

The Low Maternal Consumption of Homemade Fermented Foods in Pregnancy Is an Additional Risk Factor for Food Protein-Induced Allergic Proctocolitis: A Case-Control Study

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Keywords

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Abstract

Introduction: Food protein-induced allergic proctocolitis (FPIAP) is the most common non-IgE-mediated food allergy and it varies between 4% and 8% in infants. The aim of the study was to evaluate the potential association between FPIAP in infants and maternal daily consumption of homemade fermented foods (FFs) during pregnancy. **Methods:** Two hundred and seven infants were included in this case-control study, 106 with physician-diagnosed FPIAP (FPIAP group) and 101 age- and gender-matched healthy infants (control group), together with their mothers. The frequency and diversity of the 8 most consumed homemade FFs in traditional Turkish cuisine and daily maternal consumption of these during pregnancy were evaluated retrospectively using a structured questionnaire. **Results:** Rates of vaginal delivery, maternal smoking during pregnancy, educational status, and monthly household income were higher in the FPIAP group than the control group ($p = 0.046$, $p = 0.014$, $p < 0.001$, and $p = 0.009$, respectively). The 3 most common daily-consumed FFs during pregnancy were, in order, yogurt, cheese, and tarhana. The diversity of daily-consumed FFs during pregnancy ($p = 0.004$) and the consumption of the 3

most common FFs ($p = 0.011$) were lower in the FPIAP group than in the control group. Maternal smoking during pregnancy (odds ratio [OR]: 2.97, 95% confidence interval [CI]: 1.19–7.41, $p = 0.019$) and a higher maternal educational status (OR: 3.34, 95% CI: 1.63–6.84, $p = 0.001$) increased the risk of FPIAP at multivariate logistic regression, while the diversity of maternal FF consumption was protective against FPIAP (OR: 0.75, 95% CI: 0.58–0.96, $p = 0.025$). **Conclusion:** Daily maternal consumption of yogurt, cheese, and tarhana during pregnancy was less common in FPIAP. The diversity of traditional Turkish homemade FFs may reduce the risk of FPIAP, whereas maternal smoking and a higher maternal educational status were associated with an increased risk of FPIAP.

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Introduction

Food protein-induced allergic proctocolitis (FPIAP) is the most common non-IgE-mediated food allergy (FA). It is characterized by the presence of blood mixed, mucoid, and frothy stools in infants who usually appear to be

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healthy [1]. The prevalence of food-related allergic reactions in infants varies between 4% and 8% [2, 3]. More than half of cases with FPIAP were exclusively breastfed infants [4]. In the pathology of the disease, focal aggregates of eosinophil and lymphocyte occur in the rectum and distal sigmoid colon epithelium, lamina propria, crypt epithelium, and muscularis mucosa. Although the etiology and pathogenesis are unclear, exposure to offending food antigen(s), either through breastfeeding or complementary feeding, causes an inflammatory response in the last part of the colon, and elimination of these from the maternal diet reduces the infant's symptoms [5, 6].

Fermentation is a natural food processing method or chemical process occurring through the action of enzymes in microorganisms in the organic structure of foodstuffs and beverages [7]. Sufficient microbial growth and enzymatic transformation of food components must be present to define a food as fermented foods (FFs). Homemade FFs are traditional components of Turkish cuisine that are obtained by fermentation, produced by natural methods, and that contain lactic acid bacteria and yeast [8]. Traditional Turkish cuisine includes many FFs, including homemade yogurt, cheese, kefir, pickle, tarhana, shalgam, natural sourdough bread, and boza [8, 9]. FFs contain bioactive compounds, antioxidants, antimicrobial enzymes, essential amino acids, vitamins, probiotics, and prebiotics [8, 10–16]. FFs are more easily digested, reduce the presence of many factors that inhibit digestive enzymes such as trypsin inhibitor, and inhibit the absorption of minerals [10, 15, 17].

