



CLINICAL ARTICLE

Obstetrics

The influence of maternal respiratory allergy on obstetrics and perinatal outcomes: A nested case-control study

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Abstract

Objective: To evaluate the influence of respiratory allergy on obstetrics and perinatal outcomes.

Methods: A nested case-control retrospective study on 41035 pregnant women. Obstetrics and perinatal outcomes of women with or without respiratory allergy were compared. Rates of preterm delivery (<37 weeks of gestation), low birth weight (<2500 g), neonatal acidosis (pH < 7.20), low 5-min APGAR score (<7), cesarean section rate and indications, and perinatal morbidity and mortality were analyzed. Results are expressed as number and percentages. χ^2 and Fisher exact tests were used for comparisons. Logistic regression was used. Statistical significance was set at 95% level ($P < 0.05$).

Results: A total of 724 (1.8%) patients had respiratory allergy, and their rates of preterm delivery and low birth weight were significantly higher than those of control women (both $P < 0.001$). Nevertheless, analyzing the causes, multiple gestation rate was significantly higher in this group, and adjusting by this, no statistical difference was found in any of the perinatal outcomes studied. In addition, in vitro fertilization and sterility were also significantly higher in the respiratory allergy group (both $P < 0.001$).

Conclusion: Women with respiratory allergy are at higher risks of prematurity and low birth weight but these results are mediated by sterility, in vitro fertilization, and multiple gestation rate. Nonetheless, participation of inflammatory mechanisms should be further studied.

KEYWORDS

in vitro fertilization, multiple gestation, perinatal outcomes, pregnancy, respiratory allergy, sterility

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1 | INTRODUCTION

Atopic diseases have been increasing in the last decades in western countries^{1,2} and are currently considered one of the most common chronic disorders in pregnant women.^{3,4} The estimated prevalence of hay fever in these countries was 10%–30%.¹ In Spain it affects 21.5% of the adult population.⁵ Furthermore, rhinoconjunctivitis mostly affects individuals in this age range with interesting gender differences, affecting women in 55.4% of cases. Similar data were found for patients with asthma. Allergic rhinitis and asthma are two well-related entities. It is estimated that up to 75% of adults who suffer from asthma-associated allergic rhinitis and 50% of patients with allergic rhinitis develop asthma.^{5,6} For women in this period of life, both entities overlap on the same timeline as when most pregnancies occur.

Our immunologic system is integrated as a complex network and can express different profiles depending on need and the production of cytokines.⁷ Physiologically, during pregnancy, different factors influence a shift towards T helper type 2 (Th2) immunity to prevent adverse perinatal outcomes.^{7,8} The T helper type 1 (Th1) response is essential for cell-mediated immunity and occurs for instance in response to viral or bacterial infections.^{1,7,8} Although, Th1-associated mediators are modified during early pregnancy.⁷ Some Th1 cytokines play an essential role during this period of time, such as interferon- γ , which has been related to implantation, preventing excessive trophoblast invasion and vascular remodeling.^{7,9} In pregnant women, predominance of Th1 reactivity has been related to infections during pregnancy and a dysregulation of T helper cell immunity to obstetrical complications, such as pre-eclampsia, spontaneous abortion, and recurrent pregnancy losses.^{1,6,7,10}

Atopic diseases deviate the immunologic system to a type 2 immunologic profile.³ In addition, the immunologic response during pregnancy is to also deviate to a Th2 cytokine profile for successful maternal tolerance of the foreign fetal antigens.^{1–3} Moreover, there are common cytokines and interleukins, such as interleukin-33, which play a key role in both conditions.¹ Chemokines and cytokines represent the key mediators for maintaining immunologic stability during pregnancy^{7,9} and some published data indicate that the production of cytokines is different in allergic and non-allergic women, with certain allergen-specific responses being magnified during this period in both groups.⁹

Theoretically, atopic conditions may be influencing fertility, obstetrics, and perinatal outcomes; however, their relationships are still unknown.^{1,2} Some studies have argued that it influences fertility negatively,^{2,10} showing that patients with asthma and allergic rhinitis have a higher prevalence of irregular menstruation and endometriosis.² When time to pregnancy, rate of spontaneous natural abortion, and reproductive history (fertility rate) were studied, no differences were found in patients with rhinitis.^{2,11,12} However, other studies found associations between patients with asthma and higher time to pregnancy, risk of abortions, preterm delivery (PTD), and low birth weight (LBW).^{2,10,12}

Other published literature related atopic diseases with a favorable factor regarding pregnancy, showing that hay fever and asthma, and patients with only hay fever, were more fertile because of a higher rate of live births per 1000 person-years, and they were not at risk of PTD nor LBW.¹ As PTD and intrauterine growth restriction have been associated with a predominance of Th1 profile,¹ some authors have suggested that a deviation from a Th2 response may be the key for these adverse pregnancy outcomes to develop.^{1,10}

Asthma has been well studied,³ but other atopic comorbidities are overlooked in our daily practice, and little is known about the possible effects of these conditions on pregnancy outcomes.

