ORIGINAL ARTICLE

Urinary concentrations and determinants of pyrethroid metabolites in pregnant women from non-rural areas of Yunnan, China

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▌ Abstract

Introduction and objective. The study assesses the levels of urinary pyrethroid pesticide (PYR) in women during early pregnancy. The factors associated with exposure are also determined.
Materials and method. A total of 480 pregnant women from non-rural areas visiting hospital for prenatal examination during early pregnancy were enrolled. A self-designed, structured questionnaire was used to collect data on potential factors of PYR exposure. Urinary PYR metabolite levels were quantified using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS).
Results. The majority of urine samples (98.8%) contained one or more PYR metabolite, although only a few women self-reported pesticide exposure. Urinary 3-phenoxybenzoic acid (3PBA) levels were close to those reported in certain developed countries. However, the levels of 3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DBCA) and 4-fluoro-3-phenoxybenzoic acid (4F3PBA) were higher than those reported in previous studies. Urinary PYR levels were positively associated with exposure to pesticides, consumption of bananas and oranges, the number of fruit types the women regularly ate, being multiparous, and cooked frequently. They were negatively associated with early pregnancy body mass index (BMI), unemployment, frequent intake of apples, and washing fruits and vegetables with soda or hot water.
Conclusions. Pregnant women in non-rural areas were extensively exposed to low levels of PYRs. Dietary intake may be the primary pathway of exposure. The presented findings highlight the importance of using appropriate methods to reduce pesticide residues in food.

▌ Key words

pyrethroid pesticides, urinary metabolites, HPLC-MS/MS, pregnant women, prenatal exposure

INTRODUCTION

The hazards of pesticide exposure to human health, especially during pregnancy, is a critical research topic. Prenatal exposure to pesticides may have adverse effects on birth outcomes, including reduced birth weight, birth length, and head circumference [1], spontaneous abortion, or premature birth [2, 3]. Moreover, prenatal exposure to pesticides affects not only foetal development *in utero*, but also has a profound impact on offspring. Prenatal exposure to pesticides is associated with neurological and intellectual impairment [4–6] and an increased risk of leukemia and other cancers in children [7, 8].

Pyrethroids (PYRs) are synthetic pesticides frequently used in agriculture and horticulture, and are also used in households for insect control. The application of PYRs has become increasingly common in recent years. According to the registration information on the *China Pesticide Information Network*, PYRs are the primary components of household insecticides currently used in China. Exposure routes involve the absorption of chemicals deposited on the skin [9], ingestion of a diet containing pesticide residues [10], or inhalation of contaminated indoor dust [11, 12]. Exposure is typically determined by testing non-specific PYR metabolites in urine [13].

Research on prenatal PYR exposure is limited. A few previous studies have focused on the correlation between pesticide exposure during late pregnancy and offspring development [14, 15]. However, it is necessary to evaluate a pregnant woman for pesticide exposure during the first trimester, a critical period for foetal organogenesis. China has witnessed increasing urbanization, with more people migrating from rural to urban areas, therefore, it is important to study the effects of pesticide exposure in an urban population. This study investigated prenatal PYR exposure levels by measuring urinary PYR metabolites in pregnant women living in non-rural areas. The determinants of PYR exposure were also analyzed.

MATERIALS AND METHOD

Participant recruitment and urine collection. The pregnant women were recruited in a tertiary general hospital when taking the first-trimester prenatal examination from February to March of 2017. The inclusion criteria for initial enrolment

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were pregnant woman in the first trimester who were willing to participate in the study voluntarily and provide urine samples. Women who lived in rural areas or did not complete the questionnaire were excluded. All participants were interviewed by research fellows based on a structured questionnaire and donated 20–30 mL morning urine samples during the first trimester. Informed consent forms were signed before they volunteered to participate in the project. The Ethics Committees of Kunming Medical University approved all procedures and materials used in the study.

Initially, 505 women answered the questionnaire and furnished urine samples (participation rate: >80%). Of the 505 women, 25 living in rural areas were excluded. The urine samples were transported to the laboratory in an icebox and stored at -80 °C until analysis.

