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Association between Gestational Bisphenol A Exposure and Maternofoetal Outcomes: A Cohort Study in a Single Tertiary Hospital in Klang Valley

(Perkaitan antara Dedahan Bisfenol A Gestational dan Hasil Maternofoetal: Suatu Kajian Kohort di Hospital Tertiari Tunggal di Lembah Klang)

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ABSTRACT

A growing body of literature has documented the adverse effects of bisphenol A (BPA) exposure on pregnancy and birth outcomes. Regardless, how gestational BPA exposure affects mother-newborn pairs in Malaysia is yet to be explored. Hence, this study aimed to investigate urinary BPA levels of pregnant women living in Klang Valley and their associations with adverse obstetric and birth outcomes. This cross-sectional study involved pregnant women in their third trimester attending antenatal clinic in Hospital Al Sultan Abdullah (HASA), UiTM Puncak Alam, who planned to have their delivery in HASA. Information on maternal age, parity, education, household income, gestational age, and obstetric complications, such as Gestational Diabetes Mellitus (GDM), preeclampsia, preterm labour, and foetal growth restriction (FGR) were collected. Maternal urine samples were also obtained and evaluated using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Additionally, the neonatal outcomes including mode of delivery, gestational age, birth weight and need for NICU admission were documented. Our LC-MS/MS analysis showed that BPA was present in all the urine samples, with levels varying from 4.42 to 30.86 ng/mL. The median level was 15.96 ng/mL. Urinary BPA level has no significant correlation with gestational hypertension (GHTN), preterm labour and low birth weight babies. Babies who need NICU admission were born to mothers who exhibited significantly different urinary BPA levels compared to those whose babies were not admitted (p=0.049). Finding from this study suggestive of further investigation on level of gestational urinary BPA with NICU admission, ideally with a larger sample size to validate these results.
Keywords: Bisphenol A (BPA); foetal outcome; pregnancy outcome

ABSTRAK

Badan kepustakaan yang semakin meningkat telah mendokumentasikan kesan buruk bisfenol A (BPA) terhadap kehamilan dan kelahiran. Namun begitu, bagaimana pendedahan BPA semasa kehamilan memberi kesan terhadap pasangan ibu dan bayi baru lahir di Malaysia masih belum diterokai. Oleh itu, penyelidikan ini bertujuan untuk mengkaji tahap BPA dalam air kencing wanita hamil yang tinggal di Lembah Klang dan kaitannya dengan kesan buruk obstetrik dan kelahiran. Kajian keratan rentas ini melibatkan wanita hamil dalam trimester ketiga yang menghadiri klinik antenatal di Hospital Al Sultan Abdullah (HASA), UiTM Puncak Alam, yang merancang untuk bersalin di HASA. Maklumat mengenai umur ibu, pariti, pendidikan, pendapatan isi rumah, usia kehamilan dan komplikasi obstetrik, seperti Gestational Diabetes Mellitus (GDM), preeklampsia, kelahiran pramatang dan sekatan pertumbuhan janin (FGR) telah dikumpulkan. Sampel air kencing pesakit juga diambil dan dianalisis menggunakan kromatografi cecair spektrometri jisim tandem (LC-MS/MS). Di samping itu, hasil neonatal termasuk cara melahirkan, umur kehamilan, berat bayi ketika lahir dan keperluan untuk kemasukan NICU telah didokumenkan. Semua sampel air kencing didapati mengandungi BPA dan parasnya adalah antara 4.42 hingga 30.86 ng/mL. Tahap median ialah 15.96 ng/mL. Tahap BPA kencing tidak mempunyai korelasi yang signifikan dengan hipertensi semasa hamil (GHTN), kelahiran pramatang dan berat lahir bayi yang rendah. Bayi yang memerlukan kemasukan NICU dilahirkan oleh ibu yang menunjukkan tahap BPA kencing yang berbeza secara ketara berbanding mereka yang bayinya

tidak dimasukkan (p = 0.049). Penemuan daripada kajian ini mencadangkan kajian lanjut mengenai tahap BPA dalam air kencing semasa kehamilan dengan kemasukan NICU, idealnya dengan saiz sampel yang lebih besar untuk mengesahkan keputusan ini.
Kata kunci: Bisfenol A (BPA); hasil kehamilan; hasil kelahiran

