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Abstract

This study aimed to assess the relationship between exposure to Type II pyrethroids and congenital hypothyroidism (CH), particularly in leishmaniasis-endemic regions where the immunity of residents is compromised.

In this population-based case-control study, we used all mothers and newborns secondary data for the period 2017-2022 in eastern Isfahan province. Cases were newborns confirmed with diagnosis of CH. Data of insecticides spraying and fogging facilitated the identification of affected and unaffected regions. Propensity score (PS) matching was applied for matching controls to cases (5:1). The descriptive information reported along with the mapping generated using ArcGIS 10.8.2. Trimester-Specific analyses were conducted using STATA 17 with adjusting for possible confounders.

After PS matching, out of 37085 mother-newborn pairs registered in national Integrated Health System, 744 were included in the final analysis. After adjustment for birth and maternal characteristics, the association strengthened for second-trimester exposure ($OR_{adjusted} = 3.00$; 95% CI: 1.13-7.93), reaching statistical significance. A significant association was observed between cumulatively pyrethroid exposure with CH and strengthened after adjustment ($OR_{adjusted} = 2.33$; 95% CI: 1.22-4.45).

Our findings revealed that maternal exposure to type II pyrethroid insecticides during pregnancy, particularly in the second trimester, may increase the risk of CH.

Key words

Prenatal, Residential, Pyrethroid, Insecticides, Congenital Hypothyroidism

Introduction

Congenital hypothyroidism (CH) may occur due to abnormal growth or function of the thyroid gland, hypothalamus, or pituitary gland, or due to a disorder in thyroid hormone function [1]. The incidence of CH is reported to be 1 in 4,500 in the United States, 1 in 3,000 in Europe, and 1 in 1,000 in Iran. Many factors such as gender, weight, and prematurity of infants, complications, and medication use during pregnancy contribute to the development of this disorder, with environmental factors being particularly significant [2].

The use of insecticides plays a special role in environmental chemical pollution and can harm human health and the environment [3]. Since central Iran is considered one of the important foci of leishmaniasis in the world (leishmaniasis is a parasitic disease transmitted by the bite of sandflies, with rodents being the main reservoir in Iran), one of the main methods for controlling the vectors of leishmaniasis (sandflies) is the application of insecticides in the form of sprays on walls, insecticide-treated bed nets, and personal protection. Isfahan, located in central Iran, with a high prevalence of thyroid disorders (with an average incidence of 1 in 338 live births) [4] is also considered a hyperendemic for leishmaniasis specially in eastern regions where the control measures are employed depending on the hyperendemicity of the region to manage the transmission of leishmaniasis [5]. Although the use of pesticides can be effective in controlling parasitic diseases, it may also have negative health consequences [6]. Exposure to these chemicals can be associated with cancers, hormonal disorders, and allergies [7]. Pyrethroids including deltamethrin, cyphenothrin, cypermethrin, lambda cyhalothrin and permethrin insecticides are used in Isfahan to control leishmaniasis in endemic areas, and among these, deltamethrin is applied as an important and intensive control measure in residential areas by spraying and fogging. These substances have been linked to environmental factors in thyroid disorders [8]. Modifications to the structure of natural pyrethrins have made them resistant to light, and they are used as synthetic insecticides in homes, agricultural lands, and also in medicine. These insecticides have been in use since the 1940s, and due to their structural differences and varying clinical symptoms, they are available in two types: Type I and Type II [9, 10]. The insecticidal potency

in Type II is higher due to the presence of the cyano group in its atomic structure. Permethrin is classified as Type I, and deltamethrin, cyphenothrin, cypermethrin, and lambda cyhalothrin are classified as Type II [9,10].

A study conducted by Matsuki and colleagues in Japan, examining children and their environment, demonstrated that prenatal exposure to pesticide residues in homes, particularly those containing pyrethroids, adversely affected both fetal growth trajectories and postnatal development [11]. Ding et al. (2015) reported the inverse effects of pyrethroid exposure on urinary metabolites from a cohort of 405 mother-infant pairs, specifically regarding neonatal birth weight [12]. A cohort study by Balalain et al. (2021) indicated that the use of a combination of various insecticides (including pyrethroids and organophosphates) in pesticide applications was inversely associated with head circumference in male infants [13]. Most research focuses on agricultural settings or occupational exposure of individuals in factories producing toxic substances. This study is one of the very rare studies conducted on areas affected by leishmaniasis where insecticides are directly used in residential areas. This study aimed to assess the relationship between exposure to Type II pyrethroids and congenital hypothyroidism, particularly in leishmaniasis-endemic regions where the immunity of residents is compromised.

