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# Preterm Birth and Inflammation

*Melinda Matyas*

## Abstract

Half of all preterm births are caused or triggered by an inflammation at fetal-maternal interface. The sustained inflammation that preterm neonates are exposed is generated by maternal chorioamnionitis, premature rupture of membranes. This inflammation will facilitate the preterm labor, but also plays an important role in development of disease like: bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage and periventricular leukomalacia. Preterm neonates have immature immune system. The fragile co-regulation between immune defense mechanisms and immunosuppression (tolerance) is often disturbed at this category of patients. They are at high risk of sepsis due to this imbalance between the defense and suppression mechanisms but also several injuries can contribute to the onset or perpetuation of sustained inflammation. They experience altered antigen exposure in contact with hospital-specific germs, artificial devices, drugs, nutritional antigens, and hypoxia or hyperoxia. This is more significant at extremely preterm infants less than 28 weeks of gestation as they have not developed adaptation processes to tolerate maternal and self-antigens.

**Keywords:** preterm birth, inflammation, chorioamnionitis, premature rupture of membranes

## 1. Introduction

Preterm birth defined as birth before 37 weeks of gestation will have impact on newborns outcome not just immediately but long term. Around 70% of preterm births are spontaneous and are produced by premature rupture of membranes and preterm labor. In 50% of cases the preterm birth associates different form of inflammation, chorioamnionitis and maternal infection. The aim of this chapter is to present the impact of maternal inflammation and/or infection on their preterm health.

## 2. Preterm birth and preterm neonate particularities

Preterm birth according to the World Health Organization (WHO) is defined as birth before 37 completed weeks of gestation. In 2010, 14.9 million babies were born preterm, accounting for 11.1% of all births worldwide. In European countries, preterm birth represents approximately 5% of all births, while in certain African countries this ratio is around 18% [1]. Preterm birth represent the leading cause of childhood mortality in children under 5 years of age [2]. The high economic burden is generated by the neonatal intensive care, often followed by ongoing health care needs and a significant emotional impact experienced by families [3].

Preterm birth may occur spontaneously or based on a medical indication. About one third of all preterm births have a medical indication, determined by maternal or fetal risk factors, which are higher than the benefits generated by the continuation of pregnancy and include preeclampsia or diabetes mellitus [4]. Approximately 70% of preterm births are spontaneous, caused by premature rupture of membranes, preterm labor [4]. Preterm labor in about half of the cases is associated with inflammatory syndrome, with sustained inflammation. Preterm labor has a complex etiology; it can be induced by many factors: infection or inflammation, uteroplacental hemorrhage, placental ischemia, uterine overdistension or stress [5]. Maternal risk factors with a role in triggering preterm labor are numerous: extreme ages of the mother, high body mass index (BMI), multiple gestation, assisted reproductive technologies, history of preterm birth, and low socioeconomic status [4]. Race is also an important risk factor; African-Americans are at higher risk of preterm birth than other ethnic groups [5].

Preterm birth is an important cause of morbidity and mortality in the newborn. The pathologies induced by preterm birth are both acute and chronic. Chronic diseases may have a long-term impact on the health of preterm neonates, affecting their neurodevelopmental outcome in variable degrees.

The main acute disorders associated with preterm birth are: respiratory distress, cerebral hemorrhage, periventricular leukomalacia, necrotizing enterocolitis (NEC), while the most frequent chronic diseases with an impact on the development and long-term prognosis of newborns are: bronchopulmonary dysplasia, retinopathy of prematurity, periventricular leukomalacia, and abnormal neurological development.

Prematurely born adults will have an increased risk of hypertension at adult age, diabetes mellitus and obesity [4].

The evolution of preterm infants is dependent on sex. Some studies showed that at the age of 2 years, chronic respiratory and neurological complications were more frequent among male compared to female preterm newborns [6].

Cytokines play an important role in initiating and regulating labor. Labor occurs under pro-inflammatory conditions with the participation of cytokines. In this pro-inflammatory environment, a three-step process takes place, which is characterized by uterine contractility, cervical ripening and membrane activation/rupture [7].

There will be a considerable release of interleukin IL-1 $\beta$ , IL-6 and IL-8, and tumor necrosis factor alpha (TNF- $\alpha$ ). These pro-inflammatory substances will be released by stromal cells as well as monocytes and neutrophils that invade the myometrium and the cervix during labor. IL-1 $\beta$  and TNF- $\alpha$  will cause myometrial contraction through calcium influx in myometrial smooth muscle cells. Myometrial contraction is also stimulated by prostaglandins: PGF<sub>2 $\alpha$</sub>  and PGE<sub>2</sub>.