INTRODUCTION

Pregnancy is one of the crucial stages in life where the well-being of both mother and child are susceptible to various factors around them, such as lifestyle and environmental exposures (Rolfo et al. 2020). According to the United Nations International Children's Emergency Fund (UNICEF) (2023), the prevalence of maternal mortality in 2020 was 223 deaths per 100 000 live births, and hypertensive disorders of pregnancy are one the major causes of these deaths. Meanwhile, neonatal mortality accounted for half of all under-5 deaths in 2020, where a large part of this mortality was caused by congenital anomalies, infections, intrapartum-related complications and preterm births (World Health Organization 2023). In addition, childhood and adult health and disease have been shown to be influenced by foetal growth (Nobile, Di Sipio Morgia & Vento 2022). Foetal development depends on cell differentiation and tissue formation, which are tightly regulated by genetic, epigenetic and environmental factors (Koukoura, Sifakis & Spandidos 2012).

Experimental and epidemiological evidence has shown that environmental pollutants, labelled as endocrine-disrupting chemicals (EDCs), contaminate our food and water sources and are associated with altered human health (Mukherjee et al. 2021; Wee et al. 2020). Bisphenol A (BPA), one of the most well-known EDCs, is the first-choice plasticizer worldwide (Tamschick et al. 2016). Thermal receipts, water pipes, sporting and medical equipment, toys, and electronics are just a few examples of the many consumer products that contain BPA. In its free form, BPA imitates endogenous hormones and exerts its endocrine disruption properties by activating or inhibiting biological pathways (Pivonello et al. 2020). BPA has high affinity for uterine tissue, and the drastic changes in hormone levels during pregnancy which predispose pregnant women to the detrimental effects of BPA (Namat et al. 2021).

The transfer of BPA via the placenta and its presence in the amniotic fluid may also adversely affect the foetus (Bae et al. 2017; Namat et al. 2021). For example, a Chinese cohort study reported an inverse association between maternal urinary BPA and birth weight (Hu et al. 2019). As per the Developmental Origins of Health and Disease (DOHaD) theory, low birth weight may be indicative of the subsequent manifestation of non-communicable diseases during adulthood (Hanson & Gluckman 2014). In addition, higher BPA levels during pregnancy have been shown to decrease gestational ages and increase the risk of preterm labour, as shown by a meta-analysis (Namat et al. 2021). The same meta-analysis also pointed out that related data are scarce in several regions of the world, particularly in developing nations. Therefore, the current study determined the urinary BPA levels of pregnant women living in Klang Valley and correlated them with adverse obstetric and foetal outcomes. The findings will contribute to identifying future pregnant mothers and babies at risk in the Malaysian population so that appropriate preventive and protective measures can be taken.

MATERIALS AND METHODS

STUDY POPULATION

A total of 80 pregnant women were recruited in this cohort between year 2021 and 2022. The sample size was calculated using the single mean formula, which resulted in a calculated requirement of 81 participants. This estimation was based on predefined parameters, including the desired level of precision (0.5), confidence level (95%), and the expected variability in the population ($\sigma = 2.25$). Despite the initial target of 81 participants, we were able to recruit only 80 pregnant women due to one participant dropping out. The participants attended the antenatal clinic at Hospital Al Sultan Abdullah (HASA), Universiti Teknologi MARA (UiTM) Puncak Alam, Selangor, and were in their third trimester. This study was approved by UiTM Human Research and Ethics Committee (Code: REC/01/2022 (ST/FB/1). Those who planned to deliver in HASA, received regular prenatal care, were willing to sign informed consent, with a singleton pregnancy, and had natural conception, were eligible to participate in this study. Information on maternal age, parity, education, household income, gestational age, and obstetric complications, such as gestational diabetes mellitus (GDM), preeclampsia, preterm labour, and foetal growth restriction (FGR), was collected. The neonatal outcomes, including mode of delivery, gestational age (weeks), birth weight (grams) and need for NICU admission, were also documented.