Methods

In this population-based case-control study, we used all mothers and newborns secondary data for the period 2017-2022 in all counties located in eastern Isfahan province including: Borkhar, Ardestan, Natanz, Koochpayeh, Harand, Varzaneh, Jarghooyeh, Naeen, Koor & Biabanak and also eastern Isfahan city. These areas are also predominantly endemic for cutaneous leishmaniasis [14].

Selection of Cases: All newborns diagnosed with congenital hypothyroidism born in the specified regions were selected as cases.

Selection of Controls: Healthy newborns with no symptoms in screening tests for CH, along with their maternal information, were selected from the same regions of cases at a ratio of 5:1.

Cases and controls with incomplete or unacceptable data, as well as multiple births (non-singleton births), were excluded from the study.

Six-year data on mothers and newborns were sourced from the Integrated Health System named SIB [15], a national platform for registering child growth and development information. Maternal data, including gestational age, maternal age, BMI, education level, occupation, geographic residence, and pregnancy complications, were obtained from the information registry linked to the newborns' data. There are two advantages of the SIB system: 1) Due to national infant vaccination, this system covers data on neonates born in Isfahan province and their mothers. 2) All data are linked by a unique code, and the 98% linkage was established between information of mothers' pregnancy, the information of newborns and the follow-up of hypothyroidism disorders.

The system employed in this study utilizes standardized protocols and questionnaires, having been previously utilized in multiple studies [16-18].

This study received approvals from the ethical committee of Isfahan University of Medical Sciences (ethical code: IR.ARI.MUI.REC.1401.255) and all methods were performed in accordance with the relevant guidelines and regulations. Maternal and newborns secondary data were used in this study, and informed consent has been obtained from all participants and legal guardian of the newborns at the time of the original data collection.

Exposure Assessment:

Following the electronic collection of information, insecticide application details, including dates, locations, and quantities of insecticides, type of usage (fogging or spraying) were assessed by areas where applied, both inside and around residences. Each neonate was assigned a geocode that correlated with their mothers' residences and exposure locations. This linkage also allowed for the assessment of pregnancy stages during which insecticide applications occurred. Documentation related to insecticide applications, and usage was derived from Leishmaniasis Committee meetings, and validity was approved.

Data on insecticides spraying and fogging related to both rural and urban areas facilitated the identification of affected and unaffected regions within a 2000-meter radius [19]. The

spectrum of exposure and non-exposure was considered, and geographic information system (GIS) maps depicting insecticide utilization were constructed according to the extent of application. The annual average exposure level was classified based on the amount of insecticide (kilogram **kg**) relative to the area (square meter **m²**). Spraying and fogging were currently applied in the first half of the year for preventing the leishmaniasis. Equation (1) shows the daily amount of insecticides.

Equation (1)

Exposure Intensity

$$= (\text{Insecticide amount (kg)}) / (\text{Treated area (m}^2\text{)} \times 182.5) \\ \times \text{Number of spraying or fogging days}$$

Because in this study we assessed the insecticides used in residential areas and the amounts used were very small compared to agricultural areas or other non-residential areas, in order to avoid very small numbers, the unit microgram **µg** were used in this study instead of kg.

Outcome Assessment

In the national program for congenital hypothyroidism screening in Iran, newborns are screened using filter paper, and those with a Thyroid Stimulating Hormone (TSH) level exceeding 10 milliunits per liter (mIU/L) between days 3 and 7 of life are recalled for further evaluation. If a second test, conducted between days 7 and 14, shows TSH levels greater than 10 mIU/L and Thyroxine (T4) levels below 6.5 µg/dL, a diagnosis of congenital hypothyroidism is proven, and treatment is initiated. The outcome is assessed in the newborns based on the TSH levels by the filter test as well as serum levels. Serum TSH and T4 concentrations are measured using diagnostic kits (Cobas analyzer) [16].

Data were collected from the national thyroid screening registry in collaboration with the provincial health department and the Research Center for Endocrinology and Metabolism at Isfahan University of Medical Sciences. Additionally, anthropometric measurements of newborns, including weight, length, and head circumference at birth, were recorded. The

normality or abnormality of these metrics was evaluated according to previous studies [20]. All information was documented and maintained within the Integrated Health System.

