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Endocrine disruptors as risk factors for idiopathic premature thelarche in girls: A case-control study

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ABSTRACT

Introduction. Idiopathic premature thelarche (IPT) is defined as breast growth in girls before age 8 without activation of the gonadotrophic axis. Among the probable etiologies, endocrine disruptors (ED) with estrogenic action have been suggested.

Objective. To evaluate whether there is an association between exposure and degree of exposure to the main EDs with estrogenic action in our environment and the development of IPT.

Population and methods. Structured survey of caregivers of girls aged 3 to 8 years diagnosed with IPT and controls. The exposure evaluated included different EDs: bisphenol A (BPA), phytoestrogens, phthalates, and parabens, considering the degree of exposure according to weekly frequency.

Results. Caregivers of 50 cases (7.2±1.3 years) and 48 controls (6.7±1.5 years) were interviewed. An association was found between IPT and exposure to phytoestrogens in food (OR: 14.6; 95%CI 1.8-118; $p<0.01$), the use of BPA containers exposed to temperature changes (OR 2.6; 95%CI 1.1-6.5; $p<0.05$), contact with phthalates (OR 2.9; 95%CI 1.2-7.5; $p<0.05$) and parabens (OR 2.7; 95%CI 1.2-6,1; $p<0.05$). In all the detailed EDs, we also found an association of IPT according to their degree of exposure.

Conclusions. Exposure and degree of exposure to different sources of phytoestrogens, BPA, parabens, and phthalates were associated with the development of IPT.

Keywords: *endocrine disruptors; premature puberty; bisphenol A; phytoestrogens; parabens.*

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INTRODUCTION

One of the disorders of premature sexual development in girls is idiopathic premature thelarche (IPT). Premature thelarche is the unilateral or bilateral breast development in girls before age 8 without activating of the gonadotrophic axis, nor acceleration of growth velocity or advancement in bone maturation. It is considered a non-progressive "pubertal variant" and a benign condition, but it is a differential diagnosis of central precocious puberty.[1-3]

In several regions of the world in recent decades, an advance in the onset of breast development has been described without an association with an advance in the age of menarche. Endocrine disruptors (ED) are the most important determinants that explain this phenomenon.[2-5]

EDs were defined by the Endocrine Society in 2015 as "an exogenous chemical substance or mixture of chemicals that interferes with any aspect of hormonal action."[6] EDs with estrogenic action can act at the central level of the hypothalamic-pituitary-gonadal axis by interfering with inhibitory feedback mechanisms or in peripheral tissues by mimetic action with the natural hormone.[4,7,8] They are ubiquitous in industrial chemicals, foods, plastics, and everyday materials of daily life. These substances can enter the body via transdermal, oral, or inhalation routes.[2]

The most widespread EDs with estrogenic action of natural origin are the phytoestrogens contained in soy. These are remarkably similar in their chemical structure to natural estrogen (17βestradiol), with mimicry at the receptor level. Among the synthetic EDs, bisphenol A (BPA), phthalates, and parabens are the most widely used in materials frequently consumed in urban environments.[3,7,9]

BPA in plastic materials is released into beverages or food in plastic containers after being exposed to temperature variations, thus leading to inadvertent ingestion.[3,10] These substances are xenoestrogens and, therefore, can act as estrogens with less biological activity.[7,11] Parabens are used as preservatives in cosmetics, including make-up and hair products. Phthalates were employed as raw materials such as polyvinyl or additives in the production of plastics.[12] Research on the effects of EDs faces multiple difficulties: variable non-linear dose-response curves, additive biological effect among them, different inter-individual vulnerability, variable latency periods, and the lack of technical knowledge related to the quantification in blood/tissue of EDs and their metabolization, among others.[13,14] However, in the literature, numerous publications are linking the action of EDs with premature breast development in girls.[3,4,7,8,15-19]

OBJECTIVE

To evaluate whether there is an association between exposure and degree of exposure to the main EDs with estrogenic action in our environment and the development of IPT in girls.

POPULATION AND METHODS

Observational, analytical, case-control study. The study population was girls between 3 and 8 years old who attended the Hospital de Niños Dr. Ricardo Gutiérrez. The cases included girls who consulted for the first time in the outpatient clinics of the Endocrinology Division when the diagnosis of IPT was confirmed, defined by the onset of unilateral or bilateral breast development under 8 in the absence of other signs of puberty, without acceleration of growth velocity or progression of bone age. The controls were healthy girls seen at the longitudinal follow-up clinic who attended for health control or spontaneous demand but without premature breast development at the physical examination They were incorporated sequentially and matched by age with the cases.