The aim of this study was to evaluate the influence of respiratory allergy on obstetrics and perinatal outcomes.

2 | MATERIALS AND METHODS

An analytical observational nested case-control population-based retrospective study was performed using data from June 2000 to June 2018 from a tertiary referral center in Madrid, Spain. Demographic information, maternal comorbidities, labor data, and obstetrical and perinatal outcomes were obtained from electronic medical records. Records with missing data were excluded.

Women were classified according to their allergic comorbidities. Respiratory allergy was defined as having rhinoconjunctivitis and/or asthma symptoms due to aeroallergen sensitization. Both were physician-diagnosed. Asthma was classified based on the GINA (Global Initiative for Asthma) classification. Seasonal and perennial allergies were analyzed.

Fertility was defined as the number of previous pregnancies. Infertility was defined as the number of previous spontaneous pregnancy losses. Parity was based on previous live births and stillbirths. Sterility rate and causes, and the need for in vitro fertilization (IVF) were recorded.

The rates of PTD (<37 weeks of gestation), LBW (<2500g), neonatal acidosis (pH <7.20), low 5-min APGAR score (<7), and cesarean section rate and indications were recorded. PTD was classified according to WHO criteria into four groups based on their weeks of gestation.¹³ Birth weight was classified according to WHO criteria into two groups.¹³ A composite variable of perinatal morbidity was defined as the presence of any of the following criteria: cesarean section due to fetal distress, neonatal AP score at 5 min less than 7, umbilical artery pH less than 7.20, or admission at neonatal care intensive unit. Perinatal mortality was also evaluated.

Qualitative variables were expressed as number and percentage, and Fisher exact and χ^2 tests were used for comparisons. Quantitative variables were shown as mean and standard deviation or as median and interquartile range according to their distribution. The analysis of variance and least significant difference as post hoc tests were used to compare normally distributed variables. Logistic regression was used to identify confounders, and univariate and multivariate regression analyses were computed to evaluate the impact of maternal characteristics on perinatal outcomes. Statistical

significance was set at the 95% level ($P < 0.05$) and analyses were performed with SPSS Statistics software, version 20 (IBM).

The study was approved by the local research Medical Ethics Committee (PI-5246). As a retrospective study, we obtained the approval to waive the consent form.

3 | RESULTS

In total, 41 035 pregnant patients were included in the study. Clinical characteristics and allergy-related comorbidities are shown in Table 1. Maternal age was 32.48 ± 5.61 years. Drug allergy, asthma, and rhinoconjunctivitis were the most prevalent allergic comorbidities affecting 3234 (7.9%), 1102 (2.7%), and 782 (1.9%) patients, respectively.

Table 2 shows the clinical characteristics of pregnant women with rhinoconjunctivitis and asthma. Regarding rhinoconjunctivitis, 782 (1.9%) patients were identified, 720 (92.1%) of them had allergy. Interestingly, 1102 (2.7%) patients had asthma, and 856 (77.7%) of them were not sensitized to any aeroallergen. In relation to asthma treatment, 957 (86.8%) used it only if necessary as most were classified as having mild asthma based on GINA classification (1080, 98%). Allergy was diagnosed in 724 (1.8%) patients, all of them had seasonal allergy sensitized to pollen (Table 3).

Pregnant women were classified into two groups based on their respiratory allergy, an allergic group of 724 (1.8%) women, who represented 1.8% of the studied population, and a control group of 40 311 (98.2%) women. Obstetrical and perinatal outcomes of both groups are shown in Tables 4, 5 and 6. The mean age of the allergic group was significantly higher compared with the control group (34.1 ± 5.6 vs. 32.45 ± 4.7 years respectively; $P < 0.001$). Previous

sterility rate was significant higher in the allergic group (68, 9.4% vs. 646, 1.6%, respectively; $P < 0.001$), and they had higher rates of IVF (28, 3.9% vs. 622, 1.5% respectively; $P < 0.001$), and multiple gestation (107, 14.8% vs. 2017, 5%; $P < 0.001$). No statistical differences were found analyzing fertility, infertility, and parity.

