http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v13i03.08

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Complications of respiratory function in prematurely born children

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1 Introduction

A premature newborn baby is any newborn born before the 37th gestation week. According to their gestational age at birth, premature newborn babies are divided into extreme premature babies (< 28 week), very early premature babies (28-32 week), early premature babes (32-36 week) and late premature babies (> 36 week). Premature birth leads to disruption and alterations in the structure and function of the respiratory system as well as of the pulmonary and systemic immunity. The lung parenchyma is immature at birth because alveolarization begins at 36-37 week and continues until the eighth year of life (Figure 1).[3] Compromised development of pulmonary acini resulting in the creation of larger and fewer alveoli with thinned alveolar-capillary membranes and altered capillary vascularization directly leads to reduced respiratory ventilation and perfusion.[36] This leaves repercussions not only in this period of life but also further on as a manifested reduced lung capacity for gas exchange.[37]

Despite initial assumptions that pulmonary hypoplasia and small immature airways are a predisposing factor, multifactorial influence is a determining factor in the development of chronic obstructive disease and asthma. Numerous factors from the environment (cigarette smoke, air pollution), genetic predisposition to atopy or asthma, susceptibility to severe respiratory viral infections (RSV, HRV), alterations in the microbiome and in the immature immune system each contribute in their own way to the development of asthma in premature infants. Understanding why these preterm infants are at higher risk of developing asthma is crucial for further prevention, early detection and possibly delaying the onset of asthma, all in order to reduce the increased morbidity and mortality in this group of patients.[1]

On the other hand, improved intensive neonatal care over recent years has contributed to increased survival even of extremely premature newborns in whom the severity of the initial lung affectedness is more serious and of a larger scale, which directly leads to an increase in the number of children with BPD and chronic respiratory problems further in their lives.[2]

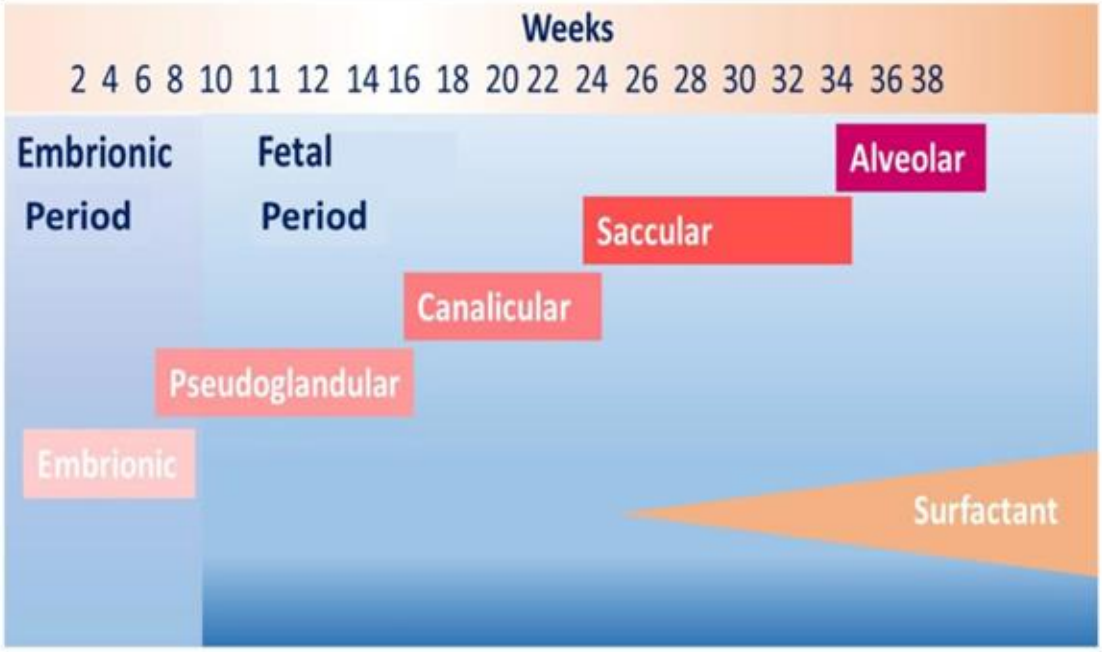

Figure 1: Embryonic and fetal stages of development of the respiratory trunk. In premature babies, especially in those born before week 30. the last stage of development of the terminal respiratory structures is compromised.