Girls on a special diet or receiving medication for chronic disease, except inhaled corticosteroids, were excluded.

A structured survey was designed to evaluate exposure to estrogenic EDs adapted to our social reality and easy to understand for caregivers. For this purpose, fieldwork was conducted in which the components of different mass-consumption products (food, personal care/hygiene products, games, and environment) were inspected by reading the labeling. Among these products, we selected 4 EDs with estrogenic action: BPA, phytoestrogens, phthalates, and parabens.

The survey consisted of 17 questions (*Supplementary Material*). Each one of them identified an exposure variable, and the degree of exposure was recorded as follows: "no exposure" when the weekly frequency was zero, "low exposure" when it was from 1 to 3 times per week, and "high exposure" when the frequency was four or more times per week. A pilot test was conducted to verify that the questions were easy to understand. The same researcher administered the survey, read and explained the questions, and recorded the answers.

The protocol of this study was approved by the Ethics Committee of the Hospital de Niños Dr. Ricardo Gutiérrez (N.° 7779). Informed consent was given in writing before the survey was conducted.

Statistical analysis

For the description of numerical variables, we used mean, standard deviation, and proportion for categorical variables.

To evaluate the association of each exposure variable and IPT, the Chi-square test and chi-square for linear trend were additionally performed to assess the association with the degree of exposure. Then, the variables with statistical significance that evaluated exposure to the same ED were grouped. To estimate the association of each ED with IPT, the Chi-squared test was used and expressed as an odds ratio (OR, 95%CI). A *p*-value <0.05 was considered significant. GraphPadPrismversion™ 5.00 (www.graphpad.com) was used.

The sample size was not estimated but corresponds to all patients attending the Endocrinology Division for IPT and age-matched controls during the period.

RESULTS

Fifty girls with IPT and 48 age-matched controls were included in the study from October 1, 2022, to October 1, 2023. Ninety-eight caregivers (95% mothers) were surveyed (*Figure 1*). At the time of the survey, girls with IPT were 7.2±1.3 years old, and controls were 6.7±1.5 years old (*p* = NS). The onset of breast development in the IPT group was 6±2.3 years.

There was no difference in the cases' and controls' geographic area of origin. The origin was the City of Buenos Aires in 36% and 24%, the first belt of the Greater Buenos Aires in 12% and 22%, the second belt in 42% and 40% of cases and controls, respectively, and the third belt in 8% in both groups (*p* = NS).

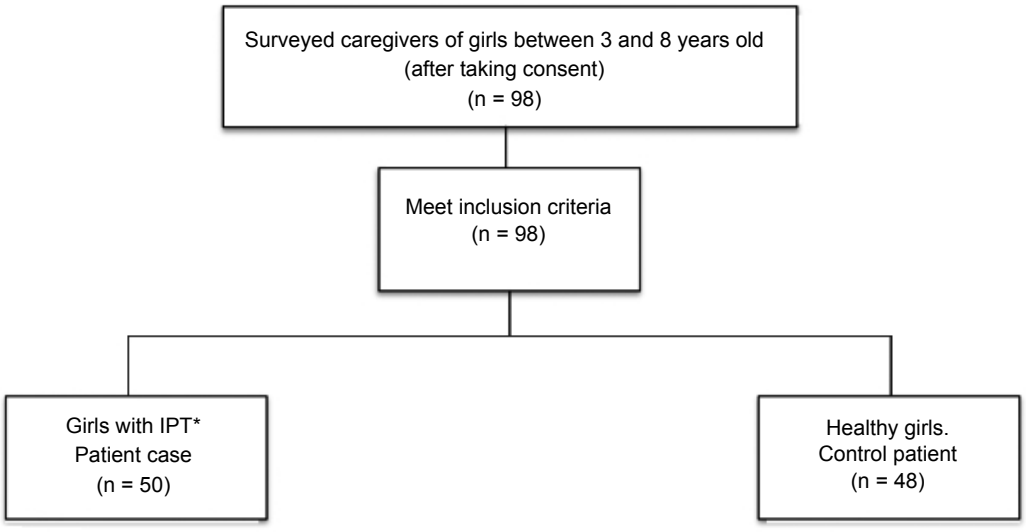
Table 1 summarizes the analysis of the association with the IPT for each variable identified in the survey and then with the degree of exposure.

Table 2 shows the association analysis of the IPT, but by category of each ED evaluated, grouping only the variables with statistical significance.