Additionally, FFs modify the immune system, intestinal microbiota composition, and activity due to their bioactive content [10, 15, 17]. When the composition of the gut microbiota is appropriately established, the ratio of type 1 T-helper/type 2 T-helper (Th1/Th2) is generally assumed to be balanced and tolerance develops in infants [18, 19]. In recent years, there has been increasing scientific evidence showing the potential effect of impaired intestinal microbiota (dysbiosis) on the development of IgE and non-IgE-mediated FA [18, 20–22]. FFs have proven benefits in terms of preventing/reducing the severity of allergic reactions, as well as lactose malabsorption and other gastrointestinal disorders, and prevention of hypertension, heart disease, diabetes, and osteoporosis [10, 11, 14–17].

Maternal gut microbial homeostasis is of great importance for fetal intrauterine immune and metabolic programming [19, 23, 24]. Eating habits of mother and the content of the maternal intestinal flora during pregnancy

affect bacterial colonization in the fetal gastrointestinal system [24–26]. Maternal diet during pregnancy may be one of the causes of early life exposure affecting both immune tolerance and the development of allergic diseases in infants [19, 23, 24]. Studies have shown that FF consumption during pregnancy reduces the future development of allergic diseases in infants [27–29]. Celik et al. [27] recently investigated the effect of maternal FFs consumption during pregnancy on the development of atopic dermatitis (AD) in infants and identified daily yogurt consumption as a protective factor against the disease.

However, no previous study has investigated the effect of maternal consumption of homemade FFs during pregnancy on non-IgE-mediated FA disease. In order to test the hypothesis that the associations between a high amount of maternal regularly consumed homemade FFs and the diversity thereof in maternal diet during pregnancy and a lower incidence of development of FPIAP in their children, we evaluated the frequency and the amount of FFs consumed during pregnancy and their diversity in mothers of infants with FPIAP and compared the results with those of mothers of healthy controls.

Materials and Methods

Study Design and Setting

This case-control study was conducted between September 2019 and June 2020 at the Aydin Adnan Menderes University School of Medicine Hospital Department of Pediatric Allergy and Immunology, and Aydin Health Ministry Family Health Center Outpatient Clinics, Turkey.

Sample

The study involved 207 infants who were fed with breast milk from birth. The FPIAP group consisted of 106 physician-diagnosed infants with FPIAP (FPIAP group). FPIAP was defined as a non-IgE-mediated condition of bloody stool in a well-appearing infant. FPIAP was diagnosed clinically based on a history of maternal consumption of the offending food(s), recovery after elimination diet(s), and recurrence of symptoms by the reintroduction of the offending food(s) by oral food challenge (OFC) after a 2–4-week elimination diet [30, 31].

Infants with other conditions capable of causing bloody diarrhea such as infections, anal fissure, perianal dermatitis/excoriations, coagulation defects, invagination (intussusception), volvulus, Hirschsprung's disease, necrotizing enterocolitis, inflammatory bowel diseases, vitamin K deficiency, malignancy, allergic diseases, IgE-mediated FA, anaphylaxis, and immune deficiencies, and infants using medications such as NSAIDs were excluded. Children with a suspected FPIAP diagnosis that could not be verified via OFCs were also excluded.

The control group constituted 101 healthy infants. Healthy controls were included in the study through routine controls in 2 family health center outpatient clinics. The clinics were selected

