To determine how frequently pregnant asthmatics are sensitive to food and inhalation allergens

Nasrin Fazel (1,2)
Michael Kundi (2)
Erika Jensen-Jarolim (3)
Isabella Maria Pali-Schöll (3)
Asghar Kazemzadeh (1)
Mojtaba Fattahi Abdizadeh (1)
Habibollah Esmaily (4)
Roya Akbarzadeh (1)
Raheleh Ahmadi (1)

(1) Sabzevar University of Medical Sciences, Sabzevar, Iran
(2) Center for Public Health, Medical University Vienna, Vienna, Austria,
(3) Institute for Pathophysiology and Allergy Research, Medical University Vienna, Vienna, Austria,
(4) Department of Biostatistics & Epidemiology, Neonatal Research Center, Mashhad University of Medical Sciences, Mashad, Iran

Correspondence:
Nasrin Fazel
Austria: Sollingergasse 8-12/9/2 ,1190 Wien
Iran: Pardis Sabzevar Medical university,
Sangsefid Road,
Sabyevar, Iran
Tel : +9851 44018300
Email: shohreh1368@yahoo.co.uk

Abstract

Background: Allergens are one of the causes of asthma attacks, i.e. an atypical immune reaction which is prompted by environmental allergens and mediated by IgE antibodies. The present study aims to identify the prevalence of inhalation and food allergens among pregnant Iranian women with asthma.

Methods: Euroimmun tests were performed to identify the prevalence of sensitivity towards allergens among pregnant asthmatics. A total of 1,603 women were selected from those who had visited Mobini Hospital in Iran August 2014-April 2015. We drew blood samples from these women and from cord blood, and postpartum, from their infants. These samples were used to measure IgE and RAST to inhalation and food allergens. Descriptive and comparative statistical analyses were performed.

Results: A total of 1,603 pregnant women referred to Mobini Hospital, Iran were included in the analysis. Thirty-four pregnant women were confirmed as having asthma. Women with asthma were significantly more often from villages (p = 0.008). There was a statistically significant negative association between atopy and location as well as exercise-dependent wheezing (p=0.048, p=0.004, respectively). The seafood mix 3 was the most frequent allergen (10, 29.4%) detected in maternal blood samples, followed by peanut (6, 17.6%), and rough pigweed (5, 14.7%). All other allergens varied from 1 (2.9%) to 4 (11.8%). No association between IgE in maternal and neonate blood samples was detected.

Conclusion: Our results suggest that there is no transfer of sensitisation to selected inhalation and food allergens from mother to child. It may be important in future studies to try to detect local allergens that have the potential of such a transfer.

Key words: asthma, allergens, pregnancy, IgE

Introduction

In recent years, there has been a noticeable increase in the clinical and social burdens that accompany food allergies. Food reactions, when they involve the lung, tend to be severe, and therefore are important confounders in those with underlying asthma. Furthermore, food allergies also increase asthma morbidity, especially in early infancy; food allergy can be correlated to the expansion of future asthma. Diagnostic cut-off standards are very significant for specific IgE levels when interpreting food allergy. About 5% of asthmatics who react to food allergens suffer either an exacerbation of their asthma or a trigger of their current asthma, 6-8% of children and 2% of adults. (1) Moreover, edibles such as wheat, soya, peanut, milk and seafood may cause food-dependent exercise-induced anaphylaxis (FDEIA) (2). Whereas IgE specific to Ara h 2 has been shown to be diagnostic of peanut allergy, (3) recently, peanut lipid transfer protein has been described to be a significant allergen in the Mediterranean region.(4) Heterogeneous patterns of sensitization to individual peanut allergens are detected in different countries (5). The literature reported stronger pollution effects during the warm seasons, despite the culmination of pediatric asthma attacks during cold seasons. Sex and age differences may also confound the asthma effects from air contaminant exposure.(6) Peanut, wheat, and soy allergy were each cross-sectionally concomitant with increased childhood asthma, atopic dermatitis, and allergic rhinitis(7). Adhering to a healthy diet, including fruits, meat and fish, seems to ameliorate asthma and allergies during childhood. However, prospective and experimental studies are necessary to show a cause and effect relationship between diet and asthma / atopy. (8) A pollutant that can be easily verified by sampling serum levels is lead. Even so, the potential and severity of biological effects cannot be easily predicted (9). House dust mite (HDM) allergic rhinitis is difficult to diagnose, although numerous techniques are available (10). In humans, allergens from HDM, cockroaches, pets such as cats and dogs, pollen, and mould s have been recognized as the most relevant allergens (11). The prevalence of respiratory allergies is on the rise, among all populations, worldwide. Common symptoms of hypersensitivity include bronchial asthma, allergic rhinitis and atopic dermatitis. (12) Zicari's (2012) study confirms that early sensitization is an essential risk factor for the development of asthma. (13) Also, he stressed the importance of testing serum blood samples for aeroallergens. Because there are different numbers and types of allergens which vary according to country, many of which are absent in our area, it is necessary to do a variety of studies in order to identify most of the sensitized subjects, cost-effectively. Consequently, it will be useful to collect relevant causes of allergic diseases across various geographic areas, seasons, as well as environmental conditions. It might help with developing a new vision of the ideal environmental setting(s) in which to minimize atopy /asthma. Therefore, the aim of this study was to evaluate the prevalence of allergens identifiable by RAST test in pregnant asthmatics and their infants.