Bisphenol A (BPA)

Among the sources of BPA evaluated, the following variables significantly associated with IPT were heating food or beverages in plastic containers (microwave oven, electric kettle), reusing plastic containers to refrigerate beverages, and using plastic film/bags for cooking food. No association was found with the transfer of beverages in plastic containers, consumption of canned food, or consumption of beverages in tetra-brick containers (both with plastic lids) (*Table 1*).

Figure 1. Flow chart showing the distribution of patients by group



**IPT: idiopathic premature thelarche.*

Considering only the variables evaluated with a significant association, the BPA category showed an OR = 2.6 (95%CI 1.1-6.5; *p* <0.05) for the development of IPT (*Table 2*).

Phytoestrogens

The survey showed a significant association between IPT and the consumption of soy or its derivatives (whether in full knowledge or inadvertently, as occurs with frozen ultra-processed foods containing it. 88% of the girls surveyed had some degree of exposure to phytoestrogens. No association was found in this sample size concerning the extensive consumption of candies/crackers containing soy derivatives. Nevertheless, the weekly frequency of consumption has an influence, as reflected by the Chi^2 of linear trend test (*Table 1*).

The evaluation of the phytoestrogen category showed an elevated risk for the development of IPT with OR = 14.6 (95%CI 1.8-118; *p* <0.01) (*Table 2*).

Table 1. Association between exposure to endocrine disruptors and premature thelarche for each variable extracted from the survey

	n total exp./ total girls	n exp. cases /total cases	n exp. control/s total controls	Chi^2	Chi$^{2\ for}$ linear trend
BISPHENOL A					
The habit of heating food or beverages in plastic containers	45/98	29/50	16/48	*p* <0.05	*p* <0.05
Transfer of beverages to plastic containers	82/98	42/50	40/48	*p* = NS	*p* = NS
Reusing plastic containers for refrigerated beverages	52/98	32/50	20/48	*p* <0.05	NA*
Use of plastic films/bags for cooking food	15/98	13/50	2/48	*p* <0.01	*p* <0.01
Consumption of canned food	77/98	40/50	37/48	*p* = NS	*p* = NS
Consumption of beverages in tetra-brik packaging	78/98	40/50	38/48	*p* = NS	*p* = NS
PHYTOESTROGENS					
Soybean consumption in ultra-processed foods	83/98	48/50	35/48	*p* <0.05	*p* <0.001
Soy food consumption	26/98	18/50	8/48	*p* <0.05	*p* <0.05
Soy derivatives in candies	97/98	50/50	47/48	*p* = NS	*p* <0.05
PARABENS					
Use of cosmetic creams with parabens in caregivers	37/98	21/50	16/48	*p* = NS	*p* = NS
Use of make-up in girls	51/98	32/50	19/48	*p* <0.05	*p* <0.05
Use of moisturizer/sunscreen with parabens on girls	45/98	25/50	20/48	*p* = NS	*p* = NS
Use of insect repellents with parabens	68/98	36/50	32/48	*p* = NS	*p* = NS
Use of lice killers with parabens	13/98	10/50	3/48	*p* = NS	*p* = NS
PHTHALATES					
Nail polish used in girls	46/98	29/50	17/48	*p* <0.05	*p* <0.001
Use of slime as a game	53/98	36/50	17/48	*p* <0.001	*p* <0.001

**NA: Not applicable, NS: Not significant.*
Exp.: exposed. Chi^2 represents the measure of association. The chi^2 for linear trend represents the association with the degree of exposure.

Table 2. Pooled analysis by category of each endocrine disruptor for risk of idiopathic premature thelarche

Category of endocrine disruptor	n total exp./ total girls	n exp. cases/ total cases	n exp. controls/ total controls	Strength of association
Phytoestrogens	86/98	49/50	37/48	OR = 14.6 (95%CI 1.8-118) *p* <0.01
Bisphenol A	69/98	40/50	29/48	OR = 2.6 (95%CI 1.1-6.5) *p*<0.05
Parabens	51/98	32/50	19/48	OR = 2.7 (95%CI 1.2-6.1) *p* <0.05
Phthalates	70/98	41/50	29/48	OR = 3 (95%CI 1.2-7.5) *p* <0.05

Exp: exposed. OR: odds ratio.

Parabens

Among the variables evaluated, it was found that the use of make-up by girls and the degree of exposure by frequency were significantly associated with IPT (*Table 1*), with an OR = 2.7 (95%CI 1.2-6.1; p <0.05) (*Table 2*). The percentage of girls surveyed who used both adult and children's make-up products was 52%.