Confounder assessment

Potential confounders such as 'newborn sex', 'birth weight', 'birth length', 'birth head circumference', 'mother's job status', 'pregnancy complications', 'gestational age', 'maternal BMI', 'maternal age', 'exposed year', 'maternal education level' were identified about exposure and the primary outcome during the study design phase. This identification was facilitated through a review of existing literature and prior knowledge, alongside the construction of Directed Acyclic Graphs (DAGs) [21], using DAGitty version 3.0 (Radboud University Nijmegen & University of Lübeck, Germany) (Figure 1).

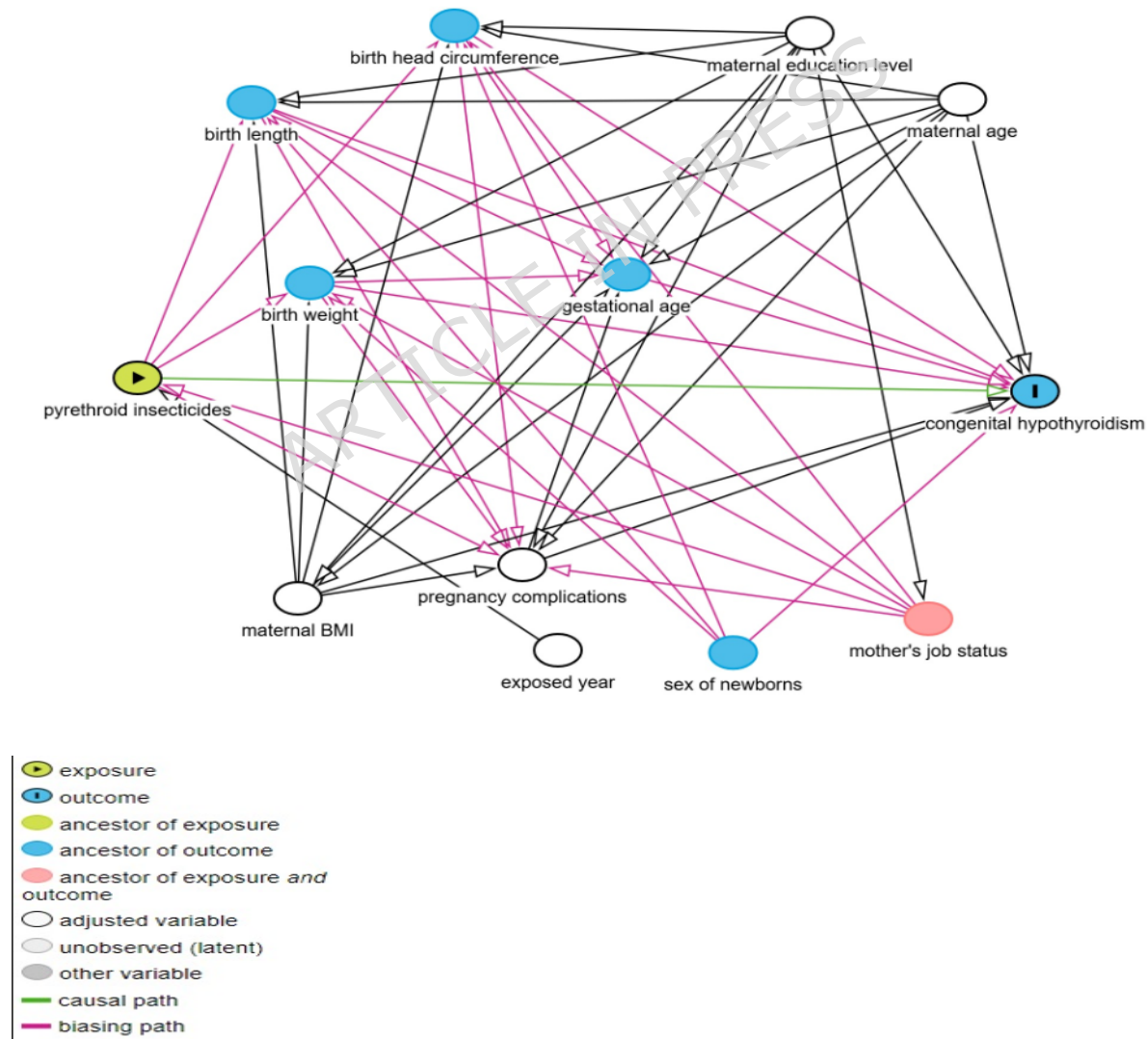


Fig. 1. Direct acyclic graph reporting the identification of potential confounders in the relationship between pyrethroid insecticides during pregnancy and congenital hypothyroidism

Propensity Score Matching

Propensity score (PS) methods can be applied for matching the subjects, and providing the propensity score to balance the baseline characteristics in the study population. This method can reduce the selection bias and affect the study's inferences. This can match the subjects with the same propensity for exposure from the exposed group to the control population. [22-25].