Concerning perinatal outcomes, gestational age at delivery (39.1 vs. 39.3 weeks; $P < 0.001$) and birth weight (3140 vs. 3210 g; $P < 0.001$) were lower in the allergic group, which caused higher rates of both PTD (106, 14.6% versus 3930, 9.7%; $P < 0.001$) and LBW (91, 12.5% vs. 3228, 8%; $P < 0.001$). No statistical differences were found regarding APGAR score, low 5-min APGAR score, pH of the umbilical cord, rates of neonatal acidosis, and perinatal morbidity and mortality. However, the rate of cesarean section was significantly higher in the allergic group (159, 22% vs. 7004, 17.4%; $P = 0.001$) (Tables 5 and 6). Analyzing cesarean section indications, different causes were reported. No statistical differences were found comparing singleton and twin pregnancies in women with or without respiratory allergy (Tables 7 and 8).

Studying the whole population, logistic regression showed that multiple gestation, maternal age, and sterility were independent factors for PTD, and multiple gestation, fertility rate, and pollen were independent factors for LBW. When adjusting for singleton pregnancies, sterility was no longer an independent factor for PTD and fertility rate was the only one left for LBW. In twin pregnancies, IVF was the only independent factor for PTD and no variables were found for LBW. When adjusting for these factors the presence of respiratory allergy was not associated with any of these perinatal complications.

4 | DISCUSSION

In the present study, women with respiratory allergy were older and had higher rates of cesarean section, PTD, and LBW. However, analyzing the possible causes, we found that the rate of multiple gestation was significantly higher in the respiratory allergy group, and adjusting by this factor, no statistical differences were found in any of the perinatal outcomes studied. Interestingly, IVF and female causes of sterility were also significantly higher in this group (both $P < 0.001$).

During their childbearing years, 18%–30% of women are affected by allergic diseases and 20%–40% report rhinitis.^{2,4,6} In this study, maternal age was similar to the mean age of the first pregnancy in Spain.^{14–16} However, the age of the patients with respiratory allergies was even higher, which has also been reported in other studies,^{4,17} suggesting a possible influence of allergy in women's fertility.^{1,10} Likewise the data reflected the increase in maternal age at the first pregnancy during the study period,^{10,14} showing that in Spain in 2000 the mean age was 30.74 years and in 2018 it was 32.2 years.¹⁴

Regarding allergic comorbidities, drug allergy was by far the most prevalent, as shown in other studies.⁶ Nevertheless, this could be a bias due to the importance of this condition, which makes it

TABLE 1 Clinical characteristics and allergy related comorbidities (N = 41 035)^a

Variable	
Age, year	32.48 ± 5.61
<25	5064
25–35	23155
≥36	12816
Allergic comorbidities	
Rhinoconjunctivitis	782 (1.91)
Asthma	1102 (2.69)
Food allergy	276 (0.67)
Drug allergy	3234 (7.88)
Atopic dermatitis	139 (0.34)
Contact dermatitis	227 (0.55)
Chronic urticaria	49 (0.12)
Latex allergy	183 (0.45)
Venom allergy	4 (0.009)

^aData are presented as mean \pm standard deviation, as number, or as number (percentage).

TABLE 2 Clinical characterization of pregnant women with rhinoconjunctivitis and asthma (N = 1688)^a

Variable	
Rhinoconjunctivitis	782 (1.91)
Allergic rhinoconjunctivitis	720 (92.1)
Non-allergic rhinoconjunctivitis	62 (7.9)
Asthma	1102 (2.69)
Allergic asthma	246 (22.3)
Non-allergic asthma	856 (77.7)
Asthma severity	
Mild	1080 (98)
Moderate	21 (1.9)
Severe	1 (0.09)
Asthma treatment	
Pro re nata	957 (86.8)
Maintenance	145 (13.2)
GINA classification ^b	
Step 1	951 (86.3)
Step 2	129 (11.7)
Step 3	11 (1)
Step 4	10 (0.91)
Step 5	1 (0.09)

^aData are presented as number (percentage).

