Ivane Javakhishvili Tbilisi State University

Faculty of Medicine

Doctoral Program:

"Clinical and Translational Medicine"

Mariam Petriashvili

Prognostic Criteria and Prevention of the Formation of Atopic Dermatitis in the Infant Population

The Thesis

of the dissertation submitted for the academic degree of

Doctor of Medicine (PhD)

Scientific Supervisor: Liana Zhorzholiani, MD., PhD

Associate Professor of TSU

Tbilisi

2021

Introduction

Atopic dermatitis (AD) is a widespread allergic disease in children, to a large extent (50-75%) presenting in an overall structure of allergic diseases. Atopic dermatitis is the most common and early presentation of allergy in children, characterized with a variety of clinical presentations, early debut, a wide range of causative factors, rapid chronicity of acute forms and increased frequency of refractory options to therapy (Garg, Silverberg JI., 2015;).

In recent decades, the prevalence of atopic dermatitis has increased 2-3 times as much in the early childhood population, as it was evidenced by large-scale studies carried out in different age groups and the countries. Atopic dermatitis is a multifactorial inflammatory skin disease, characterized by a chronic relapsing course, characteristic age-dependent features of skin lesion morphology and localization, often developed as a result of hereditary predisposition and combined with other allergic diseases (Alava A., et al, 2014). It is no coincidence that at an early age the skin is a common target organ for allergic responses. The mentioned is due to anatomical-histological features of the skin and the nature of the immune response to antigens in neonates and infants. Since the end of the 20th century, early manifestation (from 1-2 months of age) of AD, its severe course and a tendency of being accompanied by respiratory allergies (Nutten S. , 2015, Ćosićkić A1,et al, 2017) have been revealed. The early debut of atopic dermatitis in children has been stipulated by a combination of a wide range of diverse, undesirable environmental factors affecting the fetus since the prenatal period. Such factors include irrational feeding of the mother, presence of allergic and somatic pathologies, pregnancy and childbirth complications, formula feeding, early exposure to additional feeding, premature age of placing into the nursery, early exposure to food allergens, etc.

Postnatal risk factors include: sex, birth weight, type of feeding, immune system disorders, infections, early exposure to allergens, violating hygiene norms, family history of atopy, respiratory tract infections, pets in the family, exposure to smoke and other harmful factors (Sausenthaler S., et al., 2009; Miyake Y., Sa¬saki S., et al., 2010; Niggemann B., et al., 2012). The interaction of diverse risk factors contributes to the chronicity of acute forms of the disease, frequent transformation of one type of allergy into another, for example, often atopic dermatitis is followed by formation of allergic rhinitis, asthmatic bronchitis and bronchial asthma (Kantora R., Silverbergb, 2017).

Various researchers give preference to one or another cycle of AD pathogenesis, for example: hereditary loading with atopy, genetic predisposition, dysfunction of immunocompetent cells,

metabolic and mental disorders, allergies, etc. (Bieber et al, 2017). Based on molecular research studies carried out in the last years, a new concept of AD pathogenesis has been developed, containing a triad of leading mechanisms: genetic predisposition to atopy, epidermal barrier disruption and cascade of immune reactions, leading to the formation of allergic skin inflammation (Kabashima K., 2013, McPherson T., 2016).

In most cases, atopic dermatitis develops during the first months of life, with a wide spectrum of clinical presentations, and is difficult to treat (Spergel JM., 2010).

In 45% of the children population debut was fixed under 6 months of age. Children with atopic dermatitis often develop other allergic pathologies (bronchial asthma, allergic rhinitis, conjunctivitis) and show a disposition to secondary skin infections (Nutten S., 2015; Rogers N. K., 2016; Tham EH., Leung DY., 2019).

It is known that atopic dermatitis (AD) developed in infancy contributes to initiation of so-called "atopic march" and represents a high risk for development of food allergies (Worth A., Sheikh A., 2010, Tham EH., et al, 2019), allergic rhinitis and, later in life - bronchial asthma (ZhengT., et al.,2011). According to modern data, atopic march is the result of impaired skin barrier function at AD, leading to enhancement of skin permeability to allergens (Tran MM1, et al., 2018).

A leading role in atopic march formation belongs to Filaggrin an epidermal barrier protein, genetic mutation of which (Cabanillas B., Novak N, 2016), or quantitative reduction (Thyssen J., 2014) leads to disruption of skin barrier function and increased skin permeability to allergens. Atopic march is most frequently presentated at early-onset, severe, and persistent AD (Czarnowicki T., et al., 2017).

In the USA, 19.8% of children with AD had concomitant asthma and 34% of them - allergic rhinitis, correlating with AD severity. Prospective studies proved a strong correlation between AD and food allergy (laelakovská J., 2015).

Debut of atopic dermatitis at an early age is largely due to food allergies (Wong G.W., et al, 2014) The etiologically important factor determining subsequent exacerbations of the disease may be household, epidermal, and other allergens (Dharma C., et al, 2018). Food allergies in early life often correlate with the degree of disease severity (Tham EH, Leung DY, 2019).

Cow's milk is considered as an important trigger factor for atopic dermatitis early in life. 90% of AD cases developed in the first year of life are associated with Cow's Milk Protein Allergy (CMPA). Cow's Milk Protein Allergy (CMPA) often develops among the contingent being on formula or

mixed feeding. CMPA, revealed in 0.5-1.5% of children on natural feeding, is due to fetus sensitization during pregnancy, as well as excessive maternal consumption of milk products during pregnancy and lactation (Vandenplas Y., Marchand J., et al., 2015).

The development and implementation of non-invasive methods in pediatric practice to verify the cow's milk protein allergy (CMPA) in young children is an objective of great importance, as well as the basis for early prevention and treatment. The CoMiSS (The Cow's Milk-Related Symptom Score) – non-invasive clinical scale (NNI, 2015, CoMiSS-PubMed, 2016) has been developed by the world's leading expert-specialists to facilitate an early verification of CMPA symptoms and to raise awareness among pediatricians.

The special significance assigned to the food allergies in the first year of life is due to the fact that sensitization to food allergens later serves as a trigger mechanism for manifestation of atopic dermatitis, gastrointestinal allergies and various allergic pathologies in general (Worth A, et al, 2010, Wong G.W.,2015). Despite numerous studies devoted to the food allergy prevention issues, existing preventive measures are insufficient due to the difficulty in development of evidence-based ones, as well as the lack of non-invasive reliable predictive markers. This is why the use of AD predictive indexes, or different kinds of scales based on the assessment of clinical symptoms, is of particular importance in the early childhood population.

According to some researchers an increase in blood eosinophil count in the first 4 weeks of life might be considered as a predictive marker of atopic dermatitis (Rossberg S, et al, 2016, Nissen SP, et al, 2014) 127,178). There are studies where preference for identifying high-risk groups for atopy formation, is given to measuring IgE levels in umbilical cord blood (Nabavi M., 2013; Meulenbroek L., et al, 2015).

This is why determining the IgE levels in the newborn umbilical cord blood, as well as in mothers with atopy and atopic dermatitis is of particular interest (Vinkhuyzen A.A., et al., 2016).

According to the latest data, a high risk of developing allergic diseases in children is associated with vitamin D deficiency, however, the precise mechanisms of this effect still have not been studied (Wang S. S., 2014).

There is evidence in the scientific literature that vitamin D deficiency during pregnancy increases the risk of developing allergic diseases, among them atopic dermatitis, food allergies, asthma, and allergic rhinitis in children. Numerous studies show that vitamin D plays an important role in

regulation of skin homeostasis, proliferation, inhibition and differentiation of keratinocytes, while hypovitaminosis D is a potential predictor for the development of allergic and inflammatory dermatoses (Y. Miyake., 2010, Guidelines of care for the management of atopic dermatitis., 2014, Di Filippo P.,et al.,2015,). According to the data suggested by recent literature, vitamin D levels in pregnant women contribute to early debut of atopic dermatitis and its severe course in young children (Anıl O., et al, 2017).

Expert-specialists point to the importance of supplementing vitamin D deficiency for the prevention and treatment of atopic diseases. At the same time, the indications are not fully specified and further large-scale studies are required. The association of vitamin D concentrations with a family history of atopy has not been investigated as well (Thorne-Lyman A., et al., 2012, Streym V.S., et al., 2013,).

However, there are contradictory data as well. Some authors indicate to the enhancement of vitamin D synthesis in atopic dermatitis, while the others to – the reduced or unchanged concentrations. For example, a research conducted by Peroni DG, ET AL in 2011, focused on assessing the effect of vitamin D levels on the prevalence and course of AD, found that 25(OH)D levels were higher at mild AD in comparison with the moderate and severe forms of disease. Similar results were obtained in the research study conducted by Wang S. S., et al., in 2016. According to Back and co-authors high intake of vitamin D at an early age of life correlates with a higher risk of developing atopic dermatitis at 6 years of age (Bäck O., et al., 2009). This issue still remains the subject of active investigation and requires further extensive large-scale research.

The Relevance of the Study

Relevance of the study is due to the high prevalence of atopic dermatitis, debut at an early age, QoL (quality of life) deterioration, health spending growth, progressing to other allergic phenotypes, tendency of chronicity, prolonged chronic and recurrent course, physical and emotional disadaptation, frequency of refractory forms in response to standard treatment, causing deterioration in quality of life and in some cases – formation of disability (Thomas, 217).

The relevance of the study is also determined by the growing tendency of transformation from one type of allergy to another (atopic dermatitis often precede formation of allergic rhinitis or bronchial asthma) (Östblom E.,et al, 2008, Eller E, et al, 2009), persistent course, progression of comorbid

pathologies. Persistent cases of AD are associated with early onset, severe course, family anamnesis, and comorbid diseases (Silverberg JI1., 2019). It is considered that early childhood is a critical period for prevention of atopic dermatitis, food allergies and subsequent atopic march (Ricci et al., 2010). Early childhood is considered to be a critical period for preventing the development of atopic dermatitis, food allergy, and subsequent atopic dermatitis (Ricci et al., 2010).