In present study, at the first, we used $p < 0.20$ to avoid prematurely excluding potential confounders. However, after identifying the initial candidate variables, we refined with $p < 0.10$, which increases specificity and results in a more parsimonious and stable propensity score model. The eligible confounders (in this study, including 'pregnancy complications', 'maternal BMI', 'maternal age', 'exposed year', 'maternal education level') would be selected for PS matching. Matching controls to cases (5:1) was done by assigning the nearest and the most compatible option (caliper=0.05) in terms of selected covariates in this method.

Statistical analysis:

The descriptive information was reported along with the mapping to visualize the spatial distribution of CH incidence and residential pyrethroid use across the study region using ArcGIS 10.8.2 (ESRI Inc., Redlands, CA, USA).

Propensity Score Matching was performed by the programming language Python with packages of pyreadstat, pandas, numpy and scikit-learn. In addition, the amount of insecticides in each trimester of pregnant mothers was calculated. The statistical analysis considered odds ratios using the generalized linear model (GLM) to examine the relationship between insecticide exposure during pregnancy and congenital hypothyroidism. It is adjusted for possible confounders identified by DAG (Figure 1). Statistical analyses were conducted using STATA 17.

Results

Geographical Distribution of CH Incidence and Pyrethroid Use

Congenital hypothyroidism incidence across 12 regions of Eastern Isfahan province revealed substantial geographical variability (Figure 2). The cumulative CH incidence per 1,000 live births was calculated and ranged to a maximum of 5.69 in Jarghooyeh, with other high-incidence areas including Varzaneh (4.64) and Harand (4.39) (Table 1).

These regional differences appeared to align, in part, with patterns of pyrethroid insecticide use. In Harand, Jarghooyeh, and Varzaneh respectively, both fogging and spraying applications of pyrethroids were employed extensively (Table 1).