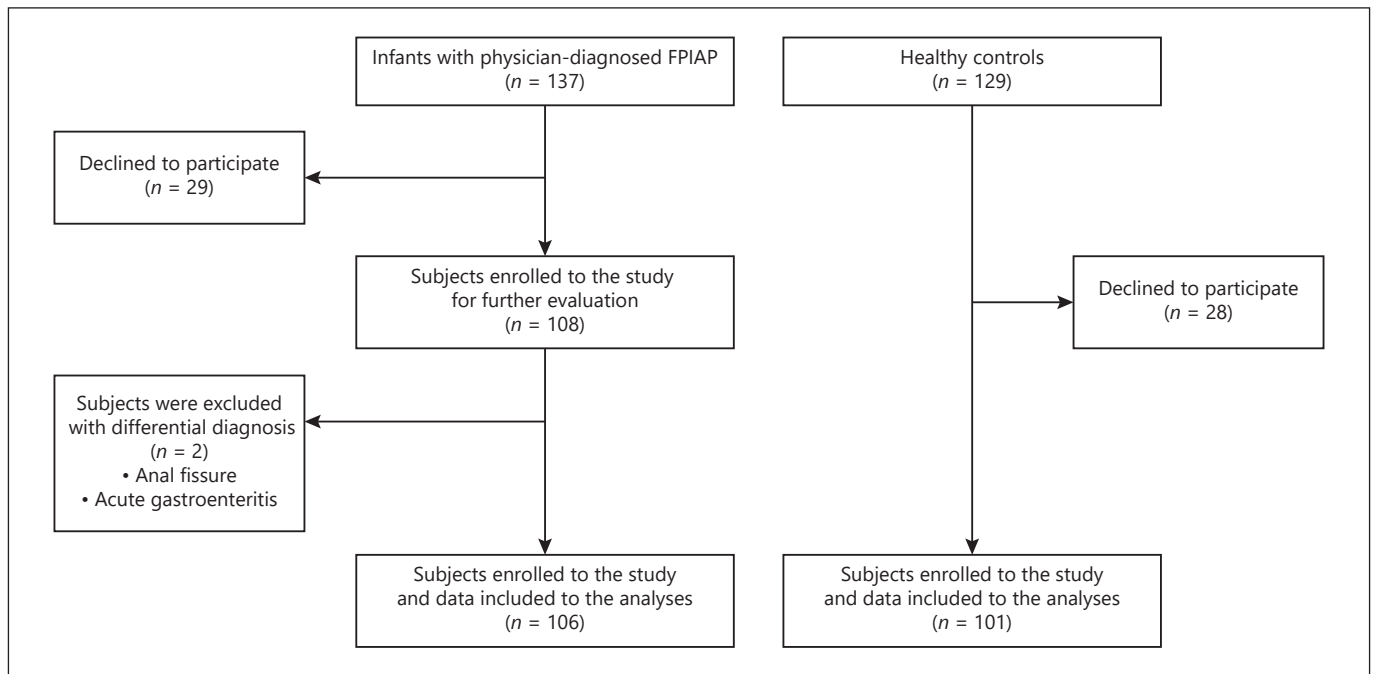


Fig. 1. Study flowchart.

using the lottery method, and the control group was randomly selected. Healthy infants with no chronic systemic disease (metabolic disorder, cardiovascular disease, immunodeficiency, etc.), infections, growth retardation, or history of prematurity, or receiving treatment for any chronic disease were enrolled as a control group.

Questionnaire

The questionnaire collected data for demographics including gender, the age of infants (in months) and maternal age (in years), mode of delivery, parental atopy history (asthma, eczema, allergic rhinitis, etc.), sociodemographic characteristics of the mother, monthly income, antibiotic treatment, maternal and paternal smoking habits, and pet ownership. Monthly income data were based on Turkish Statistical Institute figures for November 2020. Accordingly, ≤ 2.517 Turkish lira (TL) was defined as the hunger threshold, 2.518–8.198 TL as the poverty line, and ≥ 8.198 TL was defined as normal income.

The questionnaire retrospectively surveyed maternal consumption of traditional Turkish FFs during pregnancy when the median age of the infants was 12 months. It included data concerning maternal diet habits during pregnancy and the variety and amount of consumption of homemade traditional Turkish FFs including yogurt, cheese, kefir (a fermented milk product), pickle, boza (produced from bulgur, rice, sugar, yeast, and water), tarhana (produced from baker's yeast, wheat flour, salt, yogurt, and various cooked vegetables), natural leavened sourdough, and shalgam (fermented turnip and its juice).