^bGINA classification, Global Initiative for Asthma 2021.

more likely to be mentioned during any medical assessment. On the one hand, comparable studies have published similar percentages of pregnant women affected by rhinoconjunctivitis and asthma,^{3,4,11} as well as allergic rhinoconjunctivitis.⁵ On the other hand, allergic asthma was much lower than expected and mild asthma was higher compared with published data,¹ probably because most patients had mild asthma only, managed by their general practitioner, and they waited to be well-controlled and with the least medication possible to start their pregnancy. Even so, the retrospective nature of the study may be acting as a bias. Pollen was the main allergen to sensitize the population due to Madrid's geographical location.⁵

With regards to obstetrical characteristics, no differences were found in the rate of miscarriages and previous pregnancies, both in line with previous data published,^{6,10,18} which also suggested a good representation of the population attended in a tertiary hospital.

In terms of sterility, a higher rate was seen in patients with respiratory allergy, which was consistent with other published data,^{2,6} and recently led to hypothesize a biologic relation between allergy and infertility. Similar data have been published comparing male and female allergic and non-allergic patients,⁶ though no differences in sex were found.^{6,17}

Women with respiratory allergies had higher rates of IVF, which has also been seen in other studies,^{6,11} and environmental/other allergies have been associated with the number of embryos transferred⁶; although, no relation between them has been published.¹⁷

TABLE 3 Allergy classification and sensitization profile of pregnant women with allergic rhinoconjunctivitis and asthma (N = 724)^a

Variable	
Allergy ^b	724 (100)
Seasonal	724 (100)
Perennial	228 (31.5)
Pollen sensitization	724 (100)
<i>Cupressus arizonica</i>	305 (42.1)
<i>Platanys acerofila</i>	143 (19.8)
<i>Olea europaea</i>	420 (58)
Timothy grass	650 (89.8)
House dust mite	117 (16.1)
Animal dander	157 (21.7)
Cat dander	148 (94.3)
Dog dander	85 (54.1)
Other animal dander ^c	20 (12.7)

^aData are presented as number (percentage).

^bSeasonal allergy was due to pollen, and perennial allergy was due to house dust mite and animal dander. The inclusion criteria for the allergic group needed a confirmed diagnosis of allergy based on clinical history symptoms and either positive skin prick test or the detection of specific IgE in serum for aeroallergens, which were considered positive when ≥ 0.35 kUA/L.

^cOther animal dander: rabbits, hamsters, horses, and bird feathers.

Nonetheless, we did not include fertility variables that might have affected our results.

In relation to multiple gestation, a higher rate was found in the allergic group. Limited data have been published regarding this topic, as studies mainly included only singleton pregnancies. However, one study reported similar results in both groups.⁶

Regarding fertility and parity, no differences were found, which was in line with published data.^{2,11,17} Although others have reported controversial results,^{11,18} These findings have been related to the possibility that atopic patients delayed conception time or have problems conceiving.^{2,18} However, asthma has been related to higher pregnancy losses.¹⁰ Nevertheless, confounders have to be taken into consideration, especially in asthma, such as the age range of the patients included, time to pregnancy, first heterosexual vaginal intercourse, or method of contraception used; they are not usually analyzed but can influence published results.

The rates of PTD (9.8%) and LBW (8.1%) in the present study were similar to other published data from Europe and Spain, which established prevalences ranging from 5% to 13% and from 8% to 16%, respectively.^{15,16,18} However, in our population both variables were significantly higher in allergic women. Given that preterm babies are prone to have lower weights, both results were consistent. Nevertheless, when adjusting by multiple gestation, no differences were found in any of the variables studied.

To the best of our knowledge, no studies have been published showing differences in pregnant women with or without respiratory

TABLE 4 Obstetrical characteristics of pregnant women with and without respiratory allergy (N = 41 035)^a

Characteristics	Pregnant women with respiratory allergy (N = 724)	Pregnant women without respiratory allergy (N = 40 311)	P value
Age, year	34.13 ± 5.6	32.45 ± 4.7	<0.001
<25	27 (3.7)	4810 (11.9)	<0.001
25–35	419 (57.9)	22 509 (55.9)	
≥36	267 (36.9)	12 322 (30.6)	
Primigravid women	131 (18.1)	7800 (19.3)	0.095
Age of primigravid women, y ^b	32.9 ± 4.98	31.14 ± 5.8	<0.001
Number of miscarriages	198 (27.3)	12 138 (30.1)	0.263
≤3	192	11 862	0.479
>3	6	276	
Age of women with history of miscarriages, year	34.69 ± 4.77	33 ± 5.7	<0.001
Sterility	68 (9.4)	646 (1.6)	<0.001
Male cause	11 (16.2)	132 (20.4)	0.524
Female cause	57 (83.8)	514 (79.6)	
In vitro fertilization	28 (3.9)	622 (1.5)	<0.001
Multiple gestation	107 (14.8)	2017 (5)	<0.001
Fertility	594 (82)	32 726 (81)	0.595
Parity	594 (82)	32 739 (81)	0.628