Method

A cross-sectional study was done on asthmatics whose diagnosis had been clinically confirmed by physical examination and pulmonary function test (PFT)among pregnant women who were referred to Mobini Hospital in Sabzevar between August 2014 and April 2015. The Ethics Committee of Sabzevar University approved the study protocol. The Radio-allergo-sorbent test (RAST) was done, using allergen extracts, to determine the patients' sensitivity to food and inhalation allergens. (20). RASTs were carried out using standardized allergen extracts for the following 36 aeroallergens and 36 food allergen: aspergillus fumigatus, cat, dog, cow, sheep, cage bird mix, sweet vernal grass, horse, Alternaria alternata, Cladosporium herbarum, pollens [tree (Ashe, Tree mixture), (Russian thistle,], mites (Dermatophagoides pteronyssinus, Dermatophagoides farine), feathers mixture, cockroach peanut, seafood mix 3, banana, orchard grass, cultivated rye, alder, penicillium notatum, English plantain, goosefoot, rough pigweed, rice, grain mix 2, apple, cultivated oat, meadow foxtail, firebush, sorrel, tree mix 6, honeybee venom 1, house dust, cross-reactive carbohydrate determinants (CCD) marker, shrimp prawn, white pine, tree mix 4, rye flour, potato, rose, cultivated oat. From those mothers with clinically-confirmed asthma, in the final weeks of pregnancy, 7 cc of blood was drawn for total IgE and RAST. Additional blood samples from their neonates were obtained first day after delivery for the identical lab tests. The clot sample for allergens samples were transported to the laboratory quickly. Total serum was kept at -20° C until testing. Allergen samples for each series of experiments were stored at 4 ° C for up to 2 weeks, collected and tested. This methodology continued until all the required samples were gathered. Tests were performed using the ELISA kit (Euroimmun, Germany). In those patients with allergies to a wide variety of allergens, additional inhalation and food allergens were tested. Blood samples were processed in accordance with kit instructions, i.e. based upon the multiplex immunoblots method. Then the results of total serum IgE, using standard and allergens results, were evaluated with the software. Mothers were considered to be atopic if they had IgE ?160 kIU/L, infants if their serum IgE ?10 kIU/L. Any additional patient history was also recorded. The results were analysed using SPSS version 20.

Results

Cohort description

Out of 1603 pregnant women 34 (2.1%) had asthma. The majority of asthmatic patients were either 25-29 years (29 %) or ≥ 35 years (35.3%) of age. The frequency of atopy in the study population of 34 asthmatic mothers and their infants was calculated as 7 (21%) and 4 (12%), respectively. Some allergens were much more common than others. (Tables 1, 2). Food allergy was defined as sensitization to at least 1 food allergen and was present in 28%. In a multivariate analysis, we found a significant relationship between prematurity and atopy or asthma (P = 0.006).