The relevance of the study was compounded by the fact that despite intensive research conducted on atopic dermatitis in children, the prognostic criteria for the formation of atopic dermatitis in the infant population and aspects of its early prevention remain underestimated. Using invasive diagnostic methods in young children is considered as a rather difficult challenge to pediatric practice. All of the above necessitates searching for non-invasive predictive biomarkers to identify the contingent of young children predisposed to developing atopic dermatitis, and to optimize preventive measures that have been set as the aim of our study.

The Aim of the Study

To identify clinical, triggering and immunological markers of the formation of atopic dermatitis in young children, to assess their prognostic value and based on them, to develop, targeted preventive measures in the early childhood population.

The Goals of the Study

1. Formation and immunological characteristics of the target population of mother-child pairs for the purpose of conducting a prospective, cohort study;
2. Detection and multiple factor analysis of pre- and perinatal predictors for development of atopic dermatitis in young children;
3. Investigation of quantitative indicators (quartiles, interquartile range) of eosinophil, IgE and vitamin D concentrations and assessment of correlation in pregnant women;
4. Evaluation of the association between the vitamin D deficiency in pregnant women and the peculiarities of the course of atopic dermatitis in children;
5. Development of early prognostic model for the formation of atopic dermatitis based on the obtained clinical and immunological indicators.

Provisions Submitted for Defense

1. The use of medical, clinical and social predictive criteria defined on the basis of multifactorial mathematical analysis and contributing the formation of atopic dermatitis, appeared to be reasonable for development and implementation of timely and subsequent preventive measures for atopic dermatitis.

2. Vitamin D deficiency in pregnant women positively correlates with the risk of developing atopic dermatitis in the early childhood population. This factor, along with hereditary predisposition, can be considered as high risk of atopy formation.

3. The CoMISS scale can be effectively used for providing an early non-invasive diagnosis of Cow's Milk Protein Allergy (CMPA).

The Scientific Novelty of the Study

- Prognostic clinico-immunological and biochemical markers of AD formation were identified.
- Quantitative eosinophil counts and total IgE as well as correlation with hereditary load were determined in pregnant women and neonates at risk of developing atopy;
- Vitamin D status among pregnant women was studied. The correlation between the indicators obtained with hereditary load and the share in the formation of atopic dermatitis at early age of life were analyzed;
- Prognostic value of the CoMiSS score, verifying Cow's Milk Protein Allergy in children with atopic dermatitis were assessed.

The Practical Value of the Study

The results of prospective clinical study made it possible to identify patients at high risk of developing atopic dermatitis that is of great importance in terms of disease prognosis and prevention.

Knowledge of prenatal risk factors of prognostic value at the pregravidary stage serves as the basis for the development and implementation of primary preventive measures for atopic dermatitis.

The results of the study make it possible to optimize AD treatment taking into account the characteristics of child's age, disease severity and the course of disease.

Methodology of the Study

In 2017-2020, a 3-year prospective cohort study was conducted on the basis of "Chachava Clinic". A cohort of 200 mother and child pairs were observed.

Criteria for the inclusion of pregnant women in the study: reproductive age, monocarpous (single) pregnancy, consent to participate in the study.

Criteria for exclusion of pregnant women from the study: pregnancy achieved through assisted reproductive technologies (ART), presence of severe somatic and psycho-neurological diseases, termination of pregnancy.

Criteria for inclusion of children in the study: less than 2 years of age, diagnosis of atopic dermatitis confirmed by physician, presence of morphological lesions of typical localization on the skin, parental consent for children participation in research.

Criteria for exclusion of children from the study: atypical course of disease, serious congenital developmental anomalies and defects, concomitant acute somatic pathology.

Observation of the pregnant women was performed during pregnancy and the postpartum period, but infants – from birth to 2 years of age, respectively, through visits - at early neonatal period (1-7 days), and then at 1, 3, 6, 9, 12 and 24 months of age. Extraordinary review visits and telephone monitoring were allowed.

A mother-child pair survey-questionnaire included: maternal demographic and socio-hygienic data, detailed analysis of family history of atopy, peculiarities, complications of the course of pregnancy and labor; anamnesis of infancy, type of feeding, detailed information on the child health and development. Telephone survey method was used. In parallel, children's medical documentation (extracts form medical history, medical reports) was studied as well.

The studies carried out in pregnant women:

1. **Clinical studies:** demographic and socio-hygienic indicators, obstetric-gynecological anamnesis, peculiarities of the course of pregnancy and labor, allergological anamnesis, etc were studied.
2. **Standard laboratory and instrumental studies:**
3. **Biochemical studies:**

- IgE levels in peripheral blood of pregnant women using ElectroChemiLuminescence (ECL) method (COCHAS e411 automatic analyzer by ROCHE) (norm <100 IU/ ml) were detected;
- Detection of Eosinophils was conducted by automatic analyzer SYSMEX 1000 I (norm - 1-5%);
- The level of a major circulating metabolite of vitamin D - 25-hydroxyvitamin (25 [OH] D) was detrmined by ElectroChemiLuminescence (ECL) method (apparatus: COBAS e 411; manufacturer: ROCHE). Blood test was done at 34-36 weeks of pregnancy. According to the recommendations suggested by the International Society of Endocrinologists (2011), vitamin D status was assessed by the following criteria: deficiency <20.0 ng/ml, insufficiency- 20.0 - 30.0 ng/ml, normal supply> 30.0 ng/ml (Holick MF, et al, 2011).

The children underwent the following studies:

1. Clinical studies and anamnesis: family and allergological anamnesis, date of disease onset and the causes of first presentation were studied. The factors causing exacerbation of the disease were determined; peculiarities of the course of atopic dermatitis, type of feeding, presence of food allergies and respiratory infections, etc., were assessed. For effective collection of anamnetic data a structured survey -questinnaire was applied (Table 1).

Table 1: **Structured Survey -Questinnaire for Atopic Dermatitis**

Age of atopy onset	Age of infancy, up to 6 months, 6 months to 1 year, and 1 to 2 years.
Causes of atopy onset	Contact with animals, house dust, medicines, pungent odor, paints, care products, plant dust, cow milk, food, food additives
Clinical signs of atopy	Itchy skin, dry skin (xerosis), localization of morphological elements, body localization of elements, localization of elements on extensor surfaces, papulo-vesicles, exudation, cracks behind the ears
Course of atopy	Acute, subacute, recurrent, chronic
Other allergic presentations	Rhinitis, Conjunctivitis, Urticaria, Quincke, Bronchial asthma, allergic gastritis, drug allergies,

	food allergies, cow's milk allergy
Concomitant pathologies	Recurrent respiratory infections, tonsillitis, CNS pathology, colic, foaming/vomiting, soft stool, constipation, sinusitis, bronchitis, cardiovascular pathology, obesity, helminthosis, otitis and etc.

2. Verification of the diagnosis of atopic dermatitis was conducted according to the basic and additional diagnostic criteria developed by Hanifin and Rajka (Hanifin JM, Rajka G., 1980). The basic criteria were: itching, typical morphology and localization, recurrent course, family anamnesis of allergies; and the additionional criteria included: xerosis, ichthyosis, first type of skin reaction, elevation of IgE level, disease debut at early age of life, dermatitis on the limbs, conjunctivitis, Dennie-Morgan folds, keratoconus, skin pale or red skin, wrinkles on anterior neck surface, white dermographism. For disease verification the presence of at least three basic and three additional criteria were required. Monitoring of the children was carried out without interference in treatment process, i.e. based on clinical course of disease progression.

The severity of the clinical course of atopic dermatitis was assessed according to the SCORAD index (Scoring Atopic Dermatitis), which includes: skin process extension, objective symptoms of clinical presentation (erythema - hyperemia, edema, papula-like elements, crusts, excoriations, lichenification, dryness) and subjective symptoms (itching, insomnia).

Each item was graded from 0 to 3 points: 0 point - absence of symptoms, 1 point - mild expression of changes, 2 points - moderate expression of changes, and 3 points - sharp expression of symptoms. Symptoms were assessed on the skin area where they were most pronounced.

The SCORAD index was calculated using the formula:

SCORAD index = A/5 + 7B/2 + C, where: A –is defined as skin lesion extent in %, the sum of objective signs (erythema, edema, dampness, excoriation, lichenification, dryness), C - the sum of subjective symptoms (itching, insomnia). SCORAD index range lies between 0 (no disease) - 103 (maximum severity).

SCORAD Index Interpretation: 20 scores - mild course; 20-40 scores – moderate course; more than 40 scores - severe course.

3. Verification of Cow's Milk Protein Allergy (CMPA) and assessment of gastrointestinal presentations using the CoMiSS (The Cow's Milk-related Symptom Score) scale.

In recent years, with the view to raising awareness of the Cow's Milk Protein Allergy (CMPA) among the pediatricians and improving verification process, a team of experts has developed the CoMISS (The Cow's Milk-Related Symptom Score) - a non-invasive, clinical assessment tool based on the panel of general allergic symptoms (Vandenplas Y., et al, 2015, CoMiSS- PubMed, 2016).

CoMISS parameters (crying, foaming, fecal masses, skin symptoms, urticaria, respiratory symptoms) were graded on a 0- to 6-points system scale; with a total sum from 0 to 33 points. Cut off points < 12 excludes the presence of cow's milk protein allergy, while cut off points >12 indicate to a high probability of CMPA.

