, are comparable between the cases and controls. Second, we measured the BPA concentrations at one time point, which may not accurately reflect the exposure status, as an interclass correlation coefficient of 0.32 was reported for BPA, although this result did present within-person variability. However, other reports have suggested that a single BPA concentration measurement can accurately reflect one’s exposure status by classifying the patient into different exposure levels because the lifestyle and living environment of one person do not change readily. Third, we were unable to obtain the maternal smoking status for our cohort, even though the behaviour has been demonstrated to be inversely related to pre-eclampsia. Supplementary data are available at EURPUB online.

**Conclusions**

In conclusion, we found that maternal serum BPA in first half of pregnancy was significantly related to an increased risk of pre-eclampsia, thus providing a potential approach to pre-eclampsia prevention by reducing BPA exposure during pregnancy. Further studies are needed to understand the relationship between BPA exposure and the risk of pre-eclampsia in pregnant women.

**Key points**

- This the first study to measure bisphenol A (BPA) levels in maternal serum samples in first half of pregnancy in relation to pre-eclampsia.
- This nested-case control study showed that pre-eclampsia women had significantly higher levels of BPA exposure during 16–20 gestational weeks and that highest level of
BPA exposure was associated with a significantly increased risk of pre-eclampsia.

- Our study provided new evidence for the potential risk of BPA exposure on pre-eclampsia and provided clues to preventing pre-eclampsia.

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