SAMPLE PREPARATION

Urine samples were collected in the third trimester of pregnancy using sterile urine containers (LTC, China) and stored at -40 °C until further analysis. This trimester was chosen because, during the latter part of pregnancy, as the foetus ingests amniotic fluid which can contain BPA (Namat et al. 2021). This exposure results in BPA being absorbed by the foetus and then excreted into the amniotic fluid, leading to its accumulation in the uterine environment. Consequently, the foetus may experience higher BPA levels during the second half of pregnancy. One study examined BPA levels throughout pregnancy, including in the third trimester, and their association with

preterm birth (Cantonwine et al. 2015). The research indicated that sampling during the third trimester provides a closer temporal link between maternal exposure and birth outcomes, making it a crucial period for assessing BPA exposure and its potential effects on adverse outcomes.

To process and extract the samples for BPA analysis, 2.5 mL of urine was pipetted into a sterile 10 mL polypropylene tube (FisherScientific, USA). Then, 0.5 mL of 0.1 M hydrochloric acid were introduced, and the resulting combination was vigorously mixed for 10 s using a vortex mixer. The acidified urine was then loaded into a solid-phase extraction (SPE) cartridge Strata C18-E (Phenomenex, USA), which was conditioned prior with 3 mL of 100% methanol (MetOH). The acidified urine was allowed to pass through the cartridge along the column. The column was rinsed once with 3 mL of 5% methanol (MetOH). The extracted samples were eluted with 3 mL of acetonitrile (ACN) and MetOH (1:1) and dried under nitrogen gas. Dried samples were preserved at -40 °C until they were analysed using LC-MS/MS.

URINARY BPA ANALYSIS

The Agilent 6490 liquid chromatography coupled with triple quadrupole mass spectrometry (LC-MS-QQQ) was used to quantify the total BPA concentration for each sample. Dried samples were hydrated with 5 mL of 50% ACN and then passed through an Econo Filter (PTFE 0.2 µm) (Agilent, Munich, Germany) before being transferred into borosilicate glass vials. The LC-MS/MS system was set with the following parameters: column temperature = 40 °C; flow rate = 0.600 mL/min; collision energy = 30 V; electrospray ionization (ESI) = negative mode at 2.5 kV; gas temperature = 270 °C; gas flow = 11 L/min; nebulizer = 59 psi; sheath gas heater and flow = 300 °C at 11 L/min; capillary voltage = 3000 V; charging voltage = 1500 V. Ten µL from each sample was then injected into the ZORBAX RRHD Eclipse Plus C18 UHPLC guard and analytical column (95 Å, 2.1 × 50 mm, 1.8 µm). To separate BPA, a gradient mobile phase with water (LC-MS grade, ThermoFisher, USA) as solvent A and ACN (MS-grade, ThermoFisher, USA) as solvent B was used. The gradient elution was programmed as follow:

0 – 5 mins, 10% [B], 5 – 10 mins, 90% [B],
10 – 12 mins, 90% [B]

Multiple reaction monitoring transitions of mass-over-charge ratio (m/z) 227.1 to 211 and m/z 227.1 to 133.1 were used as BPA qualifier and quantifier, respectively. The MRM for each sample was then compared against a standard calibration curve constructed using eight BPA concentrations, from 1 ng/ mL to 5000 ng/mL, with a regression coefficient of > 0.999. This curve generated a limit of detection (LOD) of 111.77 ng/mL and a limit of quantification (LOQ) of 154.39 ng/mL. All data quantification was carried out using the Agilent MassHunter Quantitative software package (Agilent Technologies, Santa Clara, CA).

STATISTICAL ANALYSES

Data was statistically analysed using SPSS version 28 software package developed by IBM Corporation, USA. The Pearson and Spearman correlations were employed to calculate the coefficient of urinary BPA. Continuous variable was analysed using Mann-Whitney U, whereas Chi square test was employed to examine categorical variable.

RESULTS

SUBJECT CHARACTERISTICS

Characteristics of pregnant mothers and their newborns are shown in Table 1. Median (interquartile range, IQR) age of participating pregnant mothers (n = 80) was 31 (6) years, with a median (IQR) BMI of 28.5 (7.0) kg/m2. 28.7 % of mothers (n = 23) have GDM, while 7.5 % of the pregnant women (n = 6) have GHTN. In addition, 23.8 % of the mothers (n = 19) were diagnosed with anaemia. Meanwhile, the median (IQR) birth weight of newborns 3.05 (.58) kg. 6.3 % of newborns (n = 5) have low birth weight and 2.5 % (n = 2) were admitted in NICU (Table 1). Additionally, 3.8% (n = 3) of newborns were birthed before 37 weeks.