The severity and the clinical manifestation of chronic respiratory disease will depend on the degree of prematurity, the severity of initial respiratory affectedness, and the duration of mechanical ventilation and oxygen therapy required (Figure 2).[2]

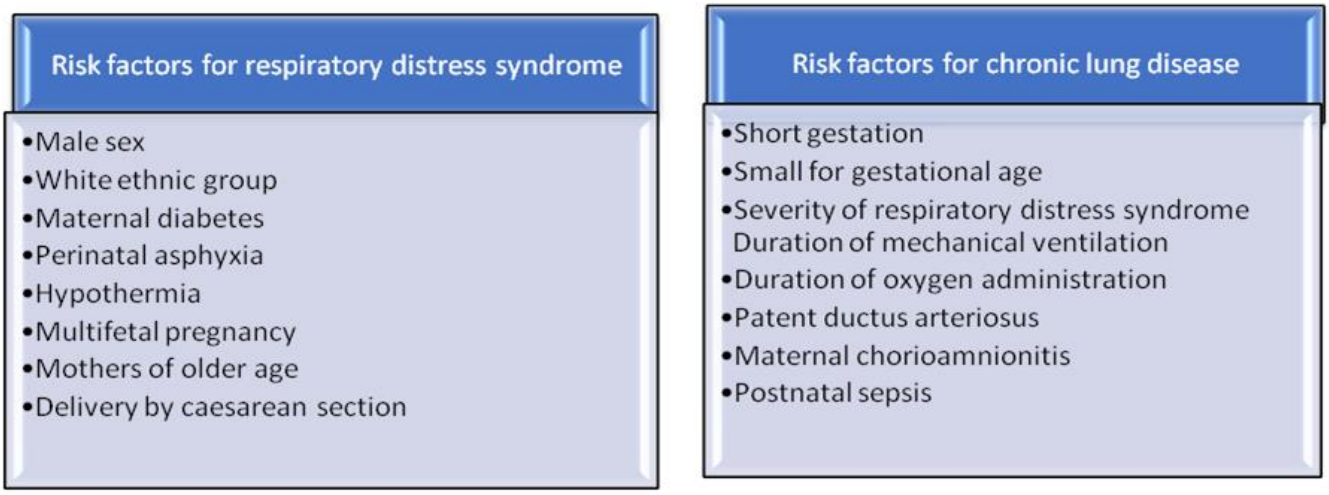

Figure 2 Risk factors for RDS and chronic lung diseases.

2 Do premature infants have a higher prevalence of developing asthma?

It is already well established that prematurity itself is a risk factor for developing asthma. It is partly due to structural immaturity, which leads to an increased risk for developing chronic lung diseases, primarily bronchopulmonary dysplasia, as well as reduced and impaired lung function.

In a national cohort study in Sweden that followed about 4,000,000 people from birth to 46 years of age, it was concluded that premature birth increases the risk of developing asthma in all age groups (< 10 years, 10-17 years, 18-46 years) [4]. In addition, the risk of developing asthma increases as the gestational age at birth is lower, which once again emphasizes the link between prematurity

and the development of asthma. In another systematic review of 19 studies (14 cohort, four cross-sectional and one case control study) it was concluded that children born prematurely have a 36% higher risk of developing asthma compared to children born at term. [5] School-aged children who were born prematurely also have a higher incidence of developing asthma than children born at term. [6-7]

3 The immune system in premature babies and its correlation with the development of asthma

Allergic sensitization is known to be responsible for the development of asthma in the majority of cases. It is due to an intense Th2 cell response to allergic triggers that leads to hyper IgE production and accompanying DC - mediated antigen presentation. Paradoxically in premature children the prevalence of atopy and allergic sensitization was lower compared to children born at term, which supports the fact that there is still a non-allergic mechanism for the development of asthma in these children. Individuals with comorbidities such as atopic dermatitis, food allergy, allergic rhinitis are certainly at a higher risk of developing asthma. [8]