Analysis of urinary PYR metabolites. All urine samples were pretreated with a modified version of the liquid-liquid extraction method described previously [16]. Briefly, the urine sample was thawed, mixed thoroughly, and centrifuged for 5 min at 5,000 rpm (SC-04, ZONKIA, Anhui, China). An aliquot (1.0 mL) of the supernatant sample was transferred into a 5.0 mL polypropylene tube, and 1.0 mL ethyl acetate was added. Next, the tube was vortexed for 30 s and centrifuged at 5,000 rpm for 3 min. Approximately 1 mL of the supernatant (organic layer) was transferred to a clean polypropylene tube. The above extraction process was repeated twice. A total of 3.0 mL of the supernatant was gathered and evaporated to dryness, dissolved in 1.0 mL acetonitrile, and filtered through a 0.22-μm organic membrane before transferring to 2.0-mL sample vials for analysis.

Non-specific PYR metabolites in urine samples were analyzed using the ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) assay method derived from the reported method and modified [13]. A UPLC system (Ekspert ultra LC-100XL) coupled with a MS/MS detector (3200 Q Trap, ABSciex, USA) was used for metabolite analysis. Briefly, an aliquot of 2.0 μL extract was injected into the UPLC system, and separated by a Kinetex C18 column (50 mm × 2.1 mm, particle size: 2.6 μm, Phenomenex, USA). An isocratic mobile phase was used with 95% acetonitrile (organic phase) and 5% water containing 5 mmol/L ammonium acetate (aqueous phase) (v/v), at a flow rate of 0.4 mL/min. The oven temperature was maintained at 40 °C. Mass spectrometry was performed in the negative mode with electrospray ionization (ESI) as the ion source. The ion spray voltage was -4500 V at the temperature of 200 °C. Mass spectrometric parameters for PYR metabolite measurement are summarized in Table 1.

Reference standards for 3-phenoxybenzoic acid (3PBA) were purchased from Sigma Aldrich (USA), and reference standards for 4-fluoro-3-phenoxybenzoic acid (4F3PBA) and 3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DBCA) were obtained from Dr. Ehrenstorfer GmbH (Germany). Calibration curves were calculated using linear regression with 1/X weighting. Quality control (QC) materials were prepared by adding the target compound to the pooled urine before extraction, which were pretreated and analyzed in the same manner as the unknown samples. The limit of detection (LOD) was defined as the lowest concentration of the analyte with a signal-to-noise ratio of at least 3:1. The LOD was 0.09 ng/mL for DBCA and 0.02 ng/mL for 3PBA and 4F3PBA.

The precision and accuracy of the method were evaluated by analyzing the QC materials simultaneously with unknown samples each day. The inter-and intra-day relative standard deviations were <15%. Urinary PYR metabolite concentrations were measured in ng/mL and adjusted based on creatinine levels (ng/mg Cre.). Urinary creatinine concentration was detected by the alkaline picric acid method (Jaffe method).

Potential predictors. A self-designed, structured questionnaire was used to collect data on participant demographics, including maternal age, education, lifestyle (e.g. alcohol use and/or passive smoking), parity (primiparous or multiparous), and body mass index (BMI) during early pregnancy. Data on potential sources of prenatal exposure to PYRs were collected using the questionnaire, including exposure to the pesticide, mosquito repellent, or lampblack (from a kitchen); living near crops (<500 m); and intake of fruits or vegetables. Methods used to reduce pesticide residues (e.g., washing vegetables and fruits with soda or hot water) were also investigated.

Statistical Analysis. All data were analyzed using SPSS (version 17.0), and Epidata3.1 was used to input the questionnaire data. Concentrations below the LOD were assigned a value of LOD divided by the square root of 2 [17]. Quartiles and 95th percentile were used to describe the distribution of skewed values of PYR metabolite concentrations. The correlations between maternal characteristics and PYR metabolite levels in urine were analyzed using multiple linear regressions with a backward selection strategy, $P < 0.1$.

RESULTS

Characteristics of the population. Participant characteristics are presented in Table 2. All women were between 20–42 years of age, and 73.3% belonged to the age group 25–34 years. Most women (85.8%) lived in urban areas, 73.1% had college or higher education, and 85.6% were employed. Overall, a few women (3.3%) lived near crops (<500 m), 35% cooked regularly (≥3 times per week), and 3.1% washed fruits and vegetables with soda or hot water. About a third of the women were primiparous at enrollment, and 71.7% had normal weight during early pregnancy. Among them, a few women (4.2%) reported exposure to insecticides, 2.7% had used mosquito repellents, 6.7% used alcohol, and 61.7% had been exposed to passive smoke.

PYR metabolite concentrations in urine samples. Urinary PYR metabolite concentrations are presented in Table 3. PYR metabolites were present in most (98.8%) of the urine samples. 4F3PBA was the most frequent metabolite (95.6%), followed by 3PBA (89.8%). The median level of total PYR metabolites (3PBA, 4F3PBA, DBCA) was 1.38 ng/mL (0.80 ng/mg Cre.).