Chemotactic activity and cytokine production differ in the case of premature rupture of membranes compared to term rupture of membranes. In the decidua, leukocyte infiltration occurs during labor. The number of neutrophils that infiltrate the decidua is much higher in the case of preterm labor with associated infection. In addition to neutrophils, the number of macrophages also increases, but this increase is present in both term and preterm labor [8].

Nuclear factor kB (NF-kB), which plays a role in the synthesis of prostaglandins and the regulation of matrix metalloproteinase (MMP) expression, thus influencing myometrial contraction and cervical ripening, should also be mentioned.

Chorioamnionitis is an inflammation caused by bacterial infections in the fetal membrane. This may induce different severe disorders in newborns, such as necrotizing enterocolitis, cerebral palsy or patent ductus arteriosus. These complications will have an immediate and long-term impact on the evolution of the neonate [9].

Inflammatory mediators will reach the fetus through the amniotic fluid or by transmission through the umbilical cord [10].

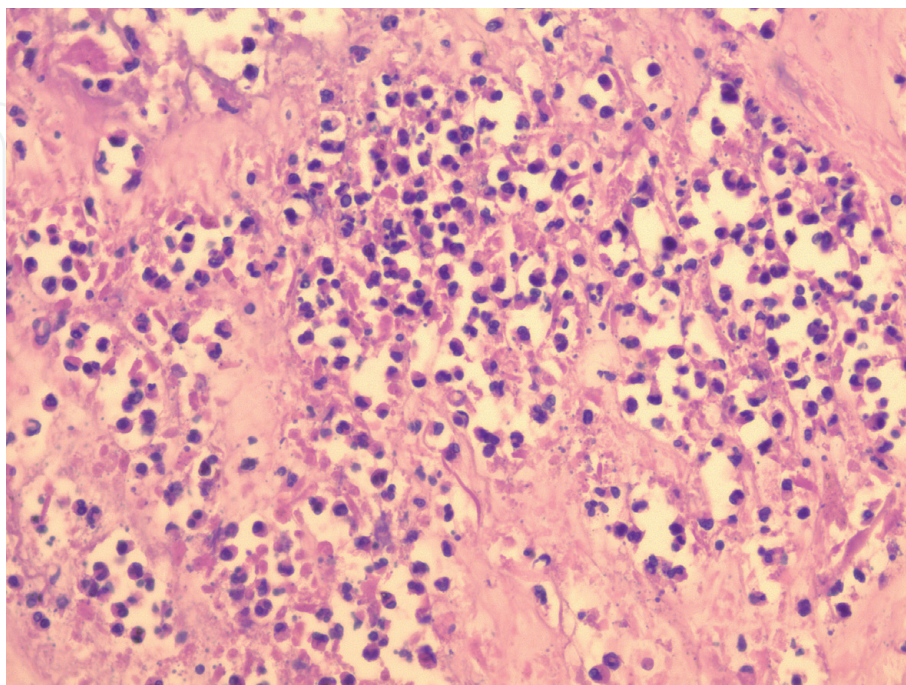
### 3. Inflammation effect on preterm neonate