In a study that investigated the concentrations of specific IgE antibodies to the most common nutritional and inhalant allergens, it was concluded that adults who were born prematurely had a 29% lower risk of sensitization compared to those born at term. [8] And in another Swedish cohort study that included 1,000,000 children, they came to the conclusion that children born before week 32 have reduced sensitization to nutritional allergens as well as a lower incidence of atopy (estimated through CPT) and specific IgE sensitization. Also, the prevalence of allergic rhinitis was reduced in young adults who were born prematurely. In individuals who were born extremely prematurely (23-28 week), the need for nasal CS was 30% lower, while the need for therapy with nasal CS and oral antihistamines was reduced by 55% compared to children born at term. And the prevalence of atopic dermatitis was also lower in children born before week 29 compared to children born at term.

And while it is not yet clear what exactly leads to this reduced susceptibility to allergic sensitization in premature infants, one of the main theories is that it is due to early exposure to the microbiome that triggers a shift in immune response from Th 2 towards a Th 1 cell response. [8] In premature newborns, the microbiological diversity is reduced compared to children born at term, due to which their pro-inflammatory response to pathogens is weaker and is associated with a Th 2 cell response. Another explanation is that this is due to the still intrauterine Th 2 cell-mediated immune reactivity that has a protective role on the fetus from atopy.

We can conclude that these paradoxical differences in allergic sensitization and asthma in children who were born prematurely speak of a special asthma endotype that may be triggered by numerous factors (smaller airways, their immune reactivity to viral pathogens, their unique microbiome, etc.).

4 The microbiome in premature newborn children

The great diversity of the intestinal microflora in early life is particularly important for the development of the immune system. [9] In children born prematurely, this diversity is reduced compared to children born at term, which is one of the reasons for the increased risk of developing asthma. [10] In addition, numerous factors can lead to microbial dysbiosis such as the way of birth [11] - caesarean section (reduced number of colonies of good bacteria in GIS - *Bacteroides*, *Bifidobacteria* , and *Lactobacilli*) [12] , AMF diet (reduction of *Bifidobacterium*) [13] , and the use of antibiotic therapy in the first year of life which is associated with a 24% increase in the incidence of asthma [14] , as it leads to a reduction in *Faecalibacterium strains* . [15] Because of all this, the use of antibiotics, which are unavoidable since

birth in prematurely born children, further increases the risk of developing asthma. [16] The intestinal production of butyrate by *Bacteroides* , *Roseburia* , and *Coprococcus* has an anti-inflammatory effect and a protective role against the development of asthma [17] . On the other hand, the increasing number of strains of *Candida* and *Rhodotorula* and the reduced number of strains of *Bifidobacteria*, *Akkermansia* and *Faecalibacterium* at 3 months of age are associated with the possible development of asthma as early as at 2 years of age. [18] The presence of such an imbalance of the microbiome is associated with CD4 T -cell dysfunction promoting the development of atopy in individuals. Intestinal bacteria that predominate in premature newborns are the asthma-promoting bacterial flora - *Staphylococcus*, *Klebsiella*, *Enterococcus* or *Escherichia* [13] , and it is particularly important to emphasize that specific IgE to Staph. aureus are associated with the development of asthma in the general population. [19]

Colonization of the respiratory tract in infants with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* on the other hand, is associated with persistent wheezing, eosinophilia and increased IgE secretion, which also increase the risk of developing asthma in the first 5 years of life [20].

It is characteristic of both premature infants and adults with asthma that they all have an increased number of Proteobacteria in the airways which is directly related to bronchial hyperreactivity [23] (promotes increased Th17 cell inflammation, increased neutrophil activation and inflammation of the respiratory tract).

From all this we can conclude that there is solid evidence that intestinal and respiratory microbiome in premature newborns is important and has a role to play in prevention of asthma, while the simultaneous reduction of the number of colonies of *Bacteroides*, *Bifidobacteria* and *Lactobacilli* may predispose to an increased risk of developing asthma.