4. Standard clinico-laboratory and instrumental studies:

5. Immunological study – determining the IgE levels in the newborn umbilical cord blood by ElectroChemiLuminescence (ECL) method (COCHAS e411 by ROCHE). Norm in infants <1.51 IU/ml);

Methods of statistical analysis:

During the study the risk factors (social, biological, medical) contributing to development of atopic dermatitis: hereditary load, gestational age, birth weight, feeding during the neonatal period, presence of food allergies and respiratory infections, etc., have been determined. Odds ratio (OR) and 95% confidence interval (95% CI) were defined for pre- and perinatal predictors and dichotomous variables. The odds ratio (OR) from 0 to 1 indicated an absence of negative effect, odds ratio equal to 1 indicated a slight risk, and ratio greater than 1 suggested an increased risk and interaction between negative impact and disease. The relative intensity coefficient (K) was determined, which is calculated by the ratio of risk factor intensity indexes. Data processing was performed using Microsoft Excel and SPSS/v15 software packages. Charts and tables were built using MS Excel software package. The probability P <0.05 was considered as the lower confidence limit.

The Results of the Study and Review

Atopic dermatitis is a widespread and early presentation of atopy in children, characterized by diversity of clinical presentations, early debut, a wide range of causative factors, rapid chronicity of acute forms, and increased rates of refractory variants to therapy (Garg N, et al, 2015, Gupta D 2015). The early debut of atopic dermatitis in children was stipulated by a combination of a wide

range of adverse environmental factors starting to act since the prenatal period. Such factors include: mother's irrational nutrition during pregnancy, alcohol and tobacco consumption increasing the risk of developing atopic dermatitis in children (Charlotte G Carson, et al, 2012).

Among the potential risk factors, acting during the pregnancy, of great importance are: perinatal complications, birth month, sex, birth weight, family history of atopy; and during the infancy - type of feeding, formula feeding, early exposure to additional feeding, premature age of placing into the nursery, respiratory tract infections (Muraro A., et al, 2016), immune system disorders, pets in the family, violating hygiene norms, impact of environmental factors (Koletzko S., Niggemann B., et al., 2012). (Sausenthaler S., et al., 2009, Kantor R, Silverberg J., 2017). Intrauterine sensitization can be considered as a risk factor for the formation of postnatal atopy, especially in the presence of provocative circumstances, such as hereditary load with allergies, drug therapy during pregnancy, maternal consumption of high allergenic products during lactation, postnatal sensitization caused by other allergens and etc.

The interaction of diverse risk factors contributes to chronicity of acute forms of the disease, transformation of one type of allergy into another is not infrequent, for example, after atopic dermatitis often develops allergic rhinitis, asthmatic bronchitis and bronchial asthma (Gurmhausen D., et al, 2013).

High prevalence of the disease, multifactorial genesis, abundance of risk factors, puts on the agenda the need to identify predictors of prognotsic value. The study was aimed at investigating the clinical, trigger and immunologic markers of the formation of atopic dermatitis, to evaluate their prognostic value, and based on them to outline preventive measures in the infant population.

As it have been mentioned, 200 mother-child pairs were involved in a 3-year prospective cohort study.

According to the study inclusion and exclusion criteria, 186 women were finally selected. Among them, 120 mothers, whose children developed atopic dermatitis under 2 years of age were assigned to the main group, and 66 mothers whose children did not show atopy during the observation - to the control group, respectively.

As for the cohort of children, 186 children were selected from the study population, 120 of them, who developed atopic dermatitis under 2 years the age, joined the main group. 66 children who did

not show clinical signs of atopic dermatitis or loaded allergic anamnesis were included in the control group. The research protocol was approved by the Research Ethics Committee.

The mother-child pairs survey-questionnaire included: maternal demographic and socio-hygienic data, spectrum of comorbid pathology, detailed analysis of family atopy, peculiarities, complications of the course of pregnancy and labor, anamnesis of the infancy, type of feeding, detailed information on the peculiarities of the course of atopic dermatitis in children, etc. Based on the retrospective data analysis in the study process, the social, biological and medical risk factors of predictive value were identified.

Table 1: **Demographic and social risk factors in pregnant women (n= 186)**

Risk factors	Cases (n=120)			Control (n=66)		OR	95% CI	p
	n	%		n	%			
Nationality								
Georgian	109	90.2%		54	81. 8%	2.20	0.84-5.78	0.120
Non-Georgian	11	9.8 %		12	18.2%	0.45.	0.17-1.18	0.120
Age								
< 25 years	27	22. 5%		5	7.6%	3.54	1.21-11.12	0.018
25-34	70	58.3%		50	75.8	0.44	0.21-0.91	0.027
> 34 years	23	19.2%		11	16.6%	1.18	0.50-2.82	0.823
Profession								
Housewife	50	41.7%		34	51.5%	0.67	0.35-1.28	0.257
Service personnel (mother)	70	58.3%		32	48.5%	1.48	0.77-2.84	0.256
Education								
Secondary Education	41	34.2%		23	34.8%	0.97	0.49-1.91	1.000
Addictions								
Tobacco	15	12.5%		8	12.1%	0.90	0,34-2.46	1.000
Alcohol	2	1.7%		1	1.5%	1.10	0.07-30.90	1.000
Family Social Status								
Low income	23	19.2%		12	18.2%	1.07	0.46-2.48	1.000
Middle income	97	80.8%		54	81.8%	0.97	0.40-2.16	1.000
Unsatisfactory living conditions	50	41.7%		9	13.6%	4.52	1.94-10.82	0.000
Incomplete family	18	15.0%		8	12.1%	1.28	0.48-3.44	0.748

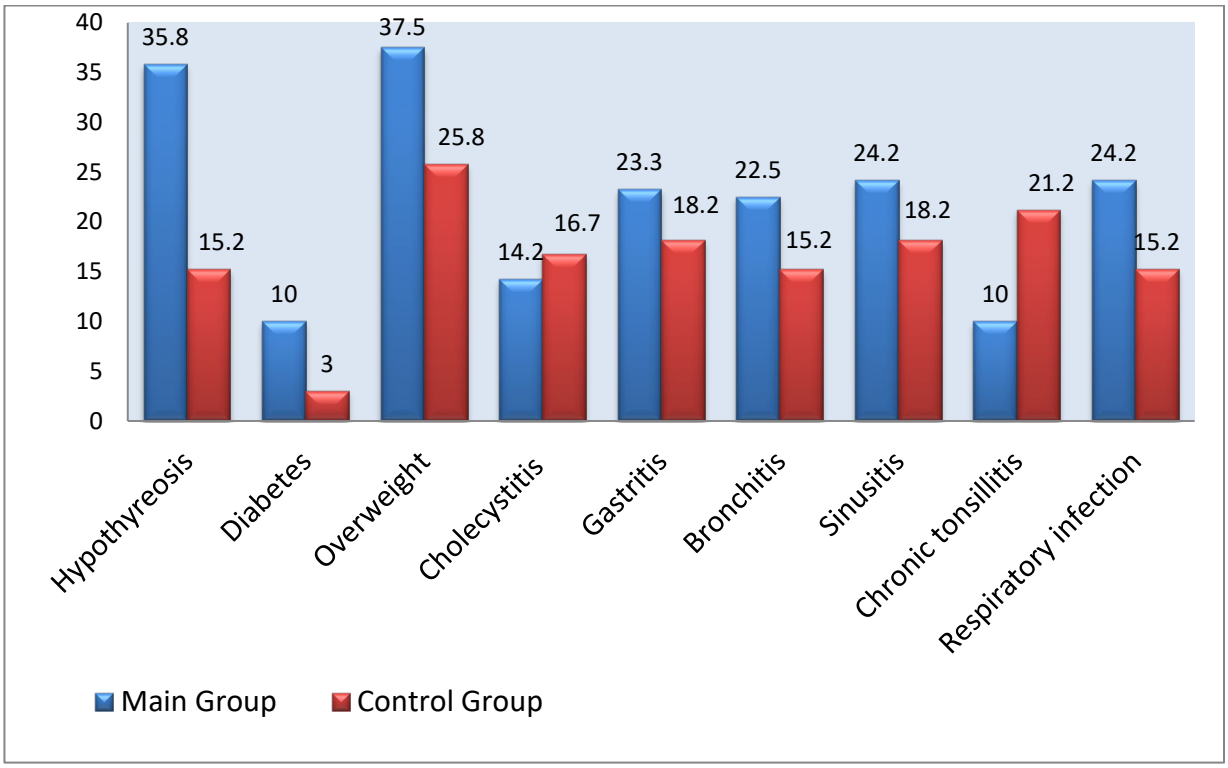
Comparative analysis of the groups showed that the age of pregnants did not differ significantly; mothers 25-34 years of age prevailed in both groups (P-0.027). The majority were ethnic Georgian women with higher education, 58.3% of whom were employed. No significant differences were found between the groups in terms of education and family status. Measuring social indicators showed that 50% of pregnant women whose children developed atopic dermatitis at an early age of life had unsatisfactory living conditions (OR – 4.52) and low material income (OR – 1.07). Maternal age <25 years (OR–3.17, CI–1.07-9.76, P-0.035) and unsatisfactory living conditions (OR– 4.52, CI–1.94-10.82, P-0.000) were statistically reliable. Incomplete families (OR – 1.28) appeared to play the role of provocing factors as well. The obtained results were consistent with the literature data showing that negative social and family factors acting during pregnancy were associated with a higher risk of developing AD in children under 2 years of age (Larsen AD., 2014, Sarkar R., Narang I.,2018, Sausenthaler S., et al., 2009).

Maternal chronic morbidity rates have been studied as antenatal risk factors.

The majority of pregnant women in the main group (71.7%) had some form of concomitant somatic pathologies. The prevalence of gastrointestinal pathologies and respiratory diseases was noteworthy.

The frequency of gastrointestinal pathology and respiratory diseases was noted.