The intake frequency was classified into 4 groups: (1) every day, (2) every 2 days, (3) every 3 days, and (4) less than every 3 days. Weekly FFs consumption was calculated by (the amount of daily FFs intake) $\times$ (number of days a week). Food frequency data were

used to calculate dietary diversity at the household level, and the 24-h diet recall data were used to calculate individual dietary diversity.

Data Collection

All participants underwent baseline physical examinations and routine assessment of anthropometry. All mothers were requested to complete a structured questionnaire including demographic data as well as the frequency and diversity of daily consumption of the 8 most common homemade FFs of traditional Turkish cuisine during pregnancy.

Sample Size

The study sample size was determined as 25 members for each group, with a total of 50 individuals, using free software G* Power (version 3.1.9.2). The study had an effect size of 0.49, a confidence interval (CI) of 95%, and a power of 80% for sampling, the frequency of daily FF consumption was used as a factor for sample size calculation [27].

Statistical Analyses

Statistical Package for the Social Sciences (SPSS; IBM, Armonk, NY, USA) for Windows 21.0 software was used for data analysis. Descriptive statistical methods (median, interquartile range, frequency, and percentage) were used to evaluate the study data. The compatibility with normal distribution of quantitative data was tested using the Kolmogorov-Smirnov test. Nominal variables were represented as percentages and compared using the χ^2 test or Fisher's exact test. The Mann-Whitney U test was used for non-normally distributed variables.

After the variables had been determined at univariate analyses, multivariate logistic regression analysis was performed to identify

Table 1. Comparison of demographic characteristics between infants with FPIAP and control groups

Demographic Characteristics	FPIAP group (n = 106)	Control group (n = 101)	p value
Gender, n (%)			
Female	55 (51.9)	48 (47.5)	0.530 ^a
Male	51 (48.1)	53 (52.5)	
Gestational age at birth, week; median (IQR)	38 (37–39)	38 (37–39)	0.757 ^b
Mode of delivery, n (%)			
Cesarean section	57 (53.8)	68 (67.3)	0.046^a
Vaginal delivery	49 (46.2)	33 (32.7)	
Infant's age, months; median (IQR)	12 (8–18)	12 (8.5–17)	0.841 ^b
Birth weight, g; median (IQR)	3,417 (3,030–4,085)	3,375 (2,600–4,130)	0.566 ^b
Maternal age, years; median (IQR)	30 (28–34)	31 (28–34)	0.598 ^b
Maternal weight before pregnancy, kg; median (IQR)	62 (56–68)	63 (52.5–70)	0.541 ^b
Maternal weight gain during pregnancy, kg; median (IQR)	12 (8–15)	11 (8–14)	0.721 ^b
Maternal education, n (%)			
Primary school	14 (13.2)	39 (38.6)	<0.001^a
High school	36 (34)	27 (26.7)	
University	56 (52.8)	35 (34.7)	
Monthly household income (TL), n (%)			
≤2.517	22 (20.8)	40 (39.6)	0.009^a
2.518–8.198	69 (65)	47 (46.5)	
>8.198	15 (14.2)	14 (13.9)	
Parental atopy history, n (%)			
Yes	26 (24.5)	20 (19.8)	0.414 ^a
No	80 (75.5)	81 (80.2)	
Antibiotic use in pregnancy, n (%)			
Yes	25 (23.6)	17 (16.8)	0.227 ^a
No	81 (76.4)	84 (83.2)	
Environmental factors, n (%)			
Maternal smoking during pregnancy	21 (19.8)	8 (7.9)	0.014^a
Paternal smoking	48 (45.3)	43 (42.7)	0.695 ^a
Passive smoking exposure at home	54 (50.9)	42 (41.6)	0.177 ^a
Indoor pets	15 (14.2)	10 (9.9)	0.348 ^a

g, gram; IQR, interquartile range; kg, kilogram; n, number; N/A, not applicable, wk, week; %, percent; FPIAP, food protein-induced allergic proctocolitis; TL, Turkish lira. ^a Comparison of the categorical variables was performed using the χ^2 test. ^b Comparison of non-normally distributed continuous variables was performed using the Mann-Whitney U test.

possible risk factors for FPIAP in the study participants. Mode of delivery, maternal education, monthly household income, and maternal smoking during pregnancy were adopted as covariates and included in multivariate analysis. A *p* value <0.05 was considered statistically significant.

