# THE CHORIOAMNIONITIS - STILL AN ENIGMA IN PERINATOLOGY

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## ABBREVIATIONS

**PPROM** - preterm premature rupture of amniotic membranes
**AHCA** - acute histological chorioamnionitis
**IL1** – interleukin 1
**IL6** – interleukin 6
**IL8** – interleukin 8
**IL10** – interleukin 10
**TNF** - tumor necrosis factor
**CD8 TLy** - cytotoxicity T lymphocytes
**CXCL9** - C-X-C motif chemokine 9
**CXCL10** - C-X-C motif chemokine 10
**CXCL11** - C-X-C motif chemokine 11
**HLA-G** - human leukocyte antigen G (histocompatibility antigen, class I, G)
**DNA** - deoxyribonucleic acid

## ABSTRACT

*Chorioamnionitis is one of the most common causes of preterm premature rupture of fetal membranes and consequent preterm birth. The variety of mechanisms underlie pathophysiology of chorioamnionitis represents its greatest enigma. The unspecific clinical manifestations of chorioamnionitis considered an aggravating issue for perinatologist to diagnose it timely. There are no absolutely sensitive, non-invasive diagnostic procedures for certain establishment of chorioamnionitis diagnosis. The more sensitive diagnostic procedures are also invasive, so the question of their application in routine practice arises. Certainly, the perinatologist is always in a dilemma when there is a suspicion of chorioamnionitis, whether and how it should be treated, having in mind the facts about possible side effects on the fetus, but also on the mother. This paper presents a summary of all known facts about the etiopathogenesis, classification and clinical manifestations of chorioamnionitis, providing a basis for further research regarding the identification of more sensitive diagnostic markers, as well as the treatment of this condition.*

***Keywords***: *Chorioamnionitis, preterm birth, inflammation, infection.*

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## INTRODUCTION

### Definition and classification of chorioamnionitis

The significance of the placenta, as a temporary organ, is defined by one simple sentence "the placenta represents the diary of gestational life" [1]. It reflects not only the intrauterine environment, but also provides valuable data related to maternal pathology [2,3]. As an extremely complex and multifunctional organ, placenta still remains insufficiently examined. It consists three main parts: the placental disc, chorioamniotic membrane and umbilical cord [4,5]. The terms placentitis and vilitis both represent the inflammation of placental disc (chorionic villi) [4,5], but reflect different stages of the same inflammatory process, therefore should not be considered as synonyms. On the other hand, funisitis is referred to inflammatory process that affects the umbilical cord [6,7].

Literally, the term chorioamnionitis refers to the inflammatory reaction that takes place in the fetal membranes (amnion and chorion) [8]. Chorioamniotic membranes form the most distant part of the conceptus [9]. On the one hand, they represent the boundary, while on the other hand they represent the connection between mother and fetus. The inflammation process can affect amnion or chorion exclusively; although the most common form represent the sublimation of the inflammatory process in both [8]. The recommendation of the US National Institutes of Health Conference is to switch autologous to the heterologous form of chorioamnionitis, which also includes inflammation of both decidua and amniotic fluid [8].

Based on the course severity, two form of chorioamnionitis can be distinguished: acute and chronic. Regarding the pathophysiological aspect, the chorioamnionitis could be defined as infectious or aseptic [4]. Another classification, regarding the absence or presence of clinical manifestations, could be arranged as clinical or asymptomatic [10,11], while some authors also considered histological, microbiological and biochemical form of chorioamnionitis as appropriate [12]. Apart from the classification into acute and chronic chorioamnionitis, all other classifications have pronounced deficiencies. However, there is no single consensus regarding classification of chorioamnionitis, due to imprecise and heterogeneous definitions [8], misunderstanding of complex molecular mechanisms and deficiency of taxonomy [13]. For example, histological chorioamnionitis (as the most common form) refers to not only clinical, but also asymptomatic, infectious, and aseptic chorioamnionitis [14].

Although the above mentioned classification is important for understanding the pathophysiology and manifestation of the clinical course of chorioamnionitis, in practical terms it is not simply applicable. Thus, histological chorioamnionitis can be of acute and chronic course, clinical chorioamnionitis can be infectious and aseptic, while any histological chorioamnionitis does not have to be clinically manifested, nor in the basis of infectious etiology.

### Incidence of the chorioamnionitis

The estimated incidence of chorioamnionitis is 2-4% of term delivery [15,16] and 40-70% of preterm birth [15,17]. The frequency of acute chorioamnionitis is inversely proportional to gestational age. Chorioamnionitis was observed in 94.4% of births occurred between 21-24 weeks of pregnancy [4], while it was found in less than 5% of term births (over 37 weeks of pregnancy) [18]. Chronic chorioamnionitis occurs in 34% of premature births, of which in 39% with rupture of fetal membranes [19,20], and this form is especially common in late premature births in as many as 70% of proven cases [19,21]. This implies that its frequency is directly proportional to gestational age in premature births.

Histological analysis of the placenta, as the gold standard, can demonstrate the presence of chorioamnionitis in 33% of preterm births with preserved amniotic membranes and in as many as (approximately) 80% of preterm premature rupture of amniotic membranes (PPROM) [9, 22]. Nasef and coworkers [23] monitored the incidence of histological chorioamnionitis in relation to gestational age, and observed that it was found in 41% of births before 27 weeks, 15% of births between 28 and 36 weeks, and in only 2% of births after 37 weeks [24]. In the term births, histological chorioamnionitis was present in 20% of patients [25,26]. However, the marked decrease, regarding the incidence of histological chorioamnionitis in the term deliveries (from 2% to 20%), was registered because the histopathological analysis of placenta was performed only in those cases where there was a clinically justified suspicion of chorioamnionitis. Moreover, we are closer to the belief of the higher chorioamnionitis incidence in term deliveries (due to the lack of clinical manifestation) [27]. This could be an explanation for the partial overlap of two forms of chorioamnionitis - clinical and histological.

Chorioamnionitis is associated with intraamniotic infection. In as many as 72% of cases, the isolation of bacteria from amniotic fluid in preterm births was accompanied by histopathological confirmation of chorioamnionitis [9]. However, the detection of microorganisms in amniotic fluid is not enough to induce, but also to confirm diagnosis of chorioamnionitis [9]. In literature data, the percentage of noninfectious histological chorioamnionitis ranges from less than 30% [27] to more than 50% [28]. This could be an explanation for the partial overlap of histological and infectious form of chorioamnionitis.

Taking into consideration the clinical criteria, chorioamnionitis is recognized in 5-12% of term pregnancies [29,30] and in almost 20% of pregnancies with premature rupture of fetal membranes [14,31]. Among patients with clinical findings of chorioamnionitis, in 54% was detected intraamniotic inflammation with the presence of microorganisms, in 24% of patients presence of intraamniotic inflammation was not accompanied with presence of microorganisms, while 22% of women had no intraamniotic infection [29,32]. This could

explain the partial overlap of the two forms of chorioamnionitis - clinical and infectious.

## HISTOLOGICAL CHORIOAMNIONITIS

The histopathological analysis represents the gold-standard diagnostic method for diagnosing chorioamnionitis [13]. Although with the greatest specificity, the sensitivity of this diagnostic procedure is quite low. This is evidenced by the weak association between histologically proven chorioamnionitis and the fetal inflammatory response syndrome (complications in fetuses caused by chorioamnionitis) [33]. Nevertheless, evaluation of histological chorioamnionitis represents the most secure diagnostic procedure, with the least possibility of false negative cases.

Acute histological chorioamnionitis is defined as an acute infiltration of granulocytes (neutrophils) of the choriodecidual space (maternal origin) and chorioamniotic membranes, chorionic villi, amniotic fluid and umbilical cord (fetal origin) [25]. By analyzing the origin of neutrophils (maternal or fetal), the exact origin of inflammation can be determined quite easily [4].

Neutrophils are usually not present in the chorioamniotic membranes and migrate from the decidua into fetal membrane in case of acute inflammation (neutrophils of maternal origin) [4,34]. However, they are present in the intervillous spaces of the placenta, but not in the chorionic plate [4,35]. The chemotactic gradient pulls them from the intervillous spaces into the chorioamnion membranes and the chorionic plate, which explains the maternal origin of neutrophils in acute chorioamnionitis (over 90%) [35].

Acute funisitis, vilitis and inflammation of the amniotic fluid are characterized by infiltration of neutrophils of fetal origin [36]. Previous studies showed a higher prevalence of interleukin 8 (IL8) as a chemotactic factor, as well as a higher expression of genes that increase the susceptibility to the inflammatory response in the umbilical vein wall than the artery [37]. The umbilical vein is the first vessel developing inflammatory changes, while umbilical arteritis represents a sign of advanced inflammation and carries a higher risk for neonatal complications [2, 26]. For that reason, in early detection of inflammation, the umbilical vein should be the first choice vessel for puncture and blood collection for laboratory analyzes of umbilical cord blood. The most serious form of funisitis is the migration of neutrophils into Warthon's jelly [4,37]. This form of inflammation is called necrotizing funisitis [12]. However, funisitis is present in about 60% of cases [14,38].

Histological analysis of the placenta with the proven chorioamnionitis, based on the localization of neutrophils, defines three stages of inflammation:

### Acute histological chorioamnionitis 1 (AHCA 1)

AHCA 1 is characterized by inflammation of the decidua and chorioamniotic space. These are the first tissues affected by the inflammatory process, and neutrophils are of mother origin [25]. It is most often detected by analysis of placenta in preterm labor (after 37 weeks) and is considered to be triggered by an inflammatory response (usually aseptic), which represents the physiological mechanism of labor initiation [25,26]. In the literature, synonymous for AHCA 1 such as deciduitis with or without chorioamnionitis can be found.

### Acute histological chorioamnionitis 2 (AHCA2)

AHCA 2 is characterized by inflammation of the amnion and / or chorion without umbilical cord inflammation, ie. by infiltration of neutrophils of mostly fetal origin. It is most common in births between the 32$^{nd}$ and 36$^{th}$ week of gestation, and represents the most common form of histological chorioamnionitis [2].

### Acute histological chorioamnionitis 3 (AHCA 3)

AHCA 3 is an advanced inflammatory process that occurs in early preterm birth (<32 weeks) [2,25]. It is characterized by an intense fetal inflammatory response, and represents the final degree of extraplacental chorioamnion inflammation [39,40] along with neutrophilic infiltration of the umbilical cord. It is synonymous with necrotizing funisitis.

Histological chorioamnionitis of acute origin is more common and more severe in preterm, in relation to term births [41], and even three times more often in relation to clinical chorioamnionitis. It occurs in the term (AHCA 1) with a frequency of 7-85%, while the prevalence in preterm births (AHCA 2 and AHCA 3) is 4-63% [42]. The literature data more precisely showed the frequency of histological chorioamnionitis in 20% of term deliveries, and 38-50% of preterm deliveries [43].

Chronic histological chorioamnionitis is defined as chronic infiltration of the placenta (decidua, chorioamnion membranes, chorionic plates and chorionic villi) by lymphocytes, plasma cells and / or macrophages [19,44]. In the largest percentage of cases, the etiology of chronic chorioamnionitis remains unknown [45]. However, infectious agents and fetomateral immune response (by type of allograft rejection) are suggested as possible reasons [20,46-52].

The latter theory is supported by the following explanation - initiation of the mother's (host's) immune response to the father's antigens (expressed in the placenta, but also in the fetus). The main effectors of this immune response are cytotoxic lymphocytes (CD8 TLy) [20,45,53]. This condition is associated with the presence of fetal antibodies to leukocytes in maternal serum and syncytiotrophoblast [54].

In the strict sense of the term, chronic chorioamnionitis is characterized by infiltration of mononuclear cells in the chorioamnion membranes. Diffuse or uneven infiltration of maternal CD8 TLy from the decidua, primary to the levae zone of chorion where interaction of these cells with trophoblast cells occurs [20] consequently led to apoptosis of trophoblast cells. The migration of CD8 TLy was stimulated by the

chemotactic factors CXCL9, CXCL10 and CXCL11 from the chorioamnion membranes [55-64]. Under normal conditions, there is no inflammatory reaction in the choriodecidual junction, due to the expression of non-polymorphic HLA-G by trophoblasts [65-68] and the silenced T-cell chemokines gene in decidual cells [69].

The gradation of chronic histological chorioamnionitis is based on the degree of lymphocyte infiltration:

- grade 0 - without infiltration,
- grade 1 - over 2 foci of infiltration or uneven infiltration,
- grade 2 - diffuse infiltration [19].

Chronic chorioamnionitis in a broader sense includes chronic vilitis, as well as chronic deciduitis. Chronic vilitis is characterized by infiltration of CD8 TLy of maternal origin [53], as well as macrophages of fetal origin (Hofbauer cells) [70]. It is a unique inflammatory process in which inflammatory cells originating from two different participating hosts. The migration of CD8 TLy is stimulated by the chemotactic factors CXCL9, CXCL10 and CXCL11 from macrophages, endothelial cells and stromal cells [46]. Chronic deciduitis is diagnosed by the presence of lymphocytes and plasma cells in the decidua [71].

| CHORIOAMNIONITIS | CHARACTERISTICS | DELIVERY | REFERENCE |
|---|---|---|---|
| **Acute histological** | Neutrophils infiltration | Treterm and term | Conti N. and al. [25] |
| AHCA 1 | Decidua and chorionic space | Mostly term, ≥ 37 week | Conti N. and al. [25]<br>Lee SM and al. [26] |
| AHCA 2 | + amnion and/or chorion | Mostly preterm, 32 -36 week | Torricelli M. and al [2] |
| AHCA 3 | + umbilical cord | Mostly preterm