Chart 1: **Structure of chronic morbidity among the studied pregnant women (n= 186)**



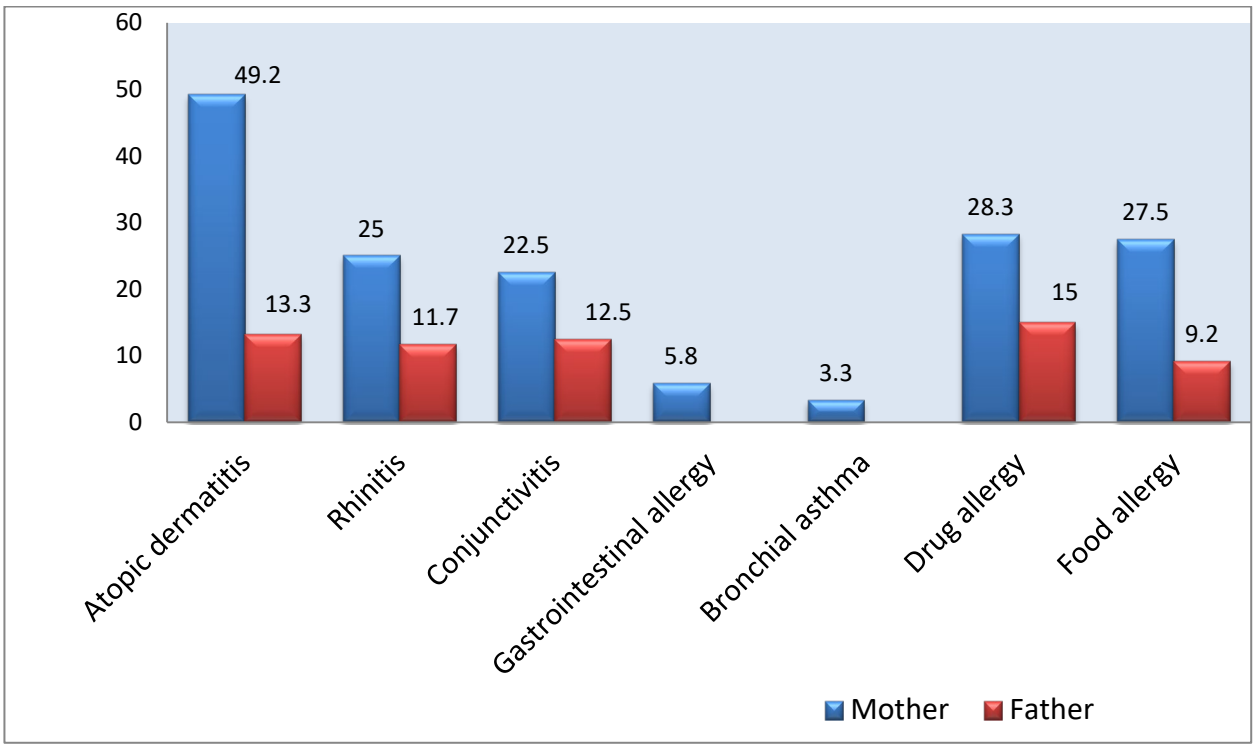
Concomitant somatic pathologies were presented with chronic diseases of digestive system (gastritis -23.3%, cholecystitis -14.2%, constipation -37.5%), respiratory tract and ENT (ear-nose-throat) (common respiratory infections - 24.2%, sinusitis 24.2%, bronchitis - 22.5%). As for the endocrine system, a high percentage of hypothyreosis (35.8%) was revealed among the patients of main group, 2 times higher than the control group (15.2%). Diabetes was reported in 10% of cases. Cardiovascular pathologies were relatively less common (5.0%).

Among the nosologies discussed, chronic constipation (OR–3.00, 95% CI–1.35-6.78, P-0.006) and hypothyreosis (OR–3.12, 95% CI–1.37-7.28, P-0.005) appeared to be statistically reliable risk factors. Family hereditary allergo-anamnesis is known as an important factor in the formation of atopic diseases in young children. According to large-scale studies, hereditary atopy is predominantly transmitted from mothers due to the presence of predisposing genes. Transplacental transmission of antigens, maternal antibodies, and cytokines leads to the formation of premature atopy (Akdis CA., et al., 2006, Bieber T., 2017, Schnopp C., et al, 2015).

As for our material, atopy and atopic reactions were revealed in 59 mothers (49.2%) of 120 pregnant women in the main group. In 19.8% of cases atopy was reported in fathers.

The incidence of allergic reactions among mothers (atopic dermatitis (OR-6.28), allergic rhinitis (OR-2.52), conjunctivitis (OR-2.03), food allergies (OR-3.02) and drug allergies (OR-2.14) was several times higher compared to fathers. According to the study results family history of atopy was associated with a higher risk of developing AD in children; particularly prominent was the role of maternal atopy, consistent with literature data (Wadonda-Kabondo N, 2004, Letourneau NL, 2017).

Chart 1: **Allergic presentations in parents**



The possibility of phenotypic realization of atopic genotype dramatically increases in presence of aggreviated obstetric-gynecological anamnesis (Pyun B.Y., 2015). Physiological mechanisms of direct contact between maternal body and the fetus, along with abnormal course of pregnancy, lead to changes in immunological reactivity, causing the infant's developing immune system to tend toward "allergic phenotype" (Kuo C. L., 2016, Lovinsky-Desir S., et al., 2012). Recent studies proved the possibility of fetal sensitization during gestosis (Kasyanova A.C., 2013; Cipriani F., et al., 2014).

From this point of view, it would be expedient to evaluate the peculiarities of the course of pregnancy and labor to obtain the evidence.

Pregnancy, both in the main and control groups, in most cases took place against the background of certain complications.

In most cases, pregnancy went on against the background of certain complications in both the main and control groups.

Table 15: **Complications of pregnancy among the studied contingent (n=186)**

Pregnancy Complications	Case (n=120)		Control (n=66)		OR	95% CI	P
	n	%	n	%			
Gestosis	47	39.2%	24	36.4%	1.12	0.58-2.19	0.827
Anemia	100	83.3%	53	80.3%	1.22	0.52-2.83	0.751
Risk of spontaneous abortion - estimated premature birth /preterm delivery)	52	43.3%	18	27.3%	2.03	1.01-0.04	0.045
Vaginal bleeding	6	5.0%	1	1.5%	3.42	0.39-78.31	0.428
Preeclampsia	8	6.7%	1	1.5%	4.64	0.56-102.66	0.227
Polyhydramnion	6	5.0%	1	1.5%	3.42	0.39-78.31	0.428
Oligohydramnion	9	7.5%	1	1.5%	5.27	0.65-15.18	0.164
Meconium-stained amniotic fluid	19	15.8%	5	7.6%	2.29	0.75-7.43	0.168
Gestational diabetes	20	16.7%	5	7.6%	2.44	0.80-7.86	0.130
Excess weight gain	63	52.5%	33	50.0%	1.10	0.58-2.10	0.863
GBS (+)	26	21.7%	10	15,2%	1.54	0.65-3.73	0.003
Antibiotics	68	56.7%	16	24.2%	4.08	1.99-8.44	0.000
Urogenital infection	41	34.2%	12	18.2%	2.33	1.06-5.18	0.032

Among the complications of pregnancy, anemia prevalence was 83.3% in the main group and 80.3% - in the control group, respectively. In both groups gestosis was presented almost equally. Particular attention was drawn to the risk of pregnancy termination - estimated preterm delivery, 1.5 times more common in pregnants of the main group compared to the control group (P-0.045). A significant difference was found in the incidence of urogenital infectious diseases (P-0.032), supposedly determining the need for frequent antibiotic use in the main group (56.7%). Relatively rare were: gestational diabetes (16.7%), meconium-stained amniotic fluid (15.8%), and anterior placenta (9.2%).

The characteristics of labor were analyzed in both the main and control groups and the following results were highlighted:

Table: **The course of delivery in the studied contingent (n=186)**

Course of Childbirth /delivery	Main group (n=120)		Control group (n=66)		P value
	n	%	n	%	
Vaginal	63	52.5%	44	66.7%	0.086
Premature	11	9.2%	3	4.5%	0.394
Protracted	2	1.7%	-	-	-
Pincer/vacuum-assisted	6	5.0%	1	1.5%	0.428
Premature discharge of amniotic fluid	57	47.5%	35	53.0%	0.569
Placental abruption	7	5.8%	2	3.0%	0.620
Oxytocin induced	3	2.5%	3	4.5%	0.747
Meconium stained amniotic fluid	19	15.8%	5	7.6%	0.168
Caesarean section on request	10	8.3%	4	6.1%	0.786
Caesarean section on indication	47	39.2%	18	27.3%	0.142
Spinal / epidural analgesia	99	82.5%	54	81.8%	1.000

In 57.1% of cases, women gave birth through physiologic delivery (on time, spontaneous, vaginal, without instrumental interventions). In single cases, childbirth was premature (9.2%) or overdue (1.7%). It is noteworthy to emphasize that premature discharge of amniotic fluid was common in both groups (47.5% and 53.0%). In the main group, caesarean section on indication was performed in 39.2% of pregnant women and on request - in 8.3%, respectively. Spinal anesthesia was used in 82.5% of cases. As for the control group, caesarean section on indication was performed in 27.3% of cases and on request - in 6.1%, respectively. Spinal anesthesia was also used in most cases (81.8%) in the control group.

Statistical processing identified several potential risk factors: anterior placenta (OR-2.11), meconium-stained amniotic fluid (OR-2.29), placental abruption (OR-2.52), preterm delivery (OR - 3.22) and cesarean section on indication (OR-1.71). Due to the low incidence of cases, a statistical reliability of these factors was not confirmed, consequently, their predictive value was low as well.

The exceptions were: risk of pregnancy termination - estimated risk of preterm birth (OR - 2.03, 95% CI - 1.01-0.04, P-0.045), antibiotic therapy during pregnancy (OR – 4.08, 95% CI -1.99-8.44, P–0.000) and urogenital infections (OR-2.33, 95% CI -1.06-5.18, P– 0.032), the incidence of which among the mothers of children with atopic dermatitis was much higher compared to the control group. The mentioned allows to assume the presence of a cause-and-effect relationship between the complications listed and AD development at an early age of life.