Predictors of PYR exposure. Correlations between potential factors and urinary PYR metabolite levels are summarized in Table 4. The findings revealed that urinary PYR metabolite levels were positively associated with exposure to pesticides, consumption of bananas or oranges, being multiparous, and frequently cooking during pregnancy. They were negatively associated with early pregnancy BMI, unemployment,

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Table 1. The parameters of tandem mass spectrometry (MS/MS) for the determination of pyrethroid pesticide (PYR) metabolites

Analyte	Precursor ion (m/z)	Product ion (m/z)	De-clustering Potential (V)	Entrance Potential (V)	Collision energy (V)
DBCA	296.7	79.2 (Q)	−18	−7	−24
		81.2 (C)	−18	−7	−24
4F3PBA	231	93.2 (Q)	−40	−10	−42
		187 (C)	−40	−10	−23
3PBA	213.1	93.1 (Q)	−38	−6	−40
		169.1 (C)	−38	−6	−25

DBCA – 3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; 4F3PBA – 4-fluoro-3-phenoxybenzoic acid; 3PBA – 3-phenoxybenzoic acid; Q – quantification; C – confirmation.

Table 2. Characteristics of the population and potential sources of exposure (n = 480)

Characteristics	No. (%)	Characteristics	No. (%)
Age (years)		Often eating apples	
≤24	28 (5.8)	No	44 (9.2%)
25–29	186 (38.8)	Yes	436 (90.8%)
30–34	166 (34.6)	Often eating bananas	
≥35	100 (20.8)	No	146 (30.4%)
Place of residence		Yes	334 (69.6%)
Urban	412 (85.8)	Often eating cantaloupes	
Suburban	68 (14.2)	No	387 (80.6%)
Education		Yes	93 (19.4%)
≤Middle school	108 (22.5)	Often eating pears	
≥College	351 (73.1)	No	188 (39.2%)
Missing	21 (4.4)	Yes	292 (60.8%)
Occupation		Often eating oranges	
Employed	411 (85.6)	No	62 (12.9%)
Unemployed	69 (14.4)	Yes	418 (87.1%)
Early pregnancy BMI (kg/m²)		Number of fruit types	
< 18.5	44 (9.2)	< 4	180 (37.5%)
18.5–23.9	344 (71.7)	≥ 4	300 (62.5%)
≥24.0	92 (19.2)	Exposure to pesticides	
Parity		No	455 (94.8)
0 (primiparous)	186 (38.8)	Yes	20 (4.2)
≥1 (multiparous)	294 (61.3)	Missing	5 (1.0)
Home near a crop (< 500m)		Mosquito repellent use	
No	464 (96.7)	No	467 (97.3%)
Yes	16 (3.3)	Yes	13 (2.7%)
Cooking meals (per week)		Passive smoking	
< 3 times	312 (65%)	No	184 (38.3%)
≥ 3 times	168 (35%)	Yes	296 (61.7%)
Washing a		Alcohol use	
No	465 (96.9%)	No	448 (93.3)
Yes	15 (3.1%)	Yes	32 (6.7)

a Washing fruits and vegetables with soda or hot water

frequent eating of apples, alcohol use, and washing fruits and vegetables with soda or hot water. No correlation was noted between urinary pesticide levels and factors such as maternal age, ethnicity, education level, and passive smoking (data not shown).

Table 3. Concentrations of PYR metabolites in the urine of early pregnancy women

Analytes	LOD	n	n > LOD (%)	Percentiles			
				25th	50th	75th	95th
Unadjusted (ng/mL)							
DBCA	0.09	480	72.3	< LOD	0.74	1.28	2.57
3PBA	0.02	480	89.8	0.25	0.33	0.44	0.90
4F3PBA	0.02	480	95.6	0.16	0.21	0.29	0.61
Σ3 PYRs a		480		0.77	1.38	1.96	3.50
Creatinine-adjusted (ng/mg Cre.)							
DBCA		480		0.08	0.41	0.78	2.08
3PBA		480		0.14	0.21	0.30	0.60
4F3PBA		480		0.10	0.13	0.21	0.44
Σ3 PYRs a		480		0.48	0.80	1.24	2.70
LOD – limit of detection.							

a Σ3 PYRs: Sum of 3 metabolites (DBCA, 3PBA, 4F3PBA)

Urinary 4F3PBA concentrations were remarkably higher in women with insecticide exposure than those without exposure. Analyte concentrations in urine did not demonstrate a correlation with mosquito repellent use (data not shown).