#### 3.1 Effects on the lung

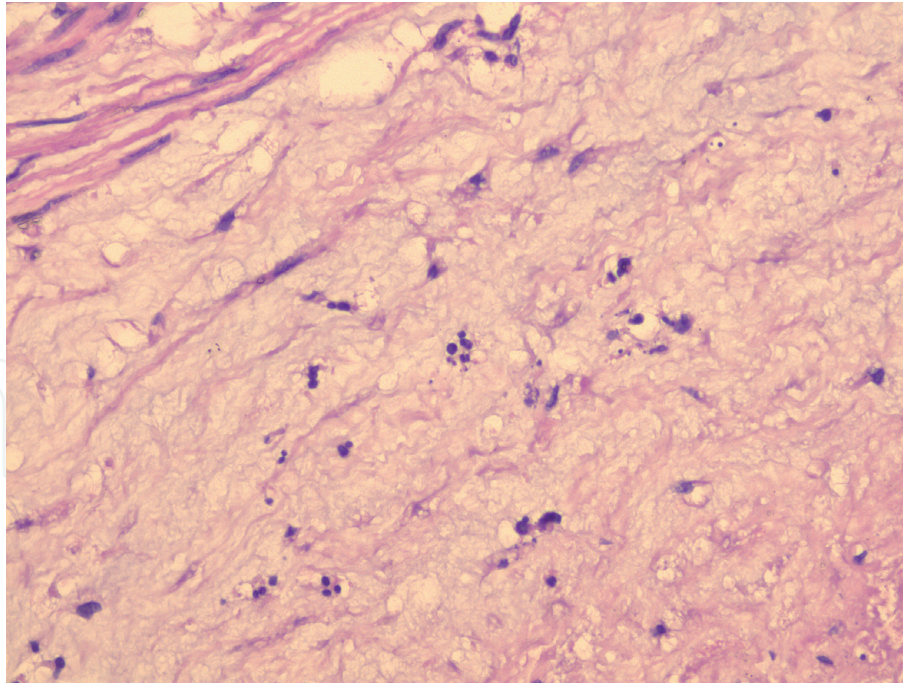
The inflammatory cytokines that reach the amniotic fluid will have an effect on the development of the fetal lung. Chorioamnionitis is an important risk factor for bronchopulmonary dysplasia. In neonates whose mothers had increased cytokine levels in the amniotic fluid: IL-8, IL-1 $\beta$  and TNF- $\alpha$ , severe forms of bronchopulmonary dysplasia were more frequent. The pathological examination of the placenta can provide important information about the placental inflammatory process. Among our cases, we had a patient with a severe form of bronchopulmonary dysplasia, with oxygen requirements until the age of 4 months, without a history of severe respiratory distress, but with abscess areas, extensive inflammation evidenced by the pathological examination of the placenta and umbilical cord (**Figures 1 and 2**). The mother showed no clinical symptoms, but inflammatory syndrome and premature rupture of membranes were evidenced 14 days prior to labor [11].

Although there are meta-analyses showing a weak association between inflammation and bronchopulmonary dysplasia, animal studies have revealed significant inflammation in the lungs after endotoxin injection in preterm lambs [12]. Inflammatory mediators have effects on the regulation of angiogenesis, morphogenesis and cell growth in the lungs [13].

Bronchopulmonary dysplasia is more frequent in extreme preterm neonates. It may have a long-term effect on respiratory function during childhood or even adulthood. These children at school age will have an increased risk to develop asthma phenotype. Treatments used in bronchopulmonary dysplasia can also have adverse effects that will be validated in the medium or long term. Thus, prolonged use of corticoids in severe disease forms can have an impact on neurological



**Figure 1.**  
*Amniotic membrane inflammation [11].*



**Figure 2.**  
*Inflammation in the umbilical cord [11].*

development; prolonged use of diuretics may influence auditory bone development in the newborn [11]. Studies have shown airway obstruction in prematurely born children or adults with a history of BPD [14]. Other factors favoring the development of the disease in preterm infants are delivery by cesarean section, infections, antibiotic therapy. The risk of infections increases with the decrease of gestational age. Humoral and cellular immunity is not prepared for extrauterine life in newborns with small gestational age.

Recent research has highlighted a correlation between microbiota and immunity, i.e. the presence of a lung - intestine axis regarding mucosal status.

Multivariate logistic regression analysis of a neonatal cohort (2527 neonates with BPD and 12826 unaffected controls) revealed that neonatal sepsis is a risk factor for BPD. Breast milk and probiotics play a role in reducing BPD incidence in preterm infants [15].

In BPD, there are changes in pulmonary vascularization, the number of alveoli, the reduction of septation, the simplification of alveolar structure with an impact on gas exchanges.

In the lungs, there is an inflammatory process mediated by pro-inflammatory cytokines, inflammation being maintained by mechanical ventilation, oxygen administration and infection. The cytokine level will depend on the duration of mechanical ventilation, tidal volume and the type of ventilation used.

Preterm neonates with BPD have in their cord blood a high level of Th17 compared to unaffected newborns [16]. A study analyzing the serum of newborns with BPD revealed high levels of IL-6, IL-8 and granulocyte-colony stimulating factor (G-CSF) in the first week of life [17].

### **3.2 Effects of inflammation on the heart**

Inflammation in the fetal period, particularly in the case of preterm neonates, will act on an immature, developing heart.

The process of formation, development of cardiomyocytes continues until the time of birth.

Currently, it is known that inflammation, cytokine release are correlated with the occurrence of pulmonary hypertension, which will have an effect on the right ventricle and will induce systolic and diastolic dysfunction. However, studies have demonstrated that maternal inflammation will have an effect on the fetal and subsequently neonatal heart. Hyperoxia induced by inflammation will affect left ventricular structure, causing systolic and diastolic dysfunction.

Extrauterine growth restriction is correlated with adaptation difficulties, limitations of physical activity in former extreme preterm infants. This limitation can be generated by a degree of heart failure in former extreme preterm neonates and by their insufficient growth due to inadequate energy intake [15].

In adults, cardiac dysfunction induced by massive cytokine release as part of an inflammatory process or associated with sepsis has been described [18].

### **3.3 Effects of inflammation on the intestine**

Due to its immaturity, the preterm neonatal intestine is at high risk for lesions caused by inflammation.

The risk factors for inflammatory lesions are represented by: immaturity of the mucosal barrier, immune cell dysfunction, low motility, reduced secretion of IgA and peptides with an antimicrobial role, high risk of dysbiosis and bacterial colonization.

Maternal chorioamnionitis determines a higher incidence of late sepsis in preterm newborns. The major intestinal consequence of maternal chorioamnionitis, chronic ischemia during pregnancy, antibiotic exposure is represented by necrotizing enterocolitis [19].

Pro-inflammatory mediators are important triggers in the development of the disease. Cyclooxygenase and platelet activating factors play a role in the inflammatory pathogenesis of NEC. The role of TLR4 receptors in NEC has been described. TLR4 recognize lipopolysaccharides and activate NF- $\kappa$ B, triggering the pro-inflammatory cascade. Enterocyte apoptosis is induced. The bacterial signal mediated by TLR4 causes mucosal lesions and allows the passage of bacteria into circulation. In mesenteric vessels, TLR4 will interact with bacteria, determining increased nitric oxide production, with severe vasoconstriction and reduced intestinal perfusion [20, 21].

The intestinal microbiota has an influence on immunity in both the intestine and the entire body.

Inflammation in NEC is caused by dysbiosis in the intestine and the exaggerated inflammatory response to this imbalance of the intestinal flora.

### **3.4 Effects of inflammation on the kidney**

Nephrogenesis occurs until the gestational age of 34–36 weeks. The intrauterine inflammatory process will have an effect on renal function. Inflammation has an effect on the nephrogenesis process. Animal studies have demonstrated that the number of nephrons is up to 25% smaller in the case of exposure to hyperoxia and concomitant inflammation [22].

The reduced number of nephrons will have an impact on long-term renal function during childhood and adulthood, and it will favor the development of arterial hypertension at adult age.

### **3.5 Effects of inflammation on the central nervous system**

Besides the impact on the pulmonary parenchyma, the inflammatory process in the intrauterine period also affects neurological development. Fetal inflammation,

as well as inflammation in the neonatal period due to infections can have consequences on the brain, causing lesions of the white matter, inducing periventricular leukomalacia, cerebral palsy, respectively.

The increased levels of IL-1  $\beta$ , IL-6 and particularly TNF- $\alpha$  will exert a toxic effect on developing oligodendrocytes, but will also have a toxic effect at neuronal level. Experimental animal models have revealed the evolution of neurological lesions in time. MRI studies have evidenced long-term cerebral changes during adult life in animal models exposed to inflammation in the intrauterine period. Although there are no data about preterm infants exposed to inflammatory syndrome in the intrauterine period, it is important to consider the fact that some authors have reported cases of autism as an effect of persistent inflammation in the fetal period, or schizophrenia as an effect of latent inflammation [23].

Inflammation will induce lesions directly in the oligodendrocytes and neurons, but also indirectly, through the activation of microglial cells with the release of pro-inflammatory cytokines, followed by neuronal and oligodendrocytes damage [24].

The ELGAN study showed that a high level of inflammatory markers during the first month of life will entail a high risk of decrease in the intelligence quotient (IQ) and executive functions [25].

The imbalance of the intestine – brain axis has an important role in neurocognitive development. Many studies describe the role of this imbalance. In its activity, endocrine, metabolic, immune and neural factors play an important role, but they have not yet been completely elucidated.

#### **4. Conclusion**

Preterm birth represents a public health problem. Inflammation during pregnancy has effects on the fetus and subsequently, on the newborn. Inflammatory mediators in the amniotic fluid induce lesions in the lung and the central nervous system.

A non-invasive respiratory approach and the limited use of invasive respiratory support will prevent severe forms of bronchopulmonary dysplasia. Enteral feeding with breast milk will have a beneficial effect on the reduction of NEC incidence, the reduction of the incidence of sepsis, BPD and ROP, as well as on the reduction of the risk for bronchial asthma during childhood and young adulthood. In the long term, implementing individualized therapeutic measures will allow a better management of each case, the decrease of fetal and neonatal mortality, and optimal neurological development.

#### **Appendices and nomenclature**

BMI	body mass index
NEC	necrotizing enterocolitis
TNF- $\alpha$	tumor necrosis factor $\alpha$
IL 1 $\beta$	interleukin 1 $\beta$
NF kB	nuclear factor kB
G-CSF	granulocyte colony stimulating factor

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