BISPHENOL A URINE CONCENTRATIONS AND MATERNOFOETAL OUTCOMES

Our LC-MS/MS analysis showed that all urine samples contained the BPA pollutant, with concentrations ranging from 4.43 to 30.86 ng/mL. The median (IQR) level was 15.96 (13.48) ng/mL. Mann-Whitney U test was performed to compare BPA levels between the different variables, such as GDM, GHTN, anaemic and COVID statuses, induction of labour, delivery method, education, low birth weight, birth term, and NICU admission. It has been shown that mothers with NICU-admitted babies have significantly higher BPA levels compared to those without (*ZU = –1.972, p = .049). No significant differences in BPA levels between mothers with and without GDM (ZU = –1.249, p = .212), GHTN (ZU = –.438, p = .661), anaemia (ZU = –.096, p = .923), and COVID (ZU z = –.952, p = .341). Similarly, mothers who were induced for labour (ZU = –.979, p = .328) and required vacuum assistance during delivery (ZU = –.199, p = .843) showed no significant difference in BPA levels compared to those with normal labour and delivery (*Table 2). Further, BPA levels did not differ significantly between mothers with secondary versus tertiary education (*ZU = –.384, p = .701). Likewise, mothers who birthed infants with low birth weight versus normal birth weight (ZU = –.348, p = .728), and mothers with preterm babies compared to those who carried pregnancy more than 37 weeks (ZU = –.595, p = .552), did not show significant difference in their BPA levels.*

Next, Spearman correlation was conducted to determine the association between BPA levels with maternal age, maternal BMI, income and birth weight. Maternal age (*rs = –.122, p = .281) and maternal BMI (rs = –.029, p = .798) are weakly negatively associated with BPA levels, whereas weak positive relationships between maternal income (rs = .074, p = .771) and neonatal birth weight (rs = .074, p = .517) with BPA concentrations were observed (*Table 3). However, none of the relationships are statistically significant.

DISCUSSION

To the best of our knowledge, this is the first study to report the effects of gestational BPA exposure on the obstetric and birth outcomes in Malaysia. Although several studies have documented the occurrence of BPA in human urine and plasma samples among the Malaysian population (Kouidhi et al. 2017; Wiraagni et al. 2019; Zhang et al. 2011), there remains a significant gap in local data regarding BPA levels in vulnerable populations, particularly pregnant mothers and children. This is especially concerning given the ongoing debate over what constitutes a 'safe' concentration of BPA. Current evidence suggests that even low levels of exposure may pose health risks (Vandenberg et al. 2012), leading to increasing caution among regulatory bodies. For instance, the European Food Safety Authority (EFSA) recently revised the tolerable daily intake (TDI) for BPA from 4 µg/kg body weight per day to just 0.2 ng/kg body weight per day (Ramirez et al. 2023), reflecting a heightened awareness of the potential dangers associated with this chemical. Importantly, BPA has been associated with various pregnancy complications, including preterm delivery, preeclampsia and FGR (Dagdeviren et al. 2023; Pergialiotis et al. 2018; Vrachnis et al. 2021). Further, the GDM prevalence in Malaysia was substantially higher than other Asian nations (13.5 % versus 2–7 %) (Heng Yaw et al. 2021), whereas preeclampsia incidence in the Klang Valley from 2010 to 2020 was 1.6% out of 40212 births (Sutan, Aminuddin & Mahdy 2022). Therefore, this study elucidated how the different urinary BPA levels of pregnant mothers living in Klang Valley, affected their obstetric and birth outcomes.

Mounting evidence indicates that infants born at 37 and 39 gestational weeks have a higher likelihood of experiencing poor respiratory outcomes, newborn sepsis, admission to the NICU, and extended hospital stays when compared with births occurring between 39 and 42 weeks of gestational age (Sengupta et al. 2013; Tita et al. 2009; Wilmink et al. 2010). Consequently, these infants are commonly categorised as early-term births. The third trimester, spanning from approximately week 28 to week 40, is a critical period for foetal growth and maturation, including the development of essential organs and systems necessary for full functionality at birth (Cleveland Clinic 2024). Measuring BPA levels in urine during this time reflects the total burden of exposure the foetus has experienced throughout pregnancy (Namat et al. 2021). Elevated BPA levels during the third trimester can interfere with these developmental processes, potentially leading to immediate neonatal complications such as lower birth weight or NICU admission. Research indicates that elevated urinary BPA levels later in pregnancy were strongly linked to a higher likelihood of spontaneous preterm birth (Cantonwine et al. 2015; Namat et al. 2021). Thus, assessing BPA levels during the third trimester helps link cumulative BPA exposure to these risks, underscoring its potential role in contributing to complications associated with early-term births.