Numerous studies have shown that the main predictive factors of the postnatal period include: male-gender, low birth weight, early exposure to formula feeding, improper additional feeding, loaded family anamnesis, exposure to allergens early in life, and poor skin hygiene (Carlsten C., et al., 2013,et al.,2016, Mann J., Flohr C., 2014).

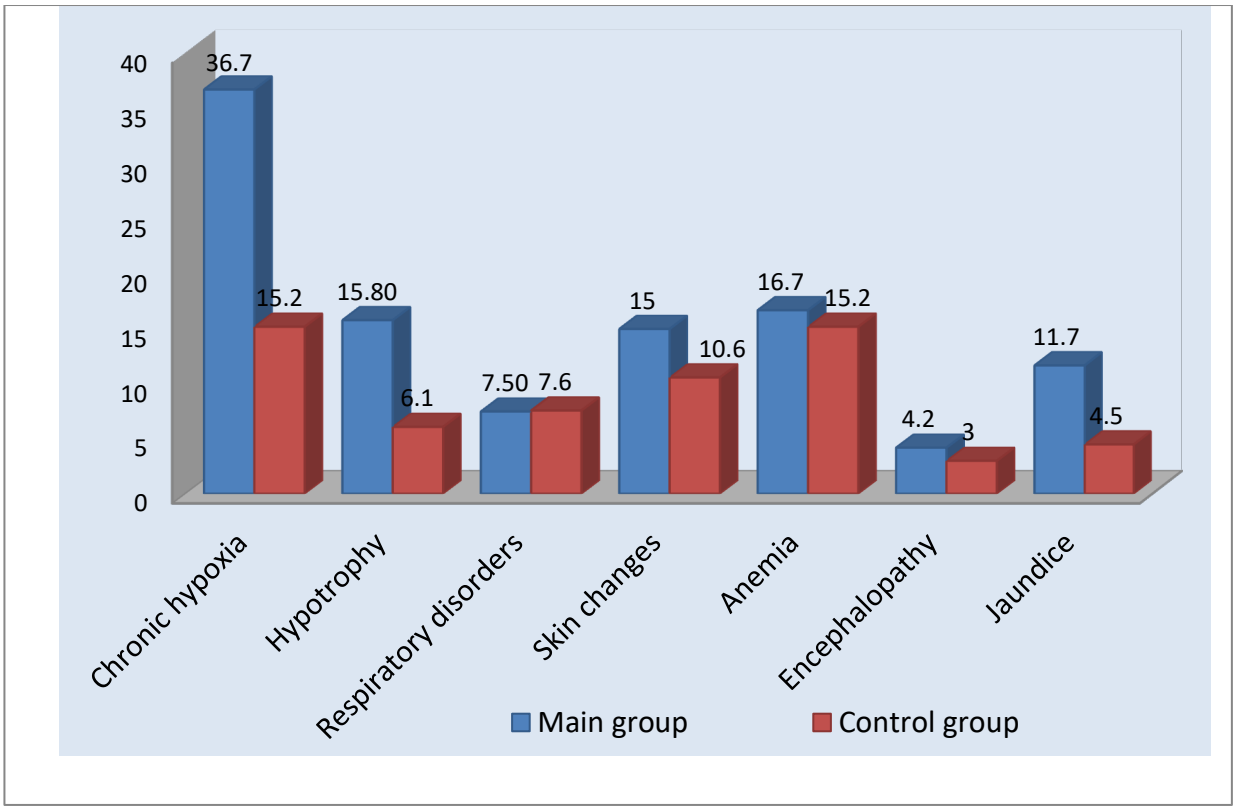
Table 4: **Newborn peculiarities in the studied contingent (n=186)**

Characteristics of newborns/neonates	Main group (n=120)	Control group (n=66)
Gestational age (GA)	38.6 ± 1.5	39.1 ± 1.1
Girl	61 (50.8%)	35(53.0%)
Boy	59 (49.2%)	31 (45.5%)
Birth weight (kg)	3.3 ± 0.5	3.4 ± 0.68
Birth length (cm)	49.7 ± 2.3	50.2 ± 2.3
Body Mass Index (BMI)	12.9	13.5
Head circumference (cm)	33.8 ± 1.2	34.9 ± 7.6
SGA	10.0 (2,5%)	3 (4.5%)
LGA	9.0 (2.3%)	4(6.1%)
1 minute Apgar score	7.8 ± 0.5	7.9 ± 0.5
2 minutes Apgar score	8.9 ± 0.4	9.0 ± 0.2
Natural (breast) feeding	48 (40%)	37 (56%)
Artificial and mixed feeding	72 (60%)	29 (44%)

As for our materials, a gender profile of newborns, anthropometric data, Apgar scores did not differ significantly according to the comparable groups. Natural feeding frequency was high in the main and control groups (40% and 56%), while the frequency of formula (OR – 1.13) and mixed (OR – 1.24) feeding was higher in children who developed atopic dermatitis under 2 years of age. During the neonatal period, syndromological disorders were revealed in both groups, among which chronic hypoxia - 36.7% (OR-3.24), fetal hypotrophy -15.8% (OR-2.91), skin changes -15.0% (OR-2.83), prolonged jaundice -11.7% (OR– 2.77) appeared to be of great significance.

The skin changes presented in newborns were the subject of detailed study. Toxic erythema was the focus of attention in both groups (72.5% and 54.5%). Dry skin (71.71%), mottled skin (39.2%) and exfoliation (55.0%) prevailed among the newborns in the main group. Mongolian spots (18.3% and 16.7%), cyanosis (7.5% and 4.5%) and petechiae (8.3% and 6.1%) were relatively less common. Percentages showed a high rate of OR for skin changes — toxic erythema, dry skin, exfoliation (OR-3.55), although no statistically significant prognostic values were found for these changes.

Chart 5: **Syndromological disorders in newborns (n=186)**



In order to assess the prognostic value of the risk factors identified in pregnant women and children, a relative intensity coefficient (K) to the factors with high ORs was determined. The relative intensity coefficient (K) was high for risk factors with a odds ratio greater than 2 (OR> 2).

Table 27: The relative intensity (K) of risk factors

Risk Factors	Case (%)	Control (%)	K
Social			
Ethnic Georgian	90.2%	81.8%	1.10
Mother's age <25 years	22.5%	7.6%	**2.96**
Unsatisfactory living conditions	41.7%	13.6%	**3.06**
Incomplete family /single-parent family	15.0%	12.1%	1.24
Somatic pathologies in mothers			
Sinusitis	24.2 %	7.6 %	**3.18**
Chronic constipation	37.5%	16.7%	1.25
Hypothyreosis	35.8%	15.2%	2.35
Atopic dermatitis	49.2%	13.3%	**3.69**
Rhinitis	25.0%	12.5%	2.0
Allergic skin lesions	28.3%	15.8%	1.79
Drug allergy	28.3%	15.0%	1.88
Food allergy	27.5%	9.2%	**2.98**
Pregnancy and labor complications			
Urogenital infection	34.2%	18.2%	**2.98**
Antibiotic therapy	56.7%)	24.2%	2.34
Estimated/expected preterm birth	9.2%	3.0%	**3.06**
Caesarean section on request	39.2%	27.3%	1.43
Syndromologic disorders in newborns /neonates			
Chronic hypoxia	36,7%	15,2%	1.43
Fetal hypotrophy	15,8%	6,1%	2.59
Prolonged jaundice	11,7%	4,5%	2.6

The relative intensity coefficient (K) to identified risk factors has been determined, that revealed statistically reliable prognostic factors in both mothers and infants.

In mothers: age <25 years (2.96), unsatisfactory living conditions (3.06), **sinusitis** (3.18), **hypothyreosis (2.35), atopic dermatitis** (3.69) **and food allergies** (2.98); in terms of pregnancy and labor pathology - **urogenital infection (2.98), taking antibiotics during pregnancy (2.34) and extimated preterm birth** (3.06).

In the postnatal period, potential risk factors were identified in the newborns of the main group, among which most common were: formula feeding (OR–1.13, 95% CI- 0.51-2.49), mixed feeding from birth (OR–1.24, 95% CI-0.51-2.49); among the syndromological disorders most attentive were chronic hypoxia (OR–3.24, 95% CI -1.42-7.54), and reliably common - fetal hypotrophy K-2.59 (OR– 2.91, 95% CI 0.87- 10.65) and prolonged jaundice K-2.6 (OR– 2.77, 95% CI 0.71-12.68), respectively.

Our results did not differ significantly from the results of other large-scale studies. Investigation of prognostic value of the risk factors for AD formation is promising, and allows development of effective preventive measures.

When evaluating the prognosis, it is important to take into account all impact factors, especially subsequently accompanying ones, the timely and effective identification of which will increase the accuracy of the prognosis.

One of the objectives of the research was to investigate the peculiarities of debut and clinical course of atopic dermatitis in young children. Based on our material, in most cases, atopic dermatitis developed under 6 months of age, among them in 25% - during the neonatal period, 46.7% - under 6 months of age, 22.5% - from 6 months to 1 year and 5.8% - 1 to 2 years of age, respectively. The study of exogenous provoking factors revealed that in most cases debut and exacerbation of the disease were associated with feeding (formula and mixed feeding) (88.1%), cow's milk (45.8%), care products (45.8%) and medication (25.0%).

In some cases, plant dust (6.8%), contact with animals (5.1%), pungent odors, paints (1.7%) and housendust (5.1%) were the causative factors. A statistically reliable factor was supplementation (OR 2.87, 95% CI - 1.00-8.47, P -0.049). Additional feeding turned out to be statistically reliable factor (OR 2.87, 95%CI - 1.00-8.47, P -0.049).

In the group of patients with atopic dermatitis, 40.0% of infants were on natural feeding, half of them - 6 months, and the other half - 1 year of age. Breastfeeding mothers did not follow any specific diet. 23.3% of infants were on formula feeding and 36.70% - mixed feeding, respectively. Adapted mixtures based on cow's milk formulas were mainly used. In the control group 47.0% of infants were on natural feeding, 21.2% - formula feeding and 31.8% - mixed feeding, respectively.