Results

Patient Characteristics

One hundred and thirty-seven infants with FPIAP and 129 healthy infants were initially enrolled in the study. However, 57 (mothers of 29 infants with FPIAP and of 28 healthy infants) refused to participate and 2 infants did

not meet the inclusion criteria. After initial evaluation, all participants were included in the study according to the flowchart described in detail below and shown in Figure 1. One hundred and three (49.8%) infants were female, and 104 (50.2%) were male. The median age of the infants was 12 (8–18) months in the FPIAP group and 12 (8.5–17) months in the control group.

A comparison of demographic variables between the FPIAP and control group is presented in Table 1. The rate of vaginal delivery, maternal educational status, monthly household income, and maternal smoking during pregnancy were all higher in FPIAP in than the control group (*p* = 0.046, *p* < 0.001, *p* = 0.009, and *p* = 0.014, respectively).

Table 2. Comparison of maternal consumption of homemade FFs during pregnancy between infants with FPIAP and control groups

Homemade FF consumption ratio and amount	FPIAP group (<i>n</i> = 106)	Control group (<i>n</i> = 101)	<i>p</i> value
Yogurt, <i>n</i> (%)	104 (98.1)	96 (95)	0.271 ^a
Homemade yogurt <i>n</i> (%)	65 (62.5)	78 (81.3)	0.003^a
Homemade yogurt amount, g/wk, median (IQR)	700 (400–700)	700 (450–700)	0.984 ^b
Cheese, <i>n</i> (%)	100 (94.3)	94 (93.1)	0.706 ^a
Homemade cheese, <i>n</i> (%)	12 (22.2)	32 (34.1)	<0.001^a
Homemade cheese amount, g/wk, median (IQR)	700 (600–700)	700 (600–800)	0.006^b
Tarhana, <i>n</i> (%)	79 (74.5)	72 (71.3)	0.600 ^a
Homemade tarhana, <i>n</i> (%)	63 (79.7)	64 (88.9)	0.017^a
Homemade tarhana amount, median (IQR)	100 (100–200)	200 (100–200)	0.014^b
Pickle, <i>n</i> (%)	84 (79.2)	64 (63.4)	0.011^a
Homemade pickle, <i>n</i> (%)	58 (69)	51 (79.7)	0.073 ^a
Homemade pickle amount, g/wk, median (IQR)	100 (100–200)	200 (100–400)	<0.001^b
Natural sourdough bread, <i>n</i> (%)	32 (30.2)	26 (25.7)	0.476 ^a
Homemade sourdough bread, <i>n</i> (%)	21 (65.6)	21 (80.8)	0.199 ^a
Homemade sourdough bread amount, g/wk, median (IQR)	700 (400–775)	400 (400–800)	0.589 ^b
Shalgam, <i>n</i> (%)	38 (35.8)	19 (18.8)	0.006^a
Homemade shalgam, <i>n</i> (%)	0 (0)	6 (2)	N/A
Homemade shalgam amount, median (IQR)	50 (50–100)	50 (50–100)	N/A
Kefir, <i>n</i> (%)	19 (17.9)	12 (11.9)	0.223 ^a
Homemade kefir, <i>n</i> (%)	4 (21.1)	5 (41.7)	0.253 ^a
Homemade kefir amount, median (IQR)	100 (100–200)	200 (100–400)	0.795 ^b
Boza, <i>n</i> (%)	8 (7.5)	6 (5.9)	0.645 ^a
Homemade boza, <i>n</i> (%)	2 (25)	2 (33.3)	N/A
Homemade boza amount, median (IQR)	50 (50–100)	50 (50–100)	0.573 ^b
Diversity of homemade FFs consumed during pregnancy; median (IQR)	3 (2–3.5)	4 (3–4)	0.004^b
Maternal consumption of homemade yogurt and cheese during pregnancy, <i>n</i> (%)	98 (92.5)	90 (89.1)	0.405 ^a
Maternal consumption of homemade yogurt, cheese, and tarhana during pregnancy, <i>n</i> (%)	21 (25)	30 (44.8)	0.011^a
Maternal consumption of homemade yogurt, cheese, tarhana, and pickle during pregnancy, <i>n</i> (%)	9 (14.5)	7 (17.5)	0.686 ^a