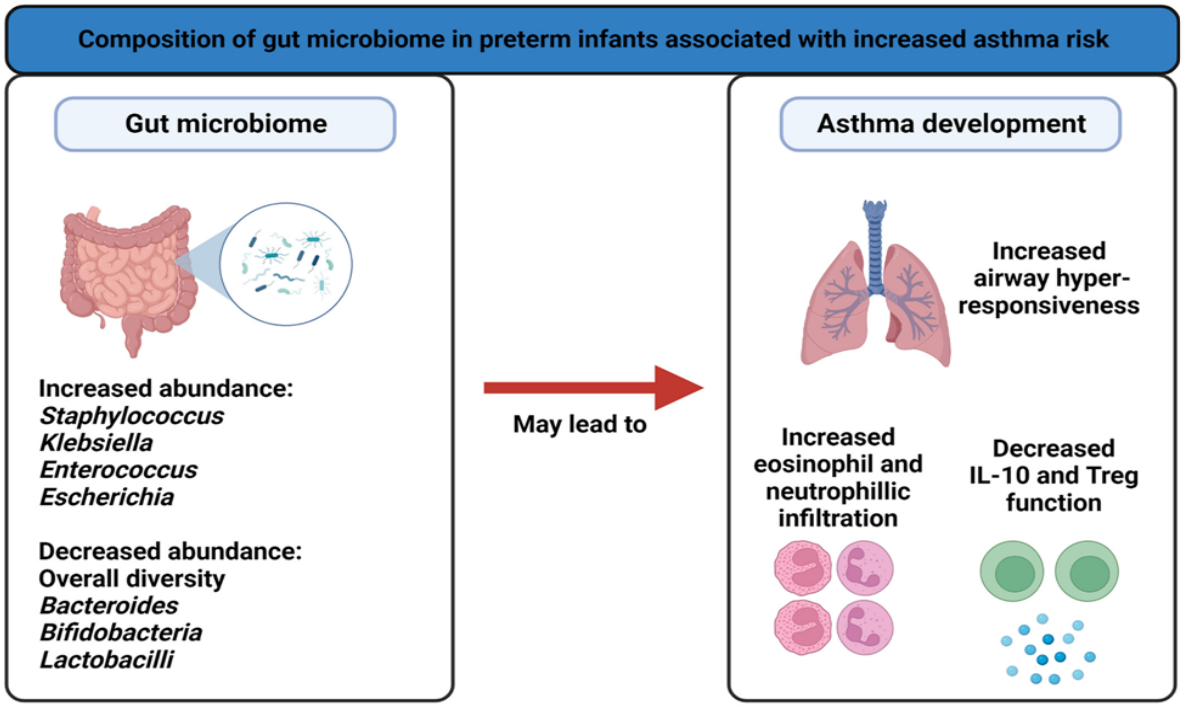

Figure 3 The effect of the microbiome on the development of asthma in premature infants. Reduced colonies of protective bacteria and increased numbers of asthma-promoting bacterial flora lead to increased adhesion of eosinophils and neutrophils, bronchial hyperreactivity and reduced production of IL-10

5 The impact of respiratory viral infections in prematurely born children and their association with chronic respiratory diseases

It is well known that RSV is one of the most common respiratory viral pathogens in children up to two years of age, which is responsible for a large number of hospitalizations in both pulmonary and intensive care units, especially in premature children whose clinical course and complications are more serious and have long-lasting character. [24] Since the early development of the respiratory tract in the infant period is a critical period, especially for prematurely born children, severe RSV infections result in long-term respiratory tract sequelae and thus an increased susceptibility to develop recurrent wheezing in early childhood.

HRV is another important viral pathogen that is of a common etiology of bronchiolitis and in recent years there have been extensive studies of its association with the development and exacerbation of asthma. Again, prematurity is a risk factor for more severe infections with this virus which, compared to RSV, is associated with a higher incidence of chronic respiratory complications, wheezing and the development of asthma in children up to 6 years of age. [25,26]

In one study, subject of analysis was the association of RSV/HRV-A present and H.influenzae in the nasopharyngeal secretions of infants. It was concluded that they lead to an increased Th17 cell response and decreased IFN-α production, thus promoting a pro-inflammatory airway response and the development of asthma.[76] Additionally, infants with RSV bronchiolitis originating from parents with asthma, IgE - mediated allergic sensitization, HRV co-infection, presence of *S. pneumoniae/M. catarrhalis* in the nasopharynx and increased levels of IFN-α/IFN-γ response have the highest risk of developing asthma until they turn 5 years of age.[22]