Table 17: **Causes of exacerbation of atopic dermatitis in children (n=120)**

Causes of exacerbation of atopic dermatitis	With family atopy (n=59)		Without family atopy (n=61)		OR	95%CI	P
	n	%	n	%			
Contact with animals	3	5.1%	3	4.9%	1.03	1.16-6.78	1.000
House dust	3	5.1%	0	0.0%	-	-	-
Medicines	15	25.4%	15	24.6%	1.06	0.42-2.58	1.000
Pungent smell, paints	1	1.7%	-	-	-	-	-
Care products/facilities	27	45.8%	32	52.5%	0.76	0.35-1.67	0.581
Plant dust	4	6.8%	-	-	-	-	-
Cow milk	27	45.8%	31	50.8%	0.81	0.37-1.78	0.710
Food	52	88.1%	44	72.1%	2.87	1.00-8.47	0.049

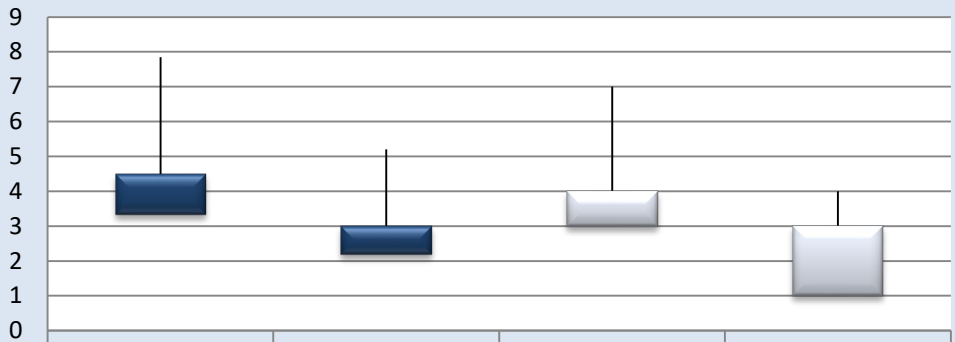
The above serves to prove that at natural feeding, excessive consumption of dairy products by mother during pregnancy or lactation plays an important role in the development of AD symptoms during the first 6 months of life.

According to the literature data, peripheral blood eosinophils, the content of which can be not only Th2 phenotype manifestation, but also a marker of disease course severity, are assigned a great importance in the development and realization of allergic inflammation at atopic diseases (Kita H, 2013).

Concentrations of eosinophils, IgE and vitamin D were determined in the peripheral blood of pregnant women.

The mean summary eosinophil count in pregnant women of the main group was 5.2 ± 2.6%, and in the control group - 3 ± 1.9%. The highest median concentration (7%) was observed in pregnant women with atopy.

Chart 3: **Eosinophil count quartiles in pregnant women (n=186)**



	Pregnant women with atopy	Pregnant women without atopy	Summary	Control group
I quartile	4.5	3	3	1
II quartile (median)	7	4	5	3
III quartile	7.85	5.2	7	4
Interquartile range	3.35	2.2	4	3

The eosinophil median concentration in pregnant women with atopy was elevated up to 7%. No quantitative increase in eosinophil count was observed in pregnant women without atopy, as well as in the control group. Other quartile indicators (first and third quartiles) ranged within the norm.

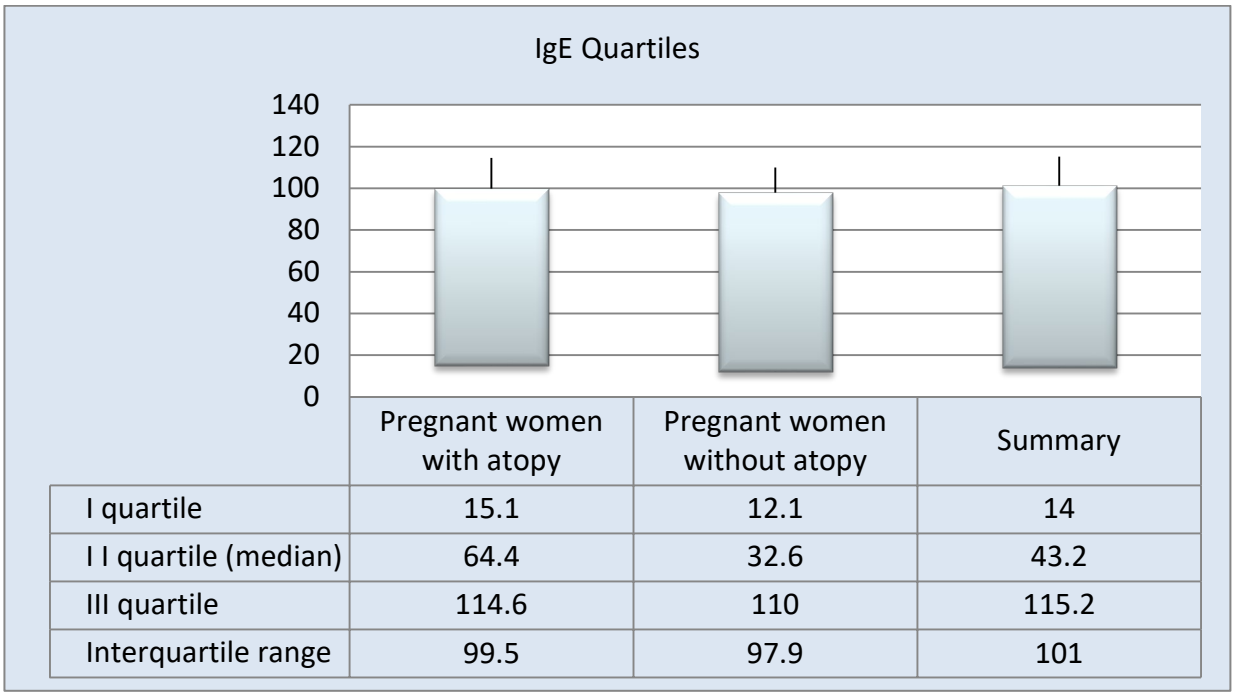
Measuring the blood eosinophil count in the newborns did not reveal a reliable differences from the data of the control group. On the 7th day of life, the mean eosinophil count was 3.6 ± 1.5 in the main group and 2.4 ± 1.4 - in the control group. A number of eosinophils did not change significantly at one month of age and equaled to 5.6 ± 2.2 in the main group and 3.4 ± 1.5 in the control group, respectively.

Based on our material a slight increase in eosinophils was observed in both pregnant women and infants with atopy, therefore the quantitative status of eosinophils could not be determined as a predictive marker of AD formation in young children. However, it should be noted that according to recent studies, timly measuring eosinophil count is of great importance to identify the risk group of developing AD. Therefore, additional studies are needed to assess and substantiate the eosinophils, as a screening method for atopy detection (Rossberg S., et al., 2016).

As it is known the basis for development of atopic dermatitis is a specific immune response of the organism to allergens often accompanied by IgE hyperproduction (Furue M., et al., 2017; Nissen SP., Et al, 2014).

Based on the above, within the frames of our study, IgE concentration in the peripheral blood of pregnant women was determined using the electrochemiluminescent method. The study was performed in 75 pregnant women of the main group. According to the obtained results: mean IgE concentration was 75.8±70.1 IU/ml, lower concentration - 1.5 IU/ml and higher - 391.6 IU/ml. The mean IgE concentration in pregnant women with atopy (44 mothers) was 75.8 ± 70.1 IU/ml, but at pregnancy without allergic reactions (31 mothers) was 72.9 ± 90.6 IU/ml. As for the group of pregnant women with atopy IgE level was elevated in 12 women, with a mean concentration - 163.5 ± 59.3 IU/ml, and in the group without atopy – in 8 mothers (OR – 1.69, CI – 0.57-5.01), respectively.

Chart 4: **IgE quartiles in the peripheral blood of pregnants (n=120)**



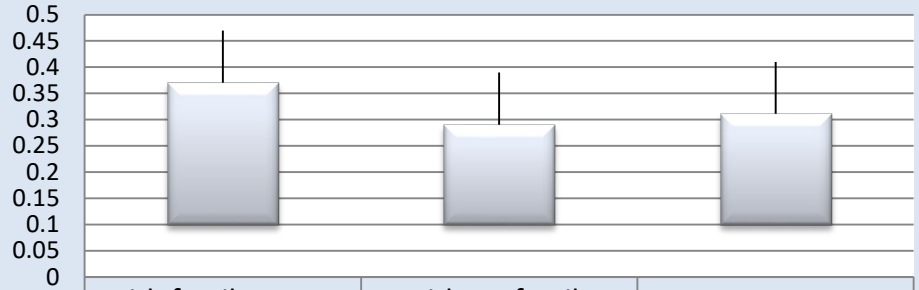
	Pregnant women with atopy	Pregnant women without atopy	Summary
I quartile	15.1	12.1	14
I I quartile (median)	64.4	32.6	43.2
III quartile	114.6	110	115.2
Interquartile range	99.5	97.9	101

According to our study materials, the mean IgE concentration in pregnants with atopy was 75.8 ± 70.1 IU / ml, and in cases of pregnancy without allergic reactions - 72.9 ± 90.6 IU / ml. IgE level was elevated in 26.7% of studied patients (178.6 ± 74.2 IU/ml). According to the quartiles, median IgE level in pregnant women with atopy were twice as high compared to pregnants without atopy.

In both groups non-homogenous character and interquartile range of IgE variables were revealed. According to the latest data, development of atopy can start in the prenatal period. To study the issue, investigations were carried out to assess the concentration of atopy markers in umbilical cord blood.

For this purpose, within the frames of our study, IgE concentration in the umbilical cord blood of newborns was detected. IgE concentration in umbilical cord blood was detected in 52 children (norm - <1.51 IU/ml). Deviation from the norm was not observed in any of the cases (Chart 6).