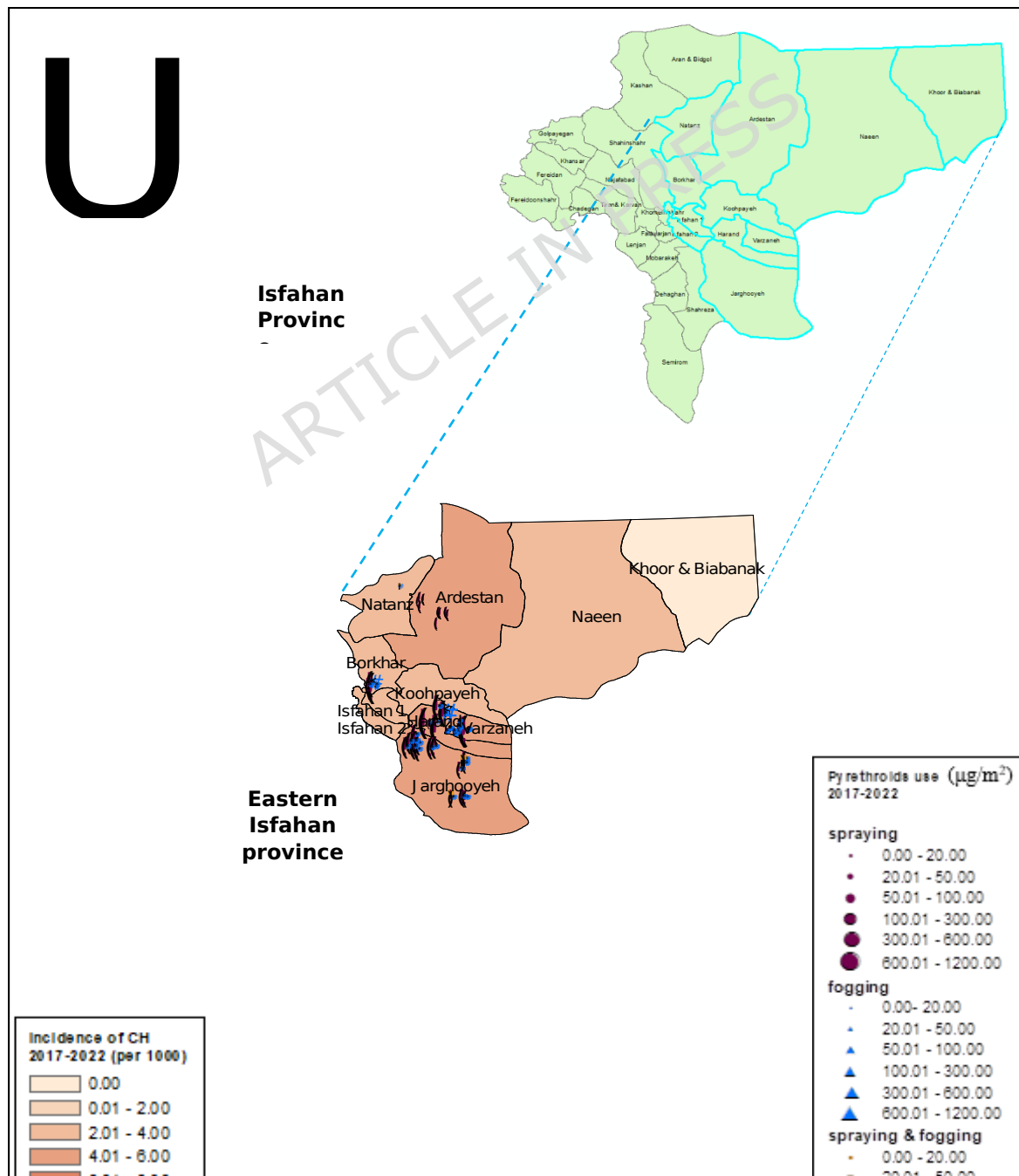


Fig 2. Geographical distributions of CH incidence and estimated residential pyrethroids high-use ($\mu\text{g}/\text{m}^2$) 2017-2022 using ArcGIS (version 10.8.2; <https://www.esri.com/en-us>)

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Table 1. Distributions of congenital hypothyroidism incidence by counties and total residential pyrethroids use ($\mu\text{g}/\text{m}^2$) 2017-

Eastern Isfahan province	Isfahan 1 ^a	Isfahan 2 ^b	Ardestan	Borkhar	Jarghooyeh	Khoor & biabanak	Varzaneh	Koohpayeh	Naeen	Natanz	Harand	
CH incidence (per 1000)	2.89	2.25	4.22	3.28	5.69	0.00	4.64	3.16	3.24	2.48	4.39	
Type of pyrethroids	Fogging	-	-	-	DM ^c	DM	-	DM & S-2703 ^d	-	-	DM	DM
	Spraying	-	-	DM & CP	DM	DM	-	DM & LCT ^e	-	-	DM	DM
	Fogging & spraying	-	-	-	-	DM	-	DM	-	-	-	-
Total amount of pyrethroids ($\mu\text{g}/\text{m}^2$)	0.00	0.00	582.53	1502.64	2771.21	0.00	2659.73	0.00	0.00	4.77	3771.71	

2022

^a One of the two important sections of eastern Isfahan city in the divisions of health centers named Isfahan 1

^b One of the two important sections of eastern Isfahan city in the divisions of health centers named Isfahan 2

^c The most commonly used insecticide in all leishmaniasis regions and in all years studied was deltamethrin

^d S-2703 was only applied in 2018

^e LCT was only applied in 2019

Abbreviations: Deltamethrin **DM**, Cypermethrin **CP**, cyphenothrin **S-2703**, lambda-cyhalothrin **LCT**

Participant Characteristics

A total of 37085 mother-newborn pairs were included in our study, with 98% linkage of maternal data and CH following data. After propensity score matching, 744 mother-newborn pairs were included in the final analysis, comprising 124 confirmed congenital hypothyroidism (CH) cases and 620 matched controls. Table 2 summarizes maternal and birth characteristics.