^aData are presented mean ± standard deviation or as number (percentage).TABLE 5 Perinatal characteristics of pregnant women with and without respiratory allergy (N = 41 035)^a

Characteristics	Pregnant women with respiratory allergy (N = 724)	Pregnant women without respiratory allergy (N = 40 311)	P value
Gestational age at delivery, week	39.1 (38–40.1)	39.3 (38.3–40.2)	<0.001
Preterm delivery	106 (14.6)	3930 (9.7)	<0.001
Extremely preterm 24–28 week	12 (1.7)	338 (0.8)	<0.001
Early preterm 28–32 week	10 (1.4)	331 (0.8)	
Moderate preterm 32–37 week	86 (11.9)	3336 (8.3)	
Late preterm 34–37 week	80 (11)	2834 (7)	
Birth weight, g	3140 (2800–3460)	3210 (2900–3520)	<0.001
Low birth weight	91 (12.5)	3228 (8)	<0.001
Extremely low weight (<1500 g)	6 (0.8)	301 (0.7)	<0.001
Very low weight (1500–2500 g)	85 (11.7)	2927 (7.3)	
APGAR score, 1 min	9 (8–9)	9 (9–9)	0.594
APGAR score, 5 min	10 (9–10)	10 (9–10)	0.692
pH	7.27 (7.19–7.32)	7.27 (7.18–7.32)	0.17
Delivery			0.001
Vaginal delivery	565 (78)	33 307 (82.6)	0.001
Cesarean section	159 (22)	7004 (17.4)	

^aData are presented median (interquartile range) or as number (percentage).

allergy and perinatal outcomes in singleton and multiple pregnancies. Although, higher rates of PTD have been published with regards to patients with asthma,^{1,3} several studies found contradictory results regarding birth weight.^{1,3,19–21} Nevertheless, few studies have investigated the effect that allergic rhinoconjunctivitis has on these

outcomes, and inconsistent results have been published.^{1,3,4,18,20–22} United airway disease can be described as a concept used to emphasize that the respiratory tract combines both systems.^{23,24} However, a different organ-specific inflammatory response has also been proposed, which could explain the differences found.²⁴ Although some

TABLE 6 Perinatal outcomes of pregnant women with and without respiratory allergy (N = 41 035)^a

Characteristics	Pregnant women with respiratory allergy (N = 724)	Pregnant women without respiratory allergy (N = 40 311)	P value
Preterm delivery ^b	106 (14.6)	3930 (9.7)	<0.001
Low birth weight ^b	91 (12.5)	3228 (8)	<0.001
Neonatal acidosis	87 (12)	4745 (11.8)	0.839
Low 5-min APGAR score	12 (1.7)	552 (1.4)	0.509
Perinatal morbidity	109 (15.1)	6162 (15.3)	0.862
Perinatal mortality	0	101 (0.25)	0.415
Cesarean section indications	159 (22)	7004 (17.4)	<0.001
Previous cesarean section and immature cervix	12 (7.55)	469 (6.7)	<0.001
Breech presentation	12 (7.55)	562 (8.02)	
Transverse situation	1 (0.63)	58 (0.83)	
Multiple gestation (first breech)	35 (22)	409 (5.84)	
Placenta previa	1 (0.63)	68 (0.97)	
Iterative cesarean section	1 (0.63)	262 (3.74)	
Previous uterine surgery	3 (1.89)	42 (0.6)	
Fibroid or tumor	0	14 (0.2)	
Abnormality or infection of the soft birth canal	1 (0.63)	4 (0.06)	
Pre-eclampsia	6 (3.77)	71 (1.01)	
Diabetes	0	8 (0.11)	
HIV infection	0	17 (0.24)	
Vaginal delivery contraindicated for other reasons	1 (0.63)	85 (1.21)	
Poor previous obstetrical history	1 (0.63)	8 (0.11)	
Induction failure	14 (8.80)	878 (12.54)	
No progression of labor	24 (15.09)	935 (13.35)	
Cephalopelvic disproportion	19 (11.95)	981 (14)	
Fetal distress	24 (15.09)	1776 (25.36)	
Other causes ^c	4 (2.52)	357 (5.1)	