Chart 6: **IgE quartiles in umbilical cord blood of newborns (n=52)**



	with family atopy (n=21)	without family atopy (n=31)	Total (n=52)
I quartile	0.1	0.1	0.1
II quartile (median)	0.1	0.18	0.17
III quartile	0.47	0.39	0.41
Interquartile range	0.37	0.29	0.31

On our material, no deviation from the norm regarding to the total IgE level in the newborn umbilical cord blood, was revealed. The mean IgE concentration in children with hereditary allergy anamnesis was 0.31 ± 0.36 IU/ml, and in the group of children without hereditary atopy - 0.39 ± 0.62 IU/ml. Madian and quartile rates ranged within the norm. The median and quartile rates varied within the norm. Even when the IgE concentration in the peripheral blood of pregnant women was several times higher than the norm, IgE level in the umbilical cord blood of the newborn ranged within the norm. This proves the view that maternal IgE does not cross the fetoplacental barrier and has virtually no effect on circulating IgE levels in neonatal umbilical cord blood (De Amici M., et al., 2017). Taking into accout the fact that the observations were carried out in newborns who

subsequently developed atopic dermatitis, it should be assumed that at birth, determining IgE concentration in umbilical cord blood is a less important predictive factor and its prognostic value is low.

According to the studies performed, exogenous factors of the formation of atopic dermatitis are characterized by certain age-specific features. At an early age of life, most children develop atopic dermatitis as a result of food allergies (Alduraywish SA., 2017, Arima K1., et al 2018).

One of the objectives of the study was to investigate the characteristics of the clinical course of atopic dermatitis (AD) in young children. According to the data obtained, 31.7% of the children involved in the study had acute course of AD and 68.3% - subacute, recurrent course. Exacerbations were recorded every 3-4 months and were caused by trophoallergens, explosure to causally important allergens, or acute infectious diseases.

In terms of clinical presentation, there prevailed skin itching, dryness, the presence of papulovesicles and morphological elements over a large area.

At diffuse course, the rash was observed on face, body, extremities, hands, and feet, while at local course, the rash was revealed only on the face, or extensor surfaces of large and medium joints. According to the SCORAD index, a mild course of atopic dermatitis (16.5 ± 3.7 points) was seen in 17.5% of patients, a moderate course (30.7 ± 5.6 points) in 59.2%, and a severe course (48.6 ± 9.4 points) in 23.3%, respectively.

In children with hereditary atopy prevailed other presentations of atopy such as allergic conjunctivitis (40.03%) and drug allergy (35.0%), compared to atopic dermatitis. A high odds ratio was revealed at gastrointestinal (OR-3.66, 95% CI-1.35-10.15) and food allergies (OR-2.45, 95%CI-1.03-5.93).

Involvement of other organs and systems, other than skin, in the pathological process allows to consider atopic dermatitis (AD) as a systemic process. Immunologic, neuroendocrine and metabolic disorders, as well as dysfunction of the digestive system are presented as comorbid pathologies, in turn contributing to the chronic course of AD (Augustin M. Radtke M.A.a,., et al., 2015, Ćosićkić A., et al., 2017, Pope E., Drucker A., 2048).

According to our data, respiratory diseases (39.2%), chronic bronchitis (22.5%) and gastrointestinal disorders such as colic (72.5%), foaming (60.0%), constipation (50 %) were common in children

with atopic dermatitis (AD). Prevalence of constipation at hereditary atopy was considered statistically reliable (OR-2.41, 95%CI-1.08-5.38) (P<0.032).

The debut of atopic dermatitis in children is most often associated with food allergies. In 90% of infants affected with atopic dermatitis in the first year of life, food allergies are associated with cow's milk proteins. Cow's milk protein allergy often develops in young children's contingent being on formula or mixed feeding. CMPA was observed in 0.5-1.5% of infants being on natural feeding that was caused by fetal sensitization during pregnancy, as well as excessive consumption of dairy products by mothers during pregnancy and lactation.

In pediatric practice, the development and implementation of non-invasive methods for verifying cow's milk protein allergy in young children is an urgent task and, meanwhile, the basis of early prevention and therapy.

Within the study, CoMiSS assessment was performeed in all patients with atopic dermatitis (120 children) and 66 children in the control group.

The analysis of clinical symptoms characteristic for cow's milk protein allergy (CMPA) showed that duration of crying, frequency of foaming, changes in faeces, skin symptoms in children with atopic dermatitis exceeded the data obtained in the control group. The mean CoMiSS score in children with atopic dermatitis was equal to 9.72±4.81 points, and in the control group - 3.52±1.9 points, respectively. That is, in both groups the indicators varied within the norm, without significant differences. In addition, skin and respiratory symptoms prevailed at loaded allergy anamnesis. In children with atopic dermatitis, CoMiSS scores ≥ 12 were recorded in 25.8% of patients, with loaded allergy anamnesis – in 39% (15.06 ± 2.33 points), and without hereditary atopy - in 61% (14.20 ± 2.28), respectively.

Applying invasive diagnostic methods in young children is considered as a major problem in international pediatric practice. Therefore, nowadays, the development and implementation of non-invasive methods in pediatric clinical practice to verify cow's milk protein allergy is of great relevance. The CoMISS tool used in the study improved the abilities of early detection of cow's milk protein allergy, differentiation of pathological disorders as well as carrying out purposeful management. It is noteworthy to emphasize that the CoMiSS scale was created by a team of experts as a tool to raise awareness on cow's milk protein allergy (CMPA) in infants, based on a panel of general allergy symptoms. But there are less opportunities to differentiate IgE-mediated CMPA

from non-IgE-mediated CMPA and the symptoms associated with cow's milk intolerance (non-allergic type) (Yvan Vandenplas, Rajat Mukherjee et al, 2015).

Recent studies clearly revealed an association between vitamin D deficiency and allergic diseases (Vestita M., et al., 2015; Lee YW., Et al., 2019).

The authors have shown that vitamin D deficiency in pregnant women increases the risk of developing AD in children under one year of age. Systematic reviews and randomized studies conducted over the past decade proved the association of vitamin D deficiency at pregnancy with AD severe course in young children (Thorne-Lyman A, et al., 2012; Amestejani M.,et al., 2012; Oh J.-W., 2013; Borzutzky A, 2013; Vestita M1, et al, 2015; Chih-Yung Chiu etal., 2015; Mirzakhani H., et al., 2016).

Therefore, one of the important objectives of the study was to assess the impact of vitamin D status during pregnancy on the formation of atopic dermatitis in children under 2 years of age. For this purpose, the 25-hydroxyvitamin (25[OH]D) concentration in the peripheral blood of pregnant women has been measured. Mothers involved in both the main and control groups did not take vitamin D and medications containing vitamin D before and during pregnancy.

Table : **Norm, insufficiency and deficiency of 25(OH)D in pregnant women (n=186)**

25(OH)D ng/ml	Main group (n=120)	Control group (n=66)	OR	95%CI	P
Norm (>30)					
n (%)	12 (10%)	20 (30.3%)	0.26	0.11 -0.60	0.001
mean ± SD	33.0 ± 2.7	35.7 ± 8.0			
Insufficiency (21-29)					
n (%)	34 (28.3%)	33 (50%)	0.39	0.20-0.77	0.006
mean ± SD	24.9 ± 2.6	24.1 ± 2.1			
Deficiency (<20)					
n (%)	74 (61.7%)	13 (19.7%)	6.56	3.07- 14.23	0.000
mean ± SD	13.4 ± 4.7	17.4 ± 2.4			

A normal supply of vitamin D was observed in 10% of mothers of children with atopic dermatitis, moderate - 33.0 ± 2.7 ng/ml, insufficiency - 28.3% (24.9 ± 2.6 ng /ml), and deficiency - 61.7% (13.4 ± 4.7 ng/ml). As for the control group, normal supply of vitamin D was in 30.3% (35.7 ± 8.0 ng/ml), insufficiency - 50% (24.1 ± 2.1 ng/ml), and deficiency - 19, 7% (17.4 ± 2.4 ng/ml), respectively. Compared to the control group, 25(OH)D deficiency was reliably more common among the mothers of children with atopic dermatitis (OR -6.56, 95% CI 3.07- 14.23, P-0.000).

During the study, clinical data and anamnesis of 74 pregnant women (61.7%) with vitamin D deficiency were analyzed. Their average age was 28.9±6.0 years. 40.5% of pregnant women had secondary education, in most cases (83.8%) they belonged to the middle- or low income families, tobacco consumtion was observed in 12.2%.