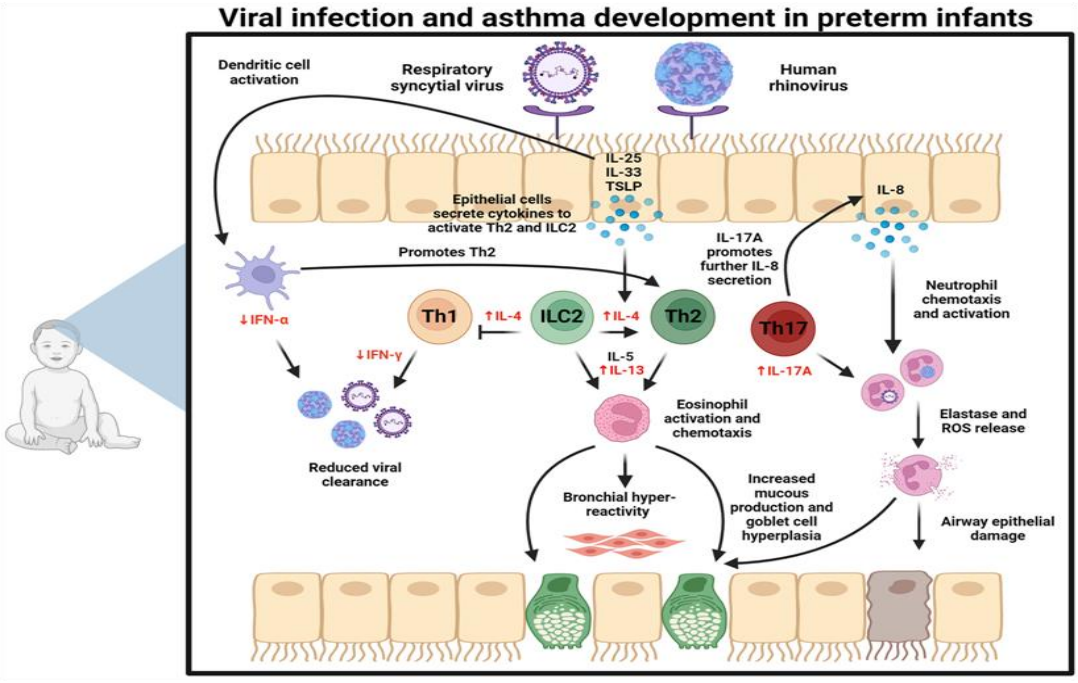

Figure 4 Immune response to RSV and HRV and its association with asthma pathogenesis

The factors that are present only in premature babies, and participate in the exacerbation of the immune response to pathogens, are marked in red. Epithelial cells secrete IL-8,25,33 and TSLP which activates dendritic cells and promotes a Th2 cell response and increased secretion of IFN-α which in premature infants reduces the clearance of viral pathogens. IL-25, IL-33 and TSLP activate both ILC2 and Th2 cells and IL-4 is produced, which in turn promotes a Th2 allergic

inflammatory response by inhibiting Th1 and IFN-γ production (which are reduced in premature infants), further reducing the clearance of viral pathogens that prolong the course of the disease. In addition, these cells secrete IL-5 and IL-13 which in turn promote chemotaxis and activation of eosinophils leading to bronchial hyper-reactivity, mucus hyper-secretion and hyperplasia of the respiratory epithelium. IL-17A (which is increased in premature infants) from Th17 cells further induces secretion of IL-8 from the respiratory epithelium which increases neutrophil chemotaxis and activation and leads to epithelial damage by released elastase.

6 Complications of respiratory function after the first year

These children in early childhood, especially in the first 2 years and preschool age, suffer from recurrent wheezing episodes more often compared to children born in term. [30] Moreover, in the school age and the period of adolescence, they also have a tendency towards more frequent but also more severe respiratory problems. [31]

7 Respiratory function in adulthood

There are several studies that have investigated the correlation between premature birth and the development of chronic respiratory diseases in adulthood. A prospective cohort study, analyzied 60 adults aged 21 years who were born prematurely and compared them to full-term adults of the same age. The prematurely born had more frequent respiratory complaints. [32] Baraldi et al. [33] came to the conclusion that those born prematurely between the ages of 18 and 20 had more frequent respiratory issues, a higher prevalence of wheezing episodes and developed pneumonia that required longer-term treatment. [34] In a third study, Gough et al. [35] concluded that adults who had BPD had twice the prevalence of wheezing and three times the prevalence of developing asthma.