The largest proportion of mothers fell within the 35–39 years category (similar in both groups of cases and controls). More than half of the mothers had a BMI within the normal range of 18.5–24.9 (54.1% in both groups), and only a minority of mothers were classified as obese. Educational level followed a similar pattern across groups. The majority of mothers had 7–12 years of education. Regarding pregnancy complications, the frequency of thyroid disorders was similar between the groups (32.3% in cases vs. 31.5% in controls). The proportion of male newborns was higher among cases (62.90%) compared to females (37.10%). Newborn outcomes also showed relevant disparities. The proportion of infants with abnormal birth weight was more than twice as high in the case group compared to controls (19.4% vs. 8.4%). Similar trends, though less pronounced, were noted for abnormal birth length (16.5% vs. 13.8%) and abnormal head circumference (16.9% vs. 13.4%). A more notable difference emerged for gestational age: 22.6% of mothers in the case group delivered at ≤ 36 weeks, compared to 9.4% in the control group, indicating a higher prevalence of preterm birth among cases. More than 91% of mothers in both groups reported being housewives, with only a small fraction employed outside the home. The distributions of maternal BMI, maternal age, pregnancy complications, exposed year, and maternal education, the matched variables according to the PS matching method, were relatively similar between the two groups.

		Controls(N=620) N (%)	Cases(N=124) N (%)
Maternal age	≤24	20(3.23%)	4(3.23%)
	25-29	90(14.52%)	18(14.52%)
	30-34	209(33.71%)	41(33.06%)
	35-39	216(34.84%)	43(34.68%)
	≥40	85(13.71%)	18(14.52%)
Maternal body mass index (BMI)	<18.5	50(8.20%)	10(8.20%)
	18.5-24.9	330(54.10%)	66(54.10%)
	25-29.9	170(27.87%)	34(27.87%)
	≥30	60(9.84%)	12(9.84%)
Mother's education level	Zero years of education	11(1.79%)	3(2.44%)
	1-6 years of education	46(7.47%)	9(7.32%)
	7-12 years of education	355(57.63%)	71(57.72%)
	More than 12 years of education	204(33.12%)	40(32.52%)
Mother's job status	House wife	497(91.19%)	104(91.23%)
	Job outside the home	48(8.81%)	10(8.77%)
Gestational age	≤36	58(9.35 %)	28(22.58 %)
	≥37	562(90.65%)	96(77.42%)
Pregnancy complications	No complications	425(68.55%)	84(67.74%)
	Thyroid disorders	195(31.45%)	40(32.26%)
Exposed year	2017	70(11.29%)	14(11.29%)
	2018	95(15.32%)	19(15.32%)
	2019	145(23.39%)	28(22.58%)
	2020	124(20.00%)	25(20.16%)
	2021	126(20.32%)	25(20.16%)
	2022	60(9.68%)	13(10.48%)
Sex of newborn	Boy	330(53.23%)	78(62.90%)
	Girl	290(46.77 %)	46(37.10%)
Birth weight	Normal	568(91.61%)	100(80.65%)
	Non-normal	52(8.39%)	24(19.35%)
Birth length	Normal	505(86.18%)	101(83.47%)
	Non-normal	81(13.82%)	20(16.53%)
Birth head circumference	Normal	537(86.61%)	103(83.06%)
	Non-normal	83(13.39%)	21(16.94%)

Table2. Maternal and birth characteristics

Association between Prenatal Pyrethroid Exposure and CH

Trimester-Specific Exposure

As shown in Table 3, maternal exposure to residential pyrethroids during pregnancy demonstrated trimester-specific differences in association with congenital hypothyroidism (CH).

In the crude analysis, second- and third-trimester exposures were each associated with a more than two-fold increase in the odds of CH compared to non-exposure ($OR_{crude} = 2.25$; 95% CI: 0.90–5.61 for both). After adjustment for sex of newborn, birth weight, birth length, head circumference, gestational age, and maternal job status, the association strengthened for second-trimester exposure ($OR_{adjusted} = 3.00$; 95% CI: 1.13–7.93), reaching statistical significance. Similarly, third-trimester exposure remained positively associated with CH in the adjusted model ($OR_{adjusted} = 2.54$; 95% CI: 0.98–6.57), although the confidence interval marginally included the null value.

First-trimester exposure was associated with weaker and statistically non-significant odds of CH ($OR_{crude} = 1.58$; 95% CI: 0.56–4.41; $OR_{adjusted} = 1.74$; 95% CI: 0.58–5.15).