^aData are presented as number (percentage).^bThe odds ratio and 95% confidence interval of preterm delivery were 1.59 (1.29–1.96) and for low birth weight were 1.65 (1.32–2.06).^cOther causes included fetal macrosomia, fetal structural abnormality, fetal disease, fetal prematurity, maternal age, and maternal request.TABLE 7 Perinatal outcomes of pregnant women with respiratory allergy and singleton pregnancy (N = 38 905)^a

Characteristics	Pregnant women with respiratory allergy (N = 617)	Pregnant women without respiratory allergy (N = 38 288)	P value
Preterm delivery	37 (6)	2797 (7.3)	0.274
Low birth weight	29 (4.7)	2217 (5.8)	0.297
Neonatal acidosis	69 (11.2)	4511 (11.8)	0.701
Low 5-min APGAR score	9 (1.5)	472 (1.2)	0.578
Perinatal morbidity	87 (14.1)	5797 (15.1)	0.495
Perinatal mortality	0	87 (0.2)	0.415
Rate of cesarean section	103 (16.7)	6132 (16)	0.622
Cesarean section due to fetal distress	22 (3.6)	1668 (4.4)	0.423

^aData are presented as number (percentage).

TABLE 8 Perinatal outcomes of pregnant women with respiratory allergy and twins (N = 2130)^a

Characteristics	Pregnant women with respiratory allergy (N = 107)	Pregnant women without respiratory allergy (N = 2023)	P value
Preterm delivery	69 (64.5)	1133 (56)	0.109
Low birth weight	62 (57.9)	1011 (50)	0.136
Neonatal acidosis	18 (16.8)	234 (11.6)	0.123
Low 5-min APGAR score	3 (2.8)	80 (4)	0.797
Perinatal morbidity	22 (20.6)	365 (18)	0.521
Perinatal mortality	0	14 (0.7)	>0.99
Rate of cesarean section	56 (52.3)	872 (43.1)	0.072
Cesarean section due to fetal distress	2 (1.9)	108 (5.3)	0.173

^aData are presented as number (percentage).

of these studies require careful evaluation as data were extracted from national registers, patients with severe rhinitis were sometimes excluded, not all had an allergic etiology, and their geographical variations may not have been considered.

Concerning perinatal morbidity and mortality, no differences between groups were found. The rates were consistent with previous publications.^{3,16} LBW and PTD have been associated with an increased risk of serious neonatal morbidity and mortality.^{15,20} Maternal asthma has also been associated with perinatal mortality.²⁵ However, little is known about the role that allergy might be playing in these outcomes.

Analyzing labor, the rate of cesarean section was slightly higher than in other series,⁴ but lower if compared with other Spanish,¹⁵ and European and US^{16,22} rates. Focusing on cesarean section indications, the two compared groups differed in the causes, probably because of the characteristics of the patients seen in this tertiary hospital. Multiple gestation was the main cause in patients with respiratory allergies, highlighting the possible relation between allergy and fertility, as previously mentioned.^{2,6} For instance many of these patients were older, needed IVF, and waited to have their comorbidities under control. Other indications showed similar results to the general population.

These findings support the hypothesis that allergic diseases may influence obstetrical and perinatal outcomes. Immunologic changes in the profile of allergic women during pregnancy might be playing a key role, although other inflammatory mechanisms cannot be ruled out. A better knowledge of these immunologic mechanisms will help to enhance our clinical practice and support patients with allergies, who may require referrals to specific departments, further procedures to conceive or a closer follow up during pregnancy.

The study has limitations, mainly its retrospective design. Mild allergic disorders are frequently underdiagnosed and no assessment regarding treatment used was reported. Also, we did not exclude those who were delivered because of other factors unrelated to the mother's immune balance or other obstetrical comorbidities. In contrast, highlighting the strengths, the study included a large sample size, a long study period and all data were reviewed from electronic medical records.

In summary, in our population, women with respiratory allergy were at higher risks of sterility, IVF, and multiple gestation. These led

to higher risks of PTD, LBW, and cesarean sections. Analyzing these immunologic mechanisms will not only lead to a better understanding of their physiopathology and reinforce preventive strategies, but will also improve our clinical practice.

AUTHOR CONTRIBUTIONS

Jose Luis Bartha designed the study. Irene Bartha wrote the first draft of the manuscript, created the tables, and participated in the design. Miguel de la Fuente, Maria de la Calle, Elena Martin Boado, Nuria Martinez-Sanchez, and Jose Luis Bartha reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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