Allergies of pregnant women are related to asthma

To describe potential factors that might be connected to asthma during pregnancy (AP), we included the following parameters: eczema, allergies, asthma severity, asthma control, atopy, IgE, seafood mix 3 and rough pigweed. As controls, the same parameters were tested in the non - asthmatic mothers. The data were analysed using the chi-square statistic and Fischer's exact test. The highest rates of allergies were in the asthmatic group: 32 (94.1%) (p = 0.001). The majority of subjects in the asthmatic group did not have eczema, 30 (88.2 %). Asthmatic patients were divided into those with intermittent/mild persistent asthma (IMPA), and moderate or severe persistent asthma (MSPA). We found no significant relationship between atopy and asthma severity, with 22% and 14% atopy in IMPA and MSPA respectively. As well, there was no significant relationship between asthma control (i.e well-controlled, vs. partly/poorly-controlled) and atopy with 23% and 19% atopy, respectively. There was no association between atopy, and allergy or eczema (Fischer's exact test p=0.37 and p=1.0, respectively). There was also no significant statistical association between atopy and seafood mix 3 or rough pigweed, (both p=1.0) or any other allergen tested.

Hence, it appeared that only having allergy at pregnancy was closely linked to asthma, and it would be interesting to determine whether asthma might also be linked to additional health issues.

Atopy and location-dependent wheezing or exercise-induced wheezing of pregnant women are related.

To investigate whether further factors might also have contributed to AP, we tested the following factors: asthma severity, common allergens, smoker, passive smoker, atopy and infant gender.

There was a positive statistical association between atopy and location-dependent wheezing or exercise-induced wheezing, p=0.048 and p=0.004, respectively. There were no association between asthma severity and the most common allergen in asthmatic mothers, p=0.71 (Table 3). Table 4 shows the distribution of the variables retrieved from the databases for atopic women included in the study. There was no significant relationship between atopy and smoking or passive smoking p=0.51 and p=0.58, respectively. Taken together, it appeared that both allergy and atopy and location-dependent wheezing and exercise-induced wheezing in pregnant women were associated with a higher prevalence of asthma.

Table 1: Positive RAST results in cord and infant blood

Cord Blood	Number	Percent	Infant Blood	Number	Percent
Shrimp prawn	1	2.9	Rough pig weed	1	2.9
Seafood mix 3	1	2.9	Rose	1	2.9
Rough pig weed	1	2.9	Dermatophagoides d 1	1	2.9
Rose	1	2.9	Dermatophagoides d 2	1	2.9
Dermatophagoides d 1	1	2.9	Peanut	4	11.8
Dermatophagoides d 2	1	2.9	Cultivated oat	1	2.9
			English plantain	1	2.9
			Russian thistle	1	2.9

Table 2: Positive RAST results in pregnant women with asthma

Allergen	Number	Percent
Peanut	6	17.6
Seafood mix 3	10	29.4
Banana	3	8.8
Sweet vernal grass	2	5.9
Orchard grass	3	8.8
Cultivated rye	2	5.9
Alder	1	2.9
Penicillium notatum	1	2.9
English plantain	3	8.8
Cat	1	2.9
Goosefoot	4	11.8
Russian thistle	4	11.8
Rough pig weed	5	14.7
Rice	1	2.9
Grain mix 2	1	2.9
Apple	1	2.9
Cultivated oat	2	5.9
Meadow foxtail	1	2.9
Firebush	1	2.9
Sorrel	1	2.9
Tree mix 6	1	2.9
Honeybee venom 1	1	2.9
House dust	1	2.9
Dermatophagoides d1	1	2.9
Dermatophagoides d2	1	2.9
CCD marker	2	5.9
Ash	1	2.9
Shrimp prawn	1	2.9
White pine	1	2.9
Tree mix 4	1	2.9
Rye flour	1	2.9
Potato	1	2.9

Table 3: Frequency of positivity to seafood mix 3 in relation to asthma severity

	Seafood mix 3		
Asthma severity	negative	positive	Total
IMPA	19 (70%)	8 (30%)	27
MSPA	5 (71%)	2 (29%)	7

IMPA: intermittent asthma/mild persistent asthma; MSPA…moderate and severe persistent asthma