Cumulative Exposure during Pregnancy

When pyrethroid exposure was assessed cumulatively across the entire pregnancy, a significant association with CH was observed. In the crude model, overall exposure was associated with nearly double the odds of CH (OR_{crude} = 1.98; 95% CI: 1.08-3.65). This relationship persisted and strengthened after adjustment (OR_{adjusted} = 2.33; 95% CI: 1.22-4.45). Figure 3 shows the crude and adjusted odds ratios (ORs) and 95% confidence intervals for pyrethroid exposure during pregnancy.

Table 3. Relationship between exposure to residential pyrethroids during pregnancy and congenital hypothyroidism

		Controls(N=620) N (%)	Cases(N=124) N (%)	Crude OR (CI)	Adjusted OR* (CI)
Pyrethroid_trimester1	Non-exposed	604(97.42 %)	119(95.97%)	1	1
	Exposed	16(2.58%)	5(4.03%)	1.58 (.56-4.41)	1.74 (.58-5.15)
Pyrethroid_trimester2	Non-exposed	604(97.42%)	117(94.35 %)	1	1
	Exposed	16(2.58%)	7(5.65%)	2.25 (.90-5.61)	3.00 (1.13-7.93)
Pyrethroid_trimester3	Non-exposed	604(97.42%)	117(94.35%)	1	1
	Exposed	16(2.58%)	7(5.65 %)	2.25 (.90-5.61)	2.54 (.98-6.57)
Pyrethroid_total	Non-exposed	577(93.06%)	108(87.10%)	1	1
	Exposed	43(6.94 %)	16(12.90%)	1.98 (1.08-3.65)	2.33 (1.22-4.45)

* Adjusted for birth and maternal characteristics including: sex of newborn, birth weight, birth length, birth head circumference, gestational age, mother's job status (with excluding matched variables)

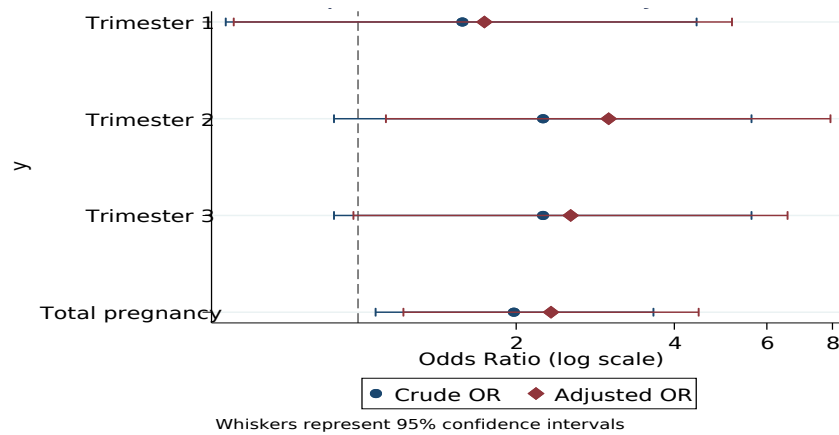


Fig 3. Forest plot showing crude and adjusted odds ratios (ORs) and 95% confidence intervals for pyrethroid exposure during pregnancy. The vertical dashed line indicates the null value (OR = 1)

Discussion

A major contribution of our study is its focus on pyrethroids used in residential areas, beyond agricultural applications. While many previous epidemiologic studies have concentrated on agricultural workers or farm-adjacent communities, our findings highlight that urban and peri-urban household use of pyrethroids for leishmaniasis control represents an additional and largely under-recognized source of exposure for pregnant women. This is particularly important in regions where vector-borne disease control programs promote indoor spraying or where domestic use of pyrethroid-based insecticides is common [26].

Supporting this, biomonitoring studies have shown detectable pyrethroid metabolites in pregnant women across both rural and urban settings, often correlating with self-reported indoor insecticide use rather than agricultural contact alone [27,28].

This population-based case-control study using propensity score matching, observed a positive association between maternal exposure to pyrethroid insecticides during pregnancy and the risk of congenital hypothyroidism (CH) in offspring. The results showed that second-trimester exposure may represent a particularly sensitive window for thyroid disruption, while cumulative exposure throughout pregnancy is consistently associated with elevated CH risk, independent of measured birth and maternal factors.

Several mechanisms support the association between pyrethroid exposure and CH. Pyrethroids and their metabolites (e.g., 3-PBA) can bind to thyroid hormone transport proteins such as transthyretin, disrupting placental thyroid hormone transfer [29]. They have also been shown to interfere with deiodinase activity and thyroid hormone receptors, leading to altered TSH and thyroxine levels in animal studies [30, 31]. Importantly, pyrethroids cross the placental barrier and accumulate in fetal tissues, where they may impair the development of the fetal thyroid gland [32].