g, gram; IQR, interquartile range; kg, kilogram; *n*, number; N/A, not applicable; wk, week; %, percent; FPIAP, food protein-induced allergic proctocolitis; FFs, fermented foods. ^a Comparison of the categorical variables was performed using the χ^2 test. ^b Comparison of non-normally distributed continuous variables was performed using the Mann-Whitney U test.

Fermented Foods

The most common daily-consumed FFs during pregnancy in the FPIAP group and the control group were yogurt (*n* = 104, 98.1% vs. *n* = 96, 95%), cheese (*n* = 100, 94.3% vs. *n* = 94, 93.1%), tarhana (*n* = 79, 74.5% vs. *n* = 72, 71.3%), pickle (*n* = 84, 79.2% vs. *n* = 64, 63.4%), and natural sourdough bread (*n* = 32, 30.2% vs. *n* = 26, 25.7%). Less commonly consumed FFs in the FPIAP group compared to the control group included shalgam (*n* = 38, 35.8% vs. *n* = 19, 18.8%), kefir (*n* = 19, 17.9% vs. *n* = 12, 11.9%), and boza (*n* = 8, 7.5% vs. *n* = 6, 5.9%) (Table 2).

A comparison of daily-consumed FFs during pregnancy between the FPIAP and control group is presented in Table 2. The consumption of homemade yogurt, cheese, and tarhana was significantly lower in the FPIAP group

than the control group ($p = 0.003$, $p < 0.001$, and $p = 0.017$, respectively), while consumptions of pickle, natural sourdough bread, shalgam, kefir, and boza were insignificantly lower ($p > 0.05$ for each). The amount of weekly cheese, tarhana, and pickle consumption was lower in the FPIAP group than in the control group ($p = 0.006$, $p = 0.014$, and $p < 0.001$, respectively).

Risk Factors for FPIAP

The consumption of the 3 most common homemade FFs (yogurt, cheese, and tarhana) together were lower in the FPIAP group than the control group ($p = 0.011$) (Table 2). There was no significant difference between children with a higher maternal education status (university) than lower maternal education status in terms of the fre-

quency ($p \geq 0.05$ for each FFs) and the diversity ($p = 0.336$) of homemade FFs.

At multivariate logistic regression analysis, maternal smoking during pregnancy (odds ratio [OR]: 3.72, 95% CI: 1.16–12.03, $p = 0.028$), and the maternal education level (university) (OR: 2.43, 95% CI: 1.09–5.47, $p = 0.031$) were found to increase the risk of FPIAP, whereas maternal daily consumption of homemade yogurt, cheese, and tarhana together was protective against FPIAP (OR: 0.45, 95% CI: 0.22–0.93, $p = 0.032$).

The diversity of the homemade FFs variable could not be included in the multivariate logistic regression analysis model. The diversity of homemade FFs during pregnancy was therefore compared with multiple logistic regression analysis in a separate model (the enter method). In this model, the diversity of homemade daily-consumed FFs during pregnancy were lower in the FPIAP group than the control group ($p = 0.004$) (Table 2). Maternal smoking during pregnancy (OR: 2.97, 95% CI: 1.19–7.41, $p = 0.019$) and a higher maternal education level (university) (OR: 3.34, 95% CI: 1.63–6.84, $p = 0.001$) were found to increase the risk of FPIAP, whereas the diversity of maternal daily FFs consumption was protective against FPIAP (OR: 0.75, 95% CI: 0.58–0.96, $p = 0.025$).