Urinary DBCA and 4F3PBA levels were positively associated with banana and orange intake, respectively. Moreover, urinary 3PBA and total PYR levels were higher in women who ate 4 or more types of fruits. Urinary 3PBA, 4F3PBA, and total PYR levels were lower in women who often ate apples or pears. Women who ate cantaloupes regularly had higher levels of DBCA but lower levels of 4F3PBA. Urinary PYR metabolite levels were not related to vegetable intake (data not shown).

Urinary 4F3PBA levels were higher in women who were multiparous or cooked frequently (≥3 times per week) during early pregnancy. However, urinary DBCA and total PYR metabolite levels were lower in unemployed women and those who drank certain alcoholic beverages, lived near crops, or washed fruits and vegetables with soda or hot water. Urinary 4F3PBA and total PYR levels were negatively associated with early pregnancy BMI.

DISCUSSION

Exposure to PYR was assessed using a questionnaire and urinalysis. Self-reported data revealed that few women were exposed to agricultural insecticides (0.4%), household insecticides (4.0%), and mosquito repellents (2.7%) in the weeks leading to sample collection. The proportion of self-reported household pesticide exposure was lower than that reported in France [18] and the United States [19]. However, laboratory analysis results revealed that most urine samples contained one or more PYR metabolites. This finding indicated that most pregnant women were unintentionally exposed to PYRs

The detection frequencies of 3PBA were close to those reported in France [18] and other places in China [20, 21], and higher than those reported in the United States [14, 22], Mexico [15], and Puerto Rico [17]. Moreover, the detection rates of DBCA and 4F3PBA in the current study were higher than those reported in previous studies; except for DBCA,

Table 4. Multiple linear regression for analysis of associations between urinary PYR metabolites and potential factors (n = 480) [a]

	DBCA β (95% CI)	3PBA β (95% CI)	4F3PBA β (95% CI)	Σ3 PYRs [b] β (95% CI)
Exposure to pesticides				
Yes vs. No			**0.17 (0.04, 0.30)***	
Often eating bananas				
Yes vs. No	**0.14 (0.02, 0.26)***			
Often eating cantaloupes				
Yes vs. No	0.13 (–0.002, 0.27)		**–0.09 (–0.16, –0.03)****	
Often eating apples				
Yes vs. No		**–0.16 (–0.30, –0.02)***	**–0.11 (–0.20, –0.02)***	**–0.10 (–0.21, 0.00)***
Often eating pears				
Yes vs. No		**–0.11 (–0.20, –0.02)***		–0.06 (–0.12, 0.01)
Often eating oranges				
Yes vs. No			**0.08 (0.003, 0.16)***	
Number of fruit types				
≥4 vs. <4		**0.13 (0.04, 0.23)****		**0.11 (0.04, 0.18)****
Alcohol use				
Yes vs. No	**–0.29 (–0.51, –0.08)****			**–0.17 (–0.28, –0.06)****
Washing [c]				
Yes vs. No	**–0.32 (–0.62, –0.01)***			**–0.20 (–0.36, –0.04)***
Home near a crop (< 500m)				
Yes vs. No	**–0.32 (–0.61, –0.02)***			–0.13 (–0.29, 0.02)
Cook meals (per week)				
≥ 3 times *vs* < 3 times			0.05 (–0.001, 0.11)	**0.06 (0.003, 0.12)***
Occupation				
Unemployed vs. employed	**–0.16 (–0.31, –0.01)***			**–0.09 (–0.17, –0.01)***
Parity				
≥1 (multiparous) *vs* 0 (primiparous)			**0.07 (0.02, 0.12)***	
Early pregnancy BMI (kg/m², continuous)	–0.02 (–0.04, 0.003)		**–0.01 (–0.02, –0.005)****	**–0.01 (–0.02, –0.003)****

[a] All variables were introduced into the model and selected with a backward strategy, $P < 0.10$; [b] Sum of 3 metabolites (DBCA, 3PBA, 4F3PBA); [c] Washing fruits and vegetables with soda or hot water. All values of PYR metabolites were log-transformed and creatinine-adjusted. Bold font means statistical significance, * means $P < 0.05$, ** means $P < 0.01$.

which was lower than that reported in France. Compared with previous studies, the detection frequencies of the 3 metabolites in this study were higher. This could be because the sensitivity of the analytical method in this study was lower than that used in the French study, but higher than those used in other studies.