Because fetal thyroid function is not fully established until mid-gestation, any maternal thyroid disruption in early pregnancy could impair fetal neurodevelopment and increase the risk of congenital hypothyroidism [29, 30].

Our findings align with growing concerns regarding the endocrine-disrupting potential of pyrethroids. Experimental studies have increasingly demonstrated their ability to disrupt thyroid hormone homeostasis [33]. Specifically, animal models have shown that prenatal exposure to pyrethroids can reduce circulating thyroxine (T4) and triiodothyronine (T3) levels, and interfere with the expression of genes involved in thyroid hormone synthesis and metabolism [34,35].

Thyroid hormones are essential for fetal brain development, growth, and metabolic regulation, and the fetal thyroid gland begins to function independently around the end of the first trimester. Thus, exposure to thyroid-disrupting chemicals during the second and

third trimesters may have more pronounced effects on fetal thyroid function [36]. Our results support this hypothesis, as associations with CH were stronger during later stages of gestation.

Previous epidemiologic studies on this topic are limited but provide supporting evidence. A study by Chevrier et al. (2011) reported a significant inverse association between pyrethroid metabolites in maternal urine and neonatal T4 levels. Similarly, studies conducted in China and the United States have observed associations between prenatal exposure to pyrethroids and altered neonatal thyroid hormone profiles [37, 38].

The Odense Child Cohort demonstrated that urinary levels of the pyrethroid metabolite 3-PBA were positively associated with maternal free T3 concentrations in early pregnancy, indicating subtle thyroid axis perturbation [39]. A South African cohort similarly observed associations between maternal pyrethroid metabolites and elevated neonatal TSH levels [40].

However, not all studies have been consistent. A Japanese birth cohort found no significant relationship between maternal 3-PBA in early pregnancy and neonatal thyroid hormone levels [41]. This variability may reflect differences in exposure intensity, timing, and sources—particularly the inclusion or exclusion of residential pesticide exposure in study designs.

A recent meta-analysis of epidemiological studies on pyrethroids and thyroid function found a modest but significant association between pyrethroid exposure and hypothyroidism (OR_{adjusted} = 1.15; 95% CI: 1.03–1.28) [42]. Our study strengthens this evidence by linking prenatal exposure specifically to congenital hypothyroidism.

However, few studies to date have directly investigated the association with clinically diagnosed CH, making our study one of the first to do so in a real-world population.

Strengths and Limitations

Key strengths of our study include the use of a well-defined population-based case-control design and assessment of trimester-specific exposure effects. Additionally, we carefully used propensity score matching for confounding control, which strengthens the internal validity

of our findings. However, limitations remain. Despite the matching and adjustment, unmeasured confounding from factors such as iodine intake, genetic predisposition, or co-exposure to other endocrine disruptors cannot be ruled out. The study evaluates a rare outcome and a relatively low frequency of exposure to residential pyrethroids. These two factors inherently reduce the statistical power to detect modest associations.

Conclusions

Our findings contribute to the limited but growing body of evidence suggesting that maternal exposure to pyrethroid insecticides during pregnancy, particularly in the second trimester, may increase the risk of congenital hypothyroidism. Given the widespread use of these compounds, these findings underscore the importance of precautionary public health measures and the need for further longitudinal studies to elucidate causality and underlying mechanisms.

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Author Contribution Statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AH, MM, AE and MRM. The first draft of the manuscript was written by AH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors declare no competing interests.

Data Availability Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics declarations

This is an observational study. This study received approvals from the ethical committee of Isfahan University of Medical Sciences (ethical code: IR.ARI.MUI.REC.1401.255).

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Figure legends

Fig. 1. Direct acyclic graph reporting the identification of potential confounders in the relationship between pyrethroid insecticides during pregnancy and congenital hypothyroidism

Fig 2. Geographical distributions of CH incidence and estimated residential pyrethroids high-use ($\mu\text{g}/\text{m}^2$) 2017-2022 using ArcGIS (version 10.8.2; <https://www.esri.com/en-us>)

Fig 3. Forest plot showing crude and adjusted odds ratios (ORs) and 95% confidence intervals for pyrethroid exposure during pregnancy. The vertical dashed line indicates the null value (OR = 1)

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