Table 4: Characteristics of pregnant women with asthma by atopy status

Characteristics		Nonatopic	Atopic	Test
		N. %	N. %	
Age	<=24	4 (14.8)	1 (14.3)	Chi-square test p=0.07
	25-29	6 (22.2)	4 (57.1)	
	30-34	5 (18.5)	2 (28.6)	
	≥35	12 (44.4)	0 (0.0)	
Ethnicity	Farsi	13 (48,1)	2 (28,6)	Fisher's exact test p=0.42
	Turk	14 (51,9)	5 (71,4)	
Education	Elementary school	11 (40.7)	1 (14.3)	Chi-square test p=0.17
	High school	14 (51.99	4 (57.1)	
	College & university	2 (7.4)	2 (28.6)	
BMI	<19.8	5 (18.5)	2 (28.6)	Fisher's exact test p=0.61
	19.8-26	22 (81.5)	5 (71.4)	
Smoking	Yes	2 (7.4)	1 (14.3)	Fisher's exact test p=0.53
	No	25 (92.6)	6 (85.7)	
Past smoker	Yes	4 (14.8)	2 (28.6)	Fisher's exact test p=0.58
	No	23 (85.2)	5 (71.4)	
Husband smoker	Yes	1 (3,7)	2 (28,6)	Fisher's exact test p=1.0
	No	26 (96,3)	5 (71,4)	
Infant weight	< 2500mg	1 (3.7)	0 (0.0)	Fisher's exact test p=1.0
	≥ 2500mg	26 (96.3)	7 (100.0)	
Delivery method	Normal	13 (48.1)	3 (42.9)	Fisher's exact test p=1.0
	Cesarean	14 (51.9)	4 (57.1)	
Apgar 1	< 7	2 (7.4)	0 (0.0)	Fisher's exact test p=1.0
	>7	25 (92.6)	7 (100.0)	
Wheezing at exercise	Yes	24 (89%)	2 (29%)	Fisher's exact test p=0.004
	No	3 (11%)	5 (71%)	
Wheezing in special places	Yes	25 (93%)	4 (57%)	Fisher's exact test p=0.048
	No	2 (7%)	3 (43%)	

Discussion

This study is the first in Sabzevar to assess the prevalence of asthma and allergic sensitization and its association with IgE factors in pregnant women with asthma. Sabzevar is a city in north-eastern Iran. The region is semi desert with hot and dry summers and is an agricultural center for grape and raisin farming. In the present study, we looked into the possible connection between asthma and allergens. We found a significant relationship between allergies and asthma as well as atopy and location-related and exercise-induced wheezing in pregnant women. Atopy and asthma severity, atopy and allergic sensitisations to various food and inhalation allergens were not statistically significantly related.

We observed that food allergens were more common than aeroallergens in both mothers and infants. The frequency of atopy in asthmatic mothers and their infants were 21% and 12%, respectively. Our results are similar to those of Nabavi (2013). (14) It is possible that there are relations between the in utero environment in asthmatic pregnancies and the development of asthma during childhood, independent of genetic factors. This is suggested by atopy in children, which was more frequently related to maternal asthma or IgE levels, rather than paternal asthma or IgE.(15) The study prospectively followed 181 AP, 62% of whom were classified as atopic.(16) Comert reported a prevalence of 32.2% atopic cases in his study (17). This difference as compared with the findings in the present study is probably due to climatic factors (12).