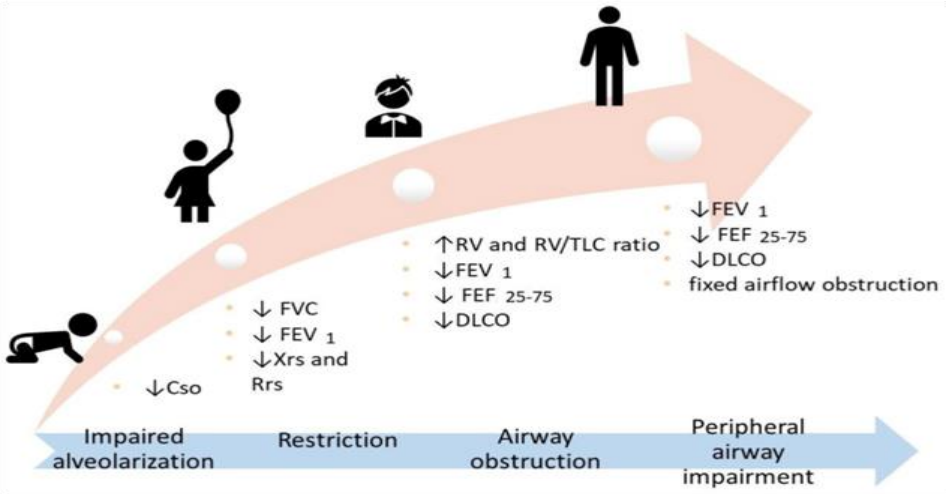

Figure 5 Respiratory symptoms at different stages of life.

Cso: Respiratory System Compliance; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in the 1st second; Xrs: Respiratory Reactance; Rrs: Respiratory Resistance; FEF25-75: Forced Expiratory Flow 25–75%; DLCO: Diffusion Lung Carbon Monoxide

8 Can development of asthma in prematurely born children be prevented and how?

Prevention should start as early as possible, i.e. even prenatally during pregnancy. There are numerous studies and evidence on the importance and role of Vitamin D for respiratory health. Since concentrations of Vitamin D are mainly transferred to the fetus in the third trimester, a large number of premature newborns are born with a Vitamin D deficiency. [27] The Vitamin D

Antenatal Asthma Reduction Trial (VDAART) conducted a study during which mothers who had atopy and mothers whose partner had atopy were supplemented with 4000 IE Vit.D per day during pregnancy. The study concluded that there was no effect observed in relation to recurrent wheezing or the development of asthma in children up to 6 years of age with prenatal supplementation with Vit. D, so this type of prevention is not justified. [28] Probiotics have also been the target of numerous analyzes and studies to see if they really have an effect in reducing allergic diseases in infants. In a study of premature children born before week 32, who received daily postnatal supplementation with a formulation comprising *Bifidobacterium infantis*, *Streptococcus thermophilus*, and *Bifidobacterium lactis*, showed that in the first 2 years of life there is no difference in the incidence of developing allergic diseases compared to the control placebo group (eczema, atopic dermatitis, nutritional allergy, wheezing). [29]

Follow-up and regular check-ups later in life would be crucial. That's why we need a suitable algorithm.