There was no association with using cosmetic creams with parabens in the caregivers, moisturizers/sunscreen with parabens in the girls, insect repellents, or lice killers with parabens (*Table 1*).

Phthalates

Using nail polish in girls and slime as a game showed significant associations with IPT and the degree of exposure by frequency (*Table 1*). For phthalates, an OR = 2.9 (95%CI 1.2-7.5; p <0.05) was determined for the development of IPT (*Table 2*). The proportion of girls surveyed who used nail polish was 47%.

DISCUSSION

In recent decades, evidence has emerged to support the hypothesis that EDs with estrogenic action may interfere with pubertal timing by acting centrally and peripherally.[8] Mechanisms include both interferences with hypothalamic inhibitory feedback mechanisms and peripheral action by mimicking the natural hormone, in addition to the influence on more complex epigenetic mechanisms that mainly modulate metabolism and development.

Although research on the health effects of EDs faces numerous obstacles,[12-14] in recent decades, evidence has been emerging on the potential role of EDs both directly and indirectly on the pathogenesis of IPT.[3-5,7,8,15-19]

This study is the first to report the situation of our population regarding the broad exposure in our environment to EDs with estrogenic action. Our results show that exposure to specific EDs is a risk factor for the development of IPT. Those with the most significant impact were soy phytoestrogens through food, but also important were BPA contained in plastic containers with beverages or food that are exposed to temperature changes, phthalates in nail polish or play (slime), and parabens in the use of make-up or cosmetic products.

Regarding BPA, consistent with the literature,[3,20] we found that only variables involving changes in container temperature were statistically significant.

The strongest association found for IPT was exposure to phytoestrogens; mainly, mass-consumed foods with added soy or soy derivatives were mainly evaluated. Even the risk of IPT was associated with the degree of exposure considered according to the highest weekly frequency of consumption. In the literature, there are reports of regional epidemics of IPT linked to natural phytoestrogens.[15-18]

A wide range of products containing soy and its derivatives was conspicuously evident during the fieldwork stage. The percentage of exposure among the girls surveyed was 88%.

Regarding parabens,[7,11] only the use of make-up by girls was statistically significant as a risk factor for IPT. The percentage of girls exposed to adult or children's make-up products was 52%.

Exposure to phthalates from slime play or nail polish use in girls would also be a risk factor associated with IPT. There are reports of such associations in the literature.[19,21]

In another aspect, it is worth mentioning that half of the girls surveyed, despite their young age, used make-up or nail polish at least weekly. This is a wake-up call for parents, caregivers, and professionals who assist girls with the commitment to protect and promote a healthy childhood. These habits could result from the influence exerted by mass sociocultural impact media, but they are modifiable.

Our study uses an evaluation tool specially designed to assess exposure to EDs with estrogenic action based on the recording of sources of daily contact adapted to the social reality of our environment, which is one of the strengths of our study. The survey was simple to answer and very well accepted by the caregivers. Although all surveys may have weaknesses such as information bias, 95% were responded to by mothers, who reported being the primary caregivers of the girls. As for recalling bias as another possible weakness, in this study, the questions were directed to habitual behaviors and their weekly frequency without evoking a specific period.

Our study is limited by the lack of quantitative measurement of EDs in biological fluids or consumed products, the lack of multivariate analysis, and the inability to discriminate the existence of an additive effect between the EDs evaluated or others. However, the degree of exposure was measured according to a scale that relates it to the weekly frequency of

exposure. We cannot know precisely whether the concentration of the EDs or the amount of the product consumed can contribute differentially to the association found.

The following recommendations emerge from our results: 1-prefer fresh and natural foods instead of ultra-processed foods, which usually contain added soy; 2-choose paraben-free products and especially avoid girls wearing make-up, 3-nail polish as well as slime, both sources of phthalates, should also be avoided; 4-do not heat food in plastic containers containing BPA or covered with film; 5-keep refrigerated water for daily consumption in glass containers and prefer to carry food or beverages in stainless steel containers.

CONCLUSION

The survey developed proved to be a valuable tool for detecting girls' exposure to estrogenic EDs in our setting.

The results show statistically significant associations between exposure and the degree of exposure to different sources of phytoestrogens, BPA, parabens, and phthalates as risk factors for developing IPT.

Our study provides the basis for further studies, specifically designed to provide more evidence and establish a causal relationship between exposure to EDs and the development of IPT. Nevertheless, awareness of the presence of EDs and their potential impact will allow for recommendations that can contribute to a safer and healthier environment for our girls. ■

The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2025/10501_AO_Palmieri_Anexo.pdf

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