Our findings showed a significant difference in BPA levels between mothers whose newborns were admitted to the NICU and those whose newborns were not. Given that only 2 out of 80 (2.5%) newborns were admitted to the NICU, it is possible that the significance observed in the test was driven by the distribution of BPA levels among the much larger group of mothers whose babies were not admitted to the NICU. The significant result may therefore reflect lower variability in BPA levels among mothers whose newborns were not admitted to the NICU, rather than an effect driven solely by the higher BPA levels in the small group of mothers whose newborns were admitted. This means that while there is a statistical difference, it may be more indicative of the uniformity within the non-NICU group rather than a strong association with NICU admission itself. With only 2 NICU admissions, the small sample size makes it challenging to draw definitive conclusions about the relationship between BPA exposure and NICU admission. To better understand the nature of this relationship, further analysis with larger sample sizes and more NICU cases would be necessary. This would help clarify whether the observed significance is indeed due to differences in BPA exposure or merely a statistical artifact arising from the small number of NICU cases.

Meanwhile, the median gestational urinary BPA level of pregnant women found in this study was 15.96 ng/mL. This value is slightly higher compared to the median or geometric mean (GM) of 13 studies analysed in this one meta-analysis with the lowest concentration from 0.48 ng/mL to the highest 6.44 ng/mL (Namat et al. 2021). Besides, subgroup analyses showed that only BPA exposure during the third trimester was linked to a reduction in gestational age substantial and preterm birth.

It is plausible that BPA exposure promotes early parturition through various mechanisms (Namat et al. 2021). One potential mechanism involves the role of BPA in placental function. Experimental studies have shown that exposure to low-level BPA increased placental cell apoptosis and disrupted normal placental development, contributing to adverse pregnancy outcomes, such as prematurity (Benachour & Aris 2009; Morice et al. 2011). Another mechanism underlying the association between BPA and preterm birth that may be resulted from medical indications for preterm termination of pregnancy (iatrogenic preterm delivery) since that BPA has also been reported to

be associated with preeclampsia and pregnancy-induced hypertension (Steinthorsdottir et al. 2020).

In addition, oxidative stress plays a critical role in preterm labour (Buonocore et al. 2002), and both animal and human studies have reported that BPA can induce oxidative stress by increasing intracellular peroxides (Babu et al. 2013; Bindhumol, Chitra & Mathur 2003). Besides, BPA is an endocrine disruptor that can disrupt endogenous hormonal functions. BPA has the potential to enhance the expression of peroxisome proliferator-activated receptor-gamma, resulting in a reduction in aromatase (Cyp19a1) expression caused by follicle-stimulating hormone (FSH) and ultimately leading to a decrease in oestradiol production in human granulosa cells (Kwintkiewicz et al. 2010). BPA has been reported to significantly diminish FSH-stimulated progesterone production (Samardzija et al. 2018). BPA can also decrease placental aromatase activity to affect oestrogen production and impact oestrogen and progesterone receptor expression in the placenta during later pregnancy (Chu et al. 2018; Rubin 2011). All the mechanisms mentioned may be related to the initiation of the parturition mechanism.

Higher BPA exposure levels during the first trimester are associated with sex-specific reduction in sheep birth weight (Veiga-Lopez et al. 2016), where birth weight is

TABLE 1. Characteristics of pregnant mothers included in the analytic sample (n = 80)