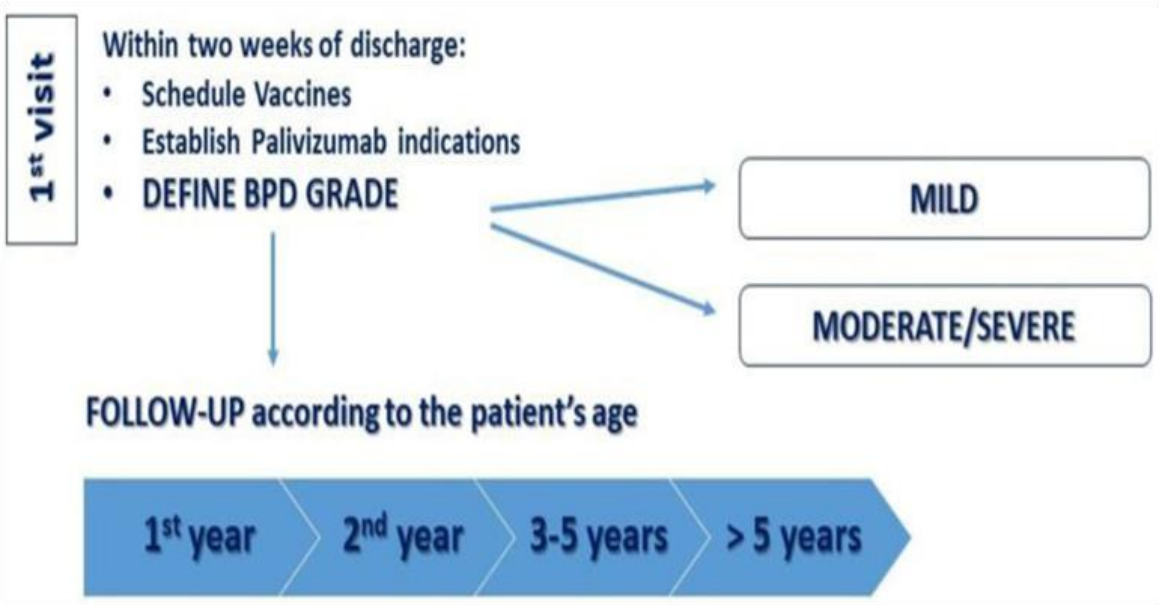

Figure 6 At the first visit to the pediatrician, it is especially important to determine the severity of respiratory function complications, as well as to give instructions for further monitoring and vaccination of these children.

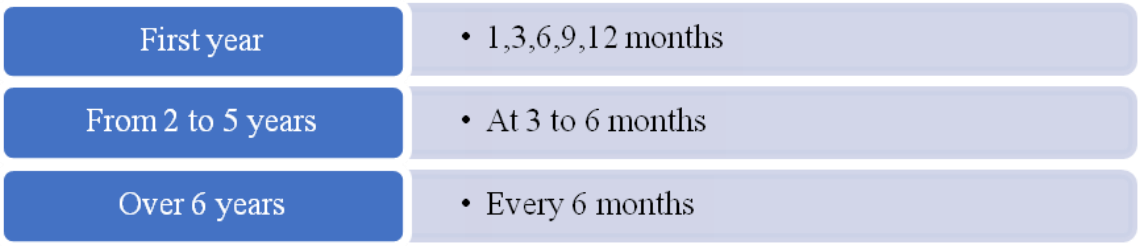

Figure 7 Algorithm for monitoring respiratory function in prematurely born children

In the first years of life, clinical observation by the pediatrician is of key importance because we do not have the possibility to perform functional lung tests. They can be carried out in children older than 6 years of age. It is also very important that these children, in addition to the vaccines included in the regular immunization calendar, in the early infancy period also receive a vaccine for RSV and later also for Influenza, which would reduce further complications of the disease.

9 Conclusion

Children born prematurely are at increased risk of developing asthma. There are numerous factors that contribute to its development, first of all the immature anatomical and functional respiratory system, then the immature immune system that leads to susceptibility to severe respiratory viral infections and the altered and reduced intestinal and respiratory microbiome. Additional risk factors are genetic predisposition to atopy or asthma and environmental factors.

Paradoxically, children born prematurely have a lower tendency to develop atopy, which supports the fact that other mechanisms and pathogenesis participate in the increased prevalence of asthma in these children. Premature birth itself and the structural and functional deficiencies of the immature respiratory tract probably lead to a "special asthma endotype" both in pediatric and adult pulmonology. Hence, regular monitoring and control of respiratory function of such children would lead to a reduction of more serious respiratory ailments and would also reduce the need for hospital treatment, the development of chronic respiratory diseases in adulthood, and thus would improve the quality of life and reduce treatment costs for the health system.

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