Discussion/Conclusion

This is the first study to examine the development of FPIAP in infants of mothers who consumed FFs during pregnancy; therefore, the results are particularly valuable in revealing an association between the development of FPIAP and maternal diet. The findings of this case-control study revealed that yogurt, cheese, and tarhana were the most consumed homemade FFs products in Turkish cuisine. The results indicated that lower consumption of homemade yogurt, cheese, and tarhana alone or in combination, as well as the diversity of homemade FFs in the maternal gestational diet, seem to be associated with the development of FPIAP in their infants. The diversity and daily consumption of these FFs in the maternal diet during pregnancy were found to be protective against the development of FPIAP. Although consumption of pickles and shalgam was higher in the mothers of children with FPIAP than healthy children's, there was no significant difference between groups in terms of the consumption of homemade products. Thus, we anticipate that one or more of these 3 nutrients may have a protective effect on the development of FPIAP by affecting the intestinal microbiota and immune regulation or a well-balanced di-

verse maternal diet (including FFs) in general may have an impact on the lower incidence of FPIAP.

FPIAP occurs as a result of food protein-dependent non-IgE-mediated reaction in the distal colon and rectum epithelium. It is also known that various immune system cells including eosinophils and lymphocytes are involved in the development of FPIAP [21, 22]. Impaired intestinal microbiota contributes to imbalance of the Treg/Th17 axis and disrupted Th1/Th2 balance. The distorted cell-skewed cytokine profile in the immature gut barrier and Th1 or Th2 cell type-skewed immune response mediate the development of FA in early childhood [24]. It may therefore be concluded that FPIAP development may be prevented through the fortification maternal gastrointestinal microbiota with probiotics naturally found in homemade traditional FFs, since these are known to cause a direct increase in the beneficial bacteria load in the intestinal flora, to improve the intestinal microbiome, and to provide protection of the homeostasis of the immune system [13, 15–17]. Preserving the balance of the maternal microbiome during pregnancy may facilitate the establishment of gut microbiota homeostasis via the transfer of beneficial bacteria or maternal regulatory T and B cells to the fetus through the amniotic fluid or umbilical cord [32].

Consistent with our results, studies investigating the effects of maternal FFs consumption during pregnancy on allergic diseases have concluded that these protect against the development of AD and FA. Celik et al. [27] reported that yogurt, fermented olive, and cheese were the most frequently consumed FFs by mothers during pregnancy and that yogurt consumption and diversity of FFs were preventive against the development of infantile AD [27]. In a prospective cohort study, Miyake et al. [33] reported that maternal consumption of whole milk and cheese, but not yogurt, during pregnancy reduced the risk of wheezing in infants aged 16–24 months but had no effect on AD development. In a later birth cohort study conducted by the same team, cheese consumption during pregnancy among mothers of infants aged 23–29 months reduced the risk of physician-diagnosed asthma, while yogurt and calcium consumption reduced the risk of physician-diagnosed atopic eczema [28]. In a hospital-based birth cohort study from Japan, the risk of AD and food sensitization at the age of 5 years was lower in children who regularly consumed yogurt in the first 2 years of life [29].

Although, in general, cesarean delivery is more associated with allergic diseases [24], there are no population-based cohort studies showing a causal relationship be-

tween birth type and the development of non-IgE-mediated FA diseases in the English language literature. Surprisingly, we observed that vaginal delivery was more frequent in infants with FPIAP than in the healthy controls. Consistent with our results, several previous cross-sectional studies have reported vaginal delivery rates between 52% and 68% in infants with FPIAP [34–36]. Several studies have also shown an increase in preference for vaginal delivery among women as their education levels increase [37–39]. We therefore conclude that the higher preference for vaginal delivery may be due to the higher maternal educational level. The possible reasons why FPIAP is more common in children of mothers with higher education levels would be the tendency to be more protective and hygienic care behaviors (bathing, washing, and protective approach from infections). We believe that the incidence of FPIAP may have increased by the concept of the hygiene hypothesis, as the mothers with a higher educational status may be more prone to prepare sterile lifestyle conditions for themselves throughout their pregnancy and their children after birth.