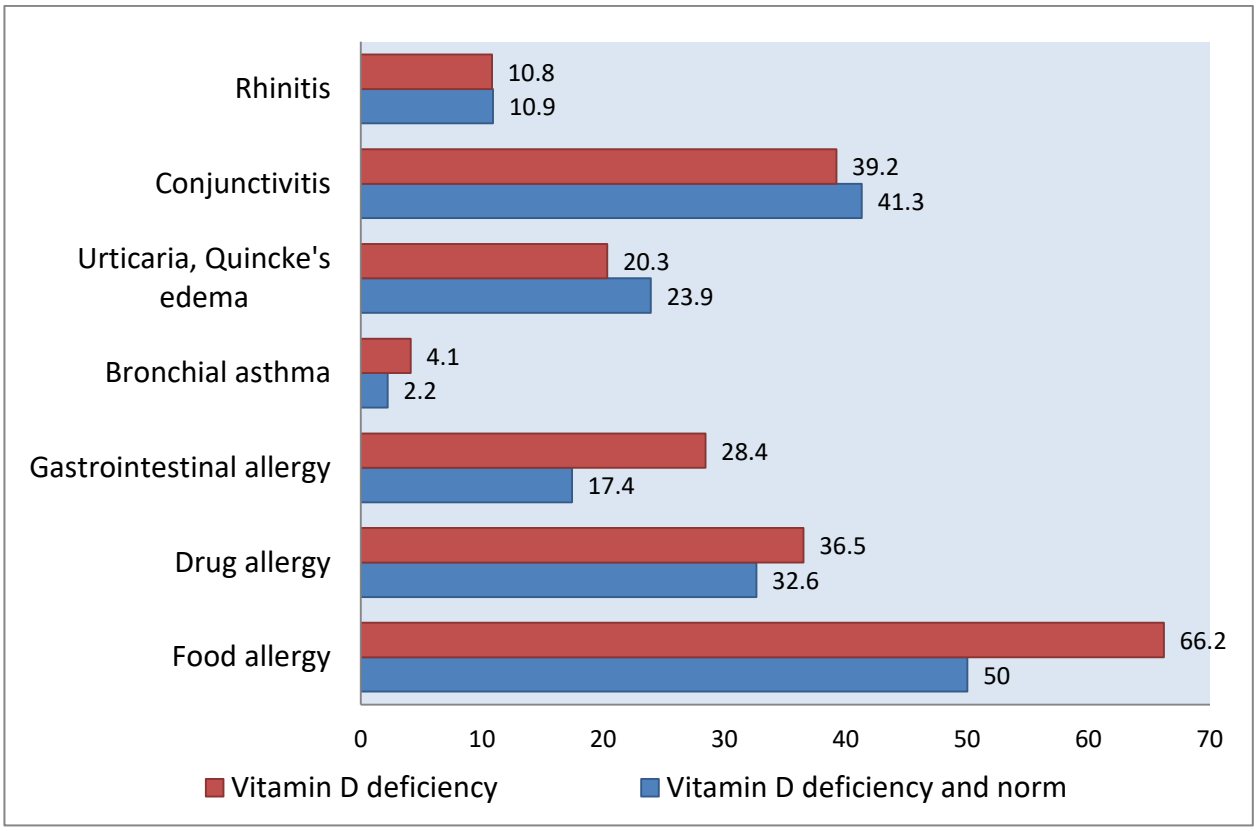
Among the concomitant chronic diseases prevailed: digestive system (enterocolitis -36.5%, gastritis -24.3%, and cholecystitis 14.9%), respiratory system and ENT (ear-nose-throat) pathologies (frequent respiratory infections - 25.7%, bronchitis – 25.7%, chronic tonsillitis – 13.5%, and sinusitis – 23%). Hypothyrosis was presented with a high incidence ratio (35.1%). Among the pregnancy complications prevailed anemia (81.1%), estimated preterm birth - 44.6%, overweight (55.4%) and antibiotic consumption (56.8%). In 40.5% of pregnants, caesarean delivery was performed.

In children, those, whose mothers have vitamin D deficiency during pregnancy, 70.3% developed atopic dermatitis under 6 months of age, 24.3% of them – at neonatal period and 45.9% - under 6 months of age. In 21.6% of cases the first signs of AD occured at 6 months to one year of age, and in 8.1% - after one year of age. In most cases (82.4%) disease debut was associated with food, mixed or formula feeding at an early age of life, cow's milk protein allergy, early exposure to additional feeding from 4-6 months of age, care products. In terms of AD clinical symptoms, skin itching (48.6%), dryness (85.1%), location of morphological elements on the body (79.7%) and papulovesicles (55.4%) were more common. An acute course of AD was revealed in 28.4% of children and a subacute, recurrent course followed by periodic remissions – in 45.6%. According to the SCORAD index, 24.3% (18 children) developed a mild form of the disease, 58.1% (43 children) – moderate course, and 17.6% (13 children) – severe course, respectively. Based on the CoMISS scores, cow's milk allergy was revealed in 33.8% (25 children). As for other allergic reactions, food

allergy (66.2%), gastrointestinal disorders (28.4%), and drug allergy (36.5%) predominated at vitamin D deficiency.

In case of vitamin D deficiency in pregnant women, children with atopic dermatitis developed a wide range of other manifestations of atopia, the incidence rate of which was compared to the data of 46 patients whose mothers showed vitamin D varing within the norm or deficiency (Chart 9).

Chart 9: **Allergic manifestations in children with atopic dermatitis (n=120)**



The study results showed that among the mothers of children with atopic dermatitis, vitamin D deficiency was observed in the majority of them (61.7%), vitamin D insufficiency – in 28.3%, and normal supply – in 10%, respectively; median 25(OH)D level -18.9 (IQR - 11.2) ng/ml was much lower compared to the control group - 24.2 (IQR - 9.6) ng /ml.

In pregnants with 25(OH) D deficiency, atopic dermatitis mostly developed in young children under 6 months of age; according to the SCORAD index, moderate and persistent course of the disease prevailed in both groups with and without hereditary atopy. According to the study results, the presence of vitamin D deficiency in pregnant women played a certain role in the formation of atopic dermatitis in young children.

Therefore, based on our data, vitamin D deficiency in mothers might serve as reliable predictor for increased risk of developing AD in young children population. According to the obtained results, vitamin D deficiency was common for the entire study population, while the pronounced vitamin D deficiency was significantly higher among mothers of children with atopic dermatitis.

The study results highlighted that the combination of atopic hereditary load and vitamin D deficiency played an important role in AD formation at an early age of life, allowing to consider these two factors as predictors of high prognostic value.

The study results indicated to the importance of medico-biological and socio-hygienic factors in the formation of atopic dermatitis, necessitating identification of the risk groups and serving as the basis for the development of appropriate preventive measures.

The risk factors could affect a child from the moment of conception. It should be emphasized that factors ranking changes according to the ages of child development, therefore, it is necessary to take into account the age evolution of risk factors and their subsequent monitoring..

Conclusions

1. According to the results of the study, the importance of socio-hygienic and medical factors in the formation of atopic dermatitis in children under 2 years of age was revealed. Statistically reliable predictive value was revealed for the following factors:

- **Demographic:** Maternal age <25 years (OR – 3.54. K – 2.96), incomplete family (OR – 1.28. K – 3.27), unsatisfactory living conditions (OR – 1.07, K-3 .06);
- **Maternal medical factors:** estimated preterm delivery (OR-3.22, K-3.06), taking antibiotics during pregnancy (OR-4.08, K2.34), urogenital infections (OR-2.33, K-2.98);
- **Maternal hereditary atopic predisposition:** atopic dermatitis (OR-6.28, K-3.69), allergic rhinitis OR-2.52, conjunctivitis OR-2.03, food allergy OR-3.02, drug allergy OR-2.14;
- **Maternal hereditary atopic predisposition:** atopic dermatitis (OR-6.28, K-3.69), allergic rhinitis OR-2.52, conjunctivitis OR-2.03, food allergy OR-3.02, drug allergy OR-2.14;
- **Among the risk factors of the postnatal period in children of the main group were identified:** formula feeding under 6 months of age (OR – 1.13); Mixed feeding from birth (OR – 1.24), fetal hypotrophy (OR – 2.91, K-2.59), prolonged jaundice (OR – 2.77, K- 2.6).

2. Vitamin D deficiency in pregnant women is reliably correlated with early debut of atopic dermatitis at 6 months of age (p-0.008), the high prevalence of cow's milk allergy (p-0.006), course of moderate persistence (p-0.037), and presence of comorbid diseases (p-0.05).
3. **The combination of atopic heredity load and vitamin D deficiency** played a significant role in terms of AD formation at an early age of life, allowing these two factors to be considered as predictors of high prognostic value.
4. A reliable correlation between early debut of atopic dermatitis (up to 6 months) and cow's milk has been revealed. Verification of cow's milk protein allergy was performed using a non-invasive CoMISS tool that improved the capabilities of early detection of cow's milk protein allergy, differentiation of pathological disorders, and targeted management among the infant population.

Practical Recommendations

1. Pregnant women with allergic pathology should be tested for vitamin D levels to detect high-risk neonates and provide early prevention of allergies.
2. Prevalence of vitamin D insufficiency and deficiency in pregnant women posed a necessity to correct daily intake of vitamin D (including foods naturally rich in vitamin D) at pregravidary stage.
3. For quantitative assessment of dynamics in the context of early diagnosis of cow's milk protein allergy and therapeutic intervention, the use of a non-invasive and simple CoMiSS tool would be recommended.

Preventive Measures for Atopic Dermatitis in the young children population

Nowadays, most scientific studies and analytical findings suggested by expert-specialists are mainly focused on the treatment rather than prevention of atopic dermatitis, which makes it more important to study the prognostic predictive markers of atopic dermatitis. Each study conducted in this direction is of great importance in terms of preventing the development of atopic dermatitis in the young children population.

Development of effective primary prevention programs requires identification of target population among young children and neonates and assessment of the effectiveness of scientific evidence-based

preventive measures. The possible spectrum of primary prevention measures focued on the study results (taking into account manageable and unmanageable risk factors) relies on the following key principles:

- Proper allergy management in pregnancy;
- Determination and correction of vitamin D levels;
- Timely identification and appropriate monitoring of allergies in neonates with symptoms or at risk of atopy in the neonatal period;
- Parental education on allergology;
- Targeted, subsequent implementation of developed preventive measures and monitoring of the effectiveness.

Publications:

1. M. Petriashvili. Pre- and Perinatal Predictors for the formation of atopic dermatitis in young children - Academician Nino Javakhishvili Scientific-Practical Journal *"Experimental and Clinical Medicine" -N4 2019; ISSN 1512-0392; 33: 60- 66*
2. Petriashvili M., Jorjoliani L.- The Pecularities of Clinical Course of Atopic Deramtitis and the Comorbid Conditions is Early Infancy - *Georgian Medical News No 1 (298) 2020 page: 53-57*
3. Mariam Petriashvili. Impact of Maternal Vitamin D Status on the Formation of Atopic Dermatitis in Young Children. - Global Pediatric Health Volume 8: 1–7 ©. First published in June 6, 2021. Section: Maternal, Newborn, and Child Morbidity and Mortality - Original Research Article