The 75th percentile level of 3PBA in the current study was close to that in the United States [14, 22], Puerto Rico [17], France [18], and Mexico [15], and lower than that in two other places in China [20, 21]. Urinary 3PBA is a common metabolite of most PYRs [23] and has been used as a biomarker for assessing PYR exposure [15]. Urinary DBCA and 4F3PBA levels in the current study were higher than those in other studies. The findings indicated that the types of PYRs used in this area were different from those in other studies.

Urinary 4F3PBA concentration in pregnant women correlated with pesticide exposure in this study. According to the *China Pesticide Information Network,* PYR is the major component of household insecticides and agricultural pesticides. However, urinary analyte levels did not correlate with mosquito repellent use in this study (data not shown). This could be because the biomarkers we analyzed were not metabolites from mosquito repellents [17, 23].

The findings of this study revealed a positive correlation between exposure to PYRs and the intake of certain fruits, indicating that the pesticides used on various crops differed. Negative correlations were found between urinary levels of certain PYR metabolites and the consumption of pears or alcohol could be attributed to reduced consumption of other foods. A consistent negative correlation between apple intake and PYR metabolite levels, suggests the possible role of apple polyphenols in the modulation of gut microbiota and body metabolic activity [24, 25]. This interesting finding was also reported by French researchers. They found increased urinary PYR levels in those consuming <1 portion of apples per week but no increase in those eating ≥1 portion of apples per week [18].

Reduced urinary levels of PYR metabolites were associated with washing fruits and vegetables with soda or hot water, but not when washed with saltwater or water (data not shown). In accordance with previous reports, washing fruits or vegetables with an alkaline solutions can effectively reduce pesticides on the surface [26, 27]. PYRs are hydrophobic organic compounds (with high log P values) [28] and difficult to be washed-off with salt water or water. Although pregnant women aspire to reduce pesticide residues in their food by washing it, most are unaware of the correct technique.

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In the current study, urinary PYR metabolite concentrations were higher in women who cooked frequently, findings suggesting that women may be exposed to PYRs by inhaling cooking fumes. PYRs are semi-volatile organic compounds, and a fraction of them can be adsorbed on particle surfaces or indoor dust [29–31]. Moreover, PYRs can evaporate from water into the air [32].

In this study, it was also found that urinary PYR metabolite levels were negatively correlated with early pregnancy BMI. To prevent adverse pregnancy outcomes, those with a high BMI are advised to reduce food intake and maintain a low gestational weight gain [33]. Furthermore, the negative correlation between PYR level and unemployment may be because these women buy fewer fruits due to their low income. This finding is in line with previous reports, wherein the general population was mainly exposed to PYR through diet [34, 35], and an organic diet intervention was able to reduce pesticide exposure [36].

The correlation between PYR metabolite levels and the residential environment was difficult to interpret. Women living in the suburbs may have had more opportunities to eat vegetables grown by self-sufficient farmers and sprayed with fewer pesticides. In addition, the urine samples were collected during the early spring (February – March, when the temperature is relatively low). Women were less likely to be exposed to pesticides in the ambient air during this season, a finding consistent with that of a previous study [21]. The number of previous pregnancies was positively associated with urinary PYR levels. This finding is similar to the French report [18], although the reasons for this result are unclear.

Inconsistent with previous reports [18], there was only one smoker in this study, and a few women (2.8%) stopped smoking during pregnancy. Passive smoking was not associated with PYR exposure.

This study has certain limitations. PYRs have a short half-life in the human body [12], therefore, a single urine analysis cannot indicate prior exposure to PYRs. Repeat sampling is the best method to overcome this limitation. In addition, although the dietary preferences of pregnant women was assessed, a quantitative analysis of intake was not performed. Nonetheless, this study has certain strengths. First, this is one of the very few studies describing PYR exposure levels during early pregnancy in non-rural areas of China. A few previous studies have focused on maternal exposure to pesticides in rural areas at delivery [20, 21]. Second, urine samples were collected, and questionnaires were administered during early pregnancy, which may have reduced any recall bias of pesticide exposure. Finally, the potential sources of PYR exposure were investigated, allowing for the estimation of long-term contact. The methods of reducing pesticide residues were also investigated. The results obtained can help reduce prenatal pesticide exposure and thereby protect the fetus.

CONCLUSION

Pregnant women in non-rural areas of China were widely exposed to low levels of PYRs, although only a few of them self-reported exposure. Exposure to PYRs is possibly associated with the frequent cooking and consumption of certain fruits. The results revealed diet as the main source of PYR exposure in pregnant women.

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