The risk of developing FPIAP in the present study was higher in infants exposed to cigarette smoke during pregnancy. We encountered no previous studies showing a relationship between maternal active smoking or exposure to cigarette smoke during pregnancy and the development of FPIAP. However, studies have shown that children exposed to environmental tobacco smoke before and after birth are at a greater risk of FA, AD, and asthma [27, 40–45]. Intrauterine exposure to cigarette smoke may increase the risk of developing an abnormal postnatal immune system [46, 47]. Smoking or exposure to passive cigarette smoke during pregnancy causes a decrease in the number of Treg cells in cord blood, and children with low Treg counts at birth have a higher risk of developing food allergen sensitivity in the first year of life [48]. Lower neonatal Th1 responses [49] and Th2 responses (IL-4, IL-5, and IL-13) and higher TNF-alpha levels [46, 50] have been shown among infants born to mothers who smoked during pregnancy. Cigarette smoke may cause placental cytotrophoblast proliferation and differentiation in placental development because it is the main source of free radicals and oxidative stress. These disruptions in antioxidant systems may in turn lead to fetal gut immune function impairment [49].

The main strengths of this study were the verification of the FPIAP by means of OFCs in the hospital setting under the supervision of an experienced team (nurses and physicians). Questionnaires were completed at face-to-face interviews with the mothers to eliminate potential

misunderstandings or recalls. Since breastfed young infants were investigated, this may have resulted in an increased likelihood that mothers would continue their nutritional habits during lactation and would remember their gestational dietary habits better. In addition, the selection of healthy infants from 2 different family health-care centers enabled mothers with different lifestyles and socioeconomic status to be included in the study, resulting in greater homogenization of the results and a better reflection of the population.

However, there are also a few potential limitations to this study. First, due to the study design, we were unable to demonstrate a temporal sequence between maternal FFs consumption and infantile FPIAP. We were also unable to show the effect of FFs consumed by the mother during pregnancy on the intestinal microbiota and immune tolerance in mothers and their infants. Another minor limitation is that the study population was selected from a single province in Turkey and the findings may not be generalizable or applicable to other populations.

Conclusion

Our findings reveal a possible association between maternal consumption of Turkish traditional FFs during pregnancy and the development of FPIAP in infants. Maternal smoking during pregnancy and a higher maternal education level (university) increased the risk of FPIAP, while maternal daily consumption of homemade FFs (yogurt, cheese, and tarhana together) or diversity of FFs seem to be protective against FPIAP. The results of this study suggest that the lifestyle and nutritional habits of mothers during pregnancy may affect the intestinal development of the next generation, particularly in the early stages of life. Further cohort studies on larger populations are now required for a more accurate determination of the real impact of maternal gestational diet on FPIAP.

Statement of Ethics

All procedures involving human participants were conducted according to the ethical standards of the Institutional and/or National Research Committee and within the guidelines of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Local Scientific Ethics Committee of the Aydin Adnan Menderes University Nursing Faculty (project no.: 2019/117). The Ethics Committee did not consider it necessary to obtain written consent from the participants. Therefore, only verbal consent was obtained from the participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.U., P.K., B.K.B., D.E., and H.C. contributed to conceptualization; P.U. contributed to data curation, formal analysis, project administration, validation, and visualization; P.U., P.K.,

B.K.B., D.E., and H.C. contributed to funding acquisition; P.U., P.K., B.K.B., D.E., and H.C. contributed to investigation; P.U. and P.K. contributed to methodology; P.U., P.K., B.K.B., D.E., and H.C. contributed to resources; P.U. and P.K. contributed to writing – original draft; B.K.B., D.E., and H.C. contributed to writing – review and editing. All authors approved the final manuscript submitted and agreed to be accountable for all aspects of the work.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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