This study is the first report of sensitization to food allergens in our region. A high rate of sensitisation to pollens was established in earlier studies in our country. A study in Mashhad (18), Iran reported that weeds had the highest rate of sensitization, among which Russian thistle (salsolakali) was the most common in childhood. This result is similar to our results in infants but, probably due to the dry climate or different method of testing, it was not the most common. Whereas we used the RAST, they applied the skin prick test. Also, in Shiraz, the prevalence pattern of sensitisations to different types of pollens (e.g weed, grass, trees), as well as in Tehranand Karaj (12) (herbacee I/II/III, sycamore, chenopodium, tree mix, grass, ash and cedar) was similar to our study. In the Comert (2014) study, the most prevalent allergen was Phleumpratense (19.3%), whereas in our study, it was seafood mix 3 (29.4%). (17) In our study, food allergens were the most common in mothers and grass and peanut allergens in infants. Herbal topography, climate and temperature could be responsible for the difference. (18) Our results were similar to most European countries in that three to four allergens were recognized in 95% of all sensitized subjects. (17) It is well-known that allergic patients are commonly co-sensitized against different allergen sources. Advancement in the field of allergen description by molecular biological techniques has now shown that sensitization against different allergen sources can be clarified as cross-reactivity of IgE antibodies with fundamentally and immunologically linked components existent on these allergen sources. (12) A survey in Kerman indicated that allergies to food and airborne allergens differ depending on the nutritional and environmental settings. (19) The sensitization rates to grass pollen varies between 19.5% and 69.9% among European countries, and it is the most common allergen in Austria, Denmark, England, Greece, Poland, Switzerland and the Netherlands (17). In contrast in Comert's study, the prevalence of Dermatophagoides pteronyssinus and Dermatophagoides farinae was also high 16.2% and 10.5%, respectively. The sensitization rates to Dermatophagoides pteronyssinus varied between 16.8% and 68.8% within European countries. Indeed, it is the most common allergen in Belgium, France, Italy and Portugal. In our results, the frequency was 2.9%. Two studies in Turkey reported the prevalence of sensitization to allergens from cats and dogs. There is a growing tendency towards pet ownership in our country (20, 21), so this may become a problem in the future. In Comert's study, the sensitization rates to Alternaria, Aspergillus and Cladosporium were 1.1%, 0.9% and 0.7%, respectively. In Europe (22), however, the rate of Cladosporium allergies was reported to be between 0% and 12.8%. The cockroach allergen would have been an important allergen to assess if we had been able to test all of the subjects against this allergen. Mert's study reported 74.22% cockroach sensitisations (17)
Whereas a study in Ahvaz found the most prevalent sensitizing mould was C. acremonium followed by Penicillium spp, we did not find that the infants were sensitized to these; although we tested them for Penicillium spp and Aspergillus allergen. (24) Penicillium, aspergillus, and basidiospores are some of the fungal species that are associated with asthma and atopy in children (25). We found only one such subject. Bunyavanich (2014) reported that exposure to wheat during early pregnancy was associated with reduced odds of mid-childhood allergy and asthma. Alterations in immune function have been proposed as a mechanism contributing to later development respiratory disease (26). Since we have only investigated neonates, the further development of this group is a matter of further study.

The group of 34 asthmatic patients tested with the 36 food and 36 aeroallergen panel were comparatively young which could overestimate the prevalence of allergen sensitivity.(17) Our findings suggest a negative relationship between location and exercise-related wheezing and atopy and a slightly positive association between atopy and maternal and passing smoking. We found no statistically significant associations between atopy and method of delivery, parity, number of gravidities, and abortions. However, Pistiner's (2008) findings suggest that cesarean delivery is associated with allergic rhinitis and atopy among children with a parental history of asthma or allergies. This likely differs from our study due to the alternative characteristics of the populations we each studied, as well as the duration of follow-up and definition of the outcomes. (23) The Mean (SD) age of our asthmatic patient group 30.97 ±6.36 versus 27.33 ±5.91 seems to be lower than in the Spanish study, i.e, 36.2 ±12.72 versus 30±15 years, respectively, which could account for the lower prevalence of atopic sensitization found in our study. Another possibility

may be that the Spanish study consisted mainly of patients with allergic rhinitis; with 37% of them having asthma. (17)

Our main limitation was the lack of lab tests in the control group. A smaller sample size in contrast to earlier studies was another weakness of our study.

Conclusion

According to the results and environmental condition in the area of our study, the most common regional allergens were food allergens such as seafood mix 3 and peanut that should be given more attention. It may be important in future studies to try to detect local allergens that have a potential of materno-fetal transfer. Acknowledgments

This work was approved by the ethics committee of the Medical University of Sabzevar, Iran (Medsab Rec.93.36). We thank the vice-chancellor of the Sabzevar university -Iran for financial support of this research .We thank the personnel of Mobini and Vaseei Hospitals for their cooperation. We also thank all the mothers who participated in the study.