	N (%)	Median ± IQR
Maternal age		31 ± 6
Maternal BMI		28.5 ± 7.0
GDM status		
No	57 (71.3)	
Yes	23 (28.7)	
GHTN status		
No	74 (92.5)	
Yes	6 (7.5)	
Anaemic status		
No	61 (76.3)	
Yes	19 (23.8)	
COVID status		
No	71 (88.8)	
Yes	9 (11.3)	
Induction of labour		
No	73 (91.3)	
Yes	7 (8.8)	
Delivery method		
Normal	76 (95.0)	
Vacuum assisted	4 (5.0)	
Education		
Secondary	6 (7.5)	
Tertiary	74 (92.5)	
Income		4850 ± 2838
Parity		
Nulliparous	20 (25.0)	
1–4	60 (75.0)	
Birth weight		3.05 ± 0.58
Low birth weight		
No	75 (93.8)	
Yes	5 (6.3)	
Birth term		
37–42 weeks	77 (96.3)	
<37 weeks	3 (3.8)	
NICU admission		
No	78 (97.5)	
Yes	2 (2.5)	

TABLE 2. Differences in maternal urinary levels based on maternofoetal outcome

		Z	Asymp. sig. (2-tailed)
Mann-Whitney U	GDM status	–1.249	.212
	GHTN status	–.438	.661
	Anaemic status	–.096	.923
	COVID status	–.952	.341
	Induction of labour	–.979	.328
	Delivery method	–.199	.843
	Education	–.384	.701
	Low birth weight	–.348	.728
	Birth term	–.595	.552
	NICU admission	–1.972	**.049**

TABLE 3. Association between maternal age, BMI, income and neonatal birth weight with BPA concentration

			BPA concentration
Spearman's rho	BPA concentration	Correlation coefficient	1.000
		Sig. (2-tailed)	.
	Maternal age	Correlation coefficient	–.122
		Sig. (2-tailed)	.281
	Maternal BMI	Correlation coefficient	–.029
		Sig. (2-tailed)	.798
	Birth weight	Correlation coefficient	.033
		Sig. (2-tailed)	.771
	Income	Correlation coefficient	.074
		Sig. (2-tailed)	.517

reflective of foetal growth. In addition, an observational study including 470 pairs of mothers and children found that higher levels of BPA in maternal urine were linked to reduced length of the foetal femur and a slower estimated increase in foetal weight between weeks 12 and 20 of pregnancy (Casas et al. 2016). On the contrary, one meta-analysis showed that BPA have a significant positive association with birth weight (Zhou et al. 2019).

Our results showed that maternal BPA levels were not significantly associated with birth weight. This is in line with two meta-analyses of previous research that showed no links between prenatal BPA exposure and measures of weight, length, or head circumference at birth, and found no correlation between prenatal BPA exposure and birth term (Hu et al. 2018; Zhong et al. 2020; Zhou et al. 2019). Furthermore, no correlations were discovered between BPA and foetal growth parameter in one cohort study in the Netherlands involving 1379 pregnant women (Sol et al. 2021), and in one case-control study involving 130 children born prematurely and 352 randomly selected children born at full term as controls (Hu et al. 2019).

Moreover, no association was found between maternal BPA levels and GHTN status in the current cohort. Meanwhile, one study demonstrated that exposure to BPA, certain phthalate metabolites, and parabens resulted in a notable reduction in systolic and/or diastolic blood pressure (Warembourg et al. 2019). These correlations were more commonly found during the second trimester of pregnancy and continued to be statistically significant even after multiple testing adjustments.

Last but not least, research indicates that even when blood sugar levels during pregnancy do not exceed the clinical threshold for diagnosing GDM, there is still a higher likelihood of experiencing poor maternofoetal outcomes, such as having a baby with a high birth weight (Wee et al. 2020), developing preeclampsia (Tamschick et al. 2016), and experiencing postnatal depression (Bellavia et al. 2018). In our cohort, maternal BPA was not significantly associated with GDM status, consistent with a previous study (Bellavia et al. 2018). Regardless, the study showed that there was a correlation between relatively high levels of BPA and higher blood sugar levels in overweight or obese

women who are already at a higher risk of experiencing increased pregnancy glucose levels.

CONCLUSIONS

BPA was detected in all urine samples of pregnant mothers. Notably, among the various parameters analysed, only NICU admission was associated with substantially different BPA levels between groups, indicating a potential link between BPA exposure and the likelihood of NICU admission. These findings underscore the need for a larger-scale study to further investigate the effect of BPA on NICU admission rates. Additionally, pregnant mothers, especially those who live in Klang Valley, should be informed about BPA exposure and take precautionary measures to reduce the risk of BPA-related pregnancy complications.

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