References

1. Ozol D, Mete E. Asthma and food allergy. Current opinion in pulmonary medicine. 2008;14(1):9-12.
2. de Silva NR, Dasanayake WMDK, Karunatilleke C, Malavige GN. Food dependant exercise induced anaphylaxis a retrospective study from 2 allergy clinics in Colombo, Sri Lanka. Allergy, Asthma & Clinical Immunology. 2015;11(1):1.
3. Pedrosa M, Boyano-Martínez T, García-Ara C, Caballero T, Quirce S. Utility of specific IgE to Ara h 6 in peanut allergy diagnosis. Annals of Allergy, Asthma & Immunology. 2015;115 (2):108-12.
4. Pedrosa M, Boyano-Martínez T, García-Ara MC, Caballero T, Quirce S. Peanut seed storage proteins are responsible for clinical reactivity in Spanish peanut?allergic children. Pediatric Allergy and Immunology. 2012;23(7):654-659.
5. Ackerbauer D, Bublin M, Radauer C, et al. Component-resolved IgE profiles in Austrian patients with a convincing history of peanut allergy. International archives of allergy and immunology. 2015;166(1):13-24.
6. Zheng X-y, Ding H, Jiang L-n, et al. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: a systematic review and meta-analysis. PloS one. 2015;10(9): e0138146.
7. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, et al. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. Journal of Allergy and Clinical Immunology. 2014;133(5):1373-1382.
8. Saadeh D, Salameh P, Caillaud D, et al. Prevalence and association of asthma and allergic sensitization with dietary factors in schoolchildren: data from the french six cities study. BMC public health. 2015;15(1):1.
9. Schwela D. Air pollution and health in urban areas. Reviews on environmental health. 2000; 15(1-2):13-42.
10. de Blay F, Doyen V, Lutz C, et al. A new, faster, and safe nasal provocation test method for diagnosing mite allergic rhinitis. Annals of Allergy, Asthma & Immunology. 2015;115(5):385-390. e381.
11. Kim H-J, Kang M-H, Park H-M. Common allergens of atopic dermatitis in dogs: comparative findings based on intradermal tests. Journal of veterinary science. 2011;12(3):287-290.
12. Singh AB, Mathur C. An aerobiological perspective in allergy and asthma. Asia Pacific Allergy. 2012;2(3):210-222.
13. Zicari A, Indinnimeo L, De Castro G, et al. Food allergy and the development of asthma symptoms. International journal of immunopathology and pharmacology. 2012;25(3):731-740.
14. Nabavi M, Ghorbani R, Asadi AM, Faranoush M. Factors associated with cord blood IgE levels. Asian Pacific Journal of Allergy and Immunology. 2013;31(2):157.
15. Murphy V, Gibson P, Smith R, Clifton V. Asthma during pregnancy: mechanisms and treatment implications. European Respiratory Journal. 2005;25(4):731-750.
16. Stenius-Aarniala B, Piirilä P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax. 1988;43(1):12-18.
17. Comert S, Demir AU, Karakaya G, Kalyoncu AF. Minimum prick test panel for adult patients with asthma and rhinitis in Ankara, Turkey. Journal of Asthma. 2014;51(4):417-422.
18. Behmanesh F, Shoja M, Khajedaluee M. Prevalence of aeroallergens in childhood asthma in Mashhad. Macedonian Journal of Medical Sciences. 2010;3(3):295-298.
19. Fouladseresht H, Safiri S, Moqaddasi M, Razeghi MS, Bazargan N. Prevalence of food and airborne allergens in allergic patients in Kerman. Journal of Kermanshah University of Medical Sciences (J Kermanshah Univ Med Sci). 2014;18(4):234-241.
20. Bostanci I, Türktas I, Türkyilmaz C. Sensitization to aeroallergens in Ankara, Turkey. Allergy. 1999;54:1332-1334.
21. Füsun KA. Cockroach sensitivity in inner-city allergic patients in Turkey. Turkish Respiratory Journal. 2001;2(1):17-20.
22. Heinzerling L, Burbach G, Edenharter G, et al. GA2LEN skin test study I: GA²LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy. 2009;64(10):1498-1506.
23. Pistiner M, Gold DR, Abdulkerim H, Hoffman E, Celedón JC. Birth by cesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy. Journal of Allergy and Clinical Immunology. 2008;122(2):274-279.
24. Yang H, Xun P, He K. Fish and fish oil intake in relation to risk of asthma: a systematic review and meta-analysis. PloS one. 2013;8(11):e80048.
25. Wen HJ, Chiang TL, Lin SJ, Guo YL. Predicting risk for childhood asthma by pre?pregnancy, perinatal, and postnatal factors. Pediatric Allergy and Immunology. 2015;26(3):272-279.
26. Hollams EM, De Klerk NH, Holt PG, Sly PD. Persistent effects of maternal smoking during pregnancy on lung function and asthma in adolescents. American journal of respiratory and critical care medicine. 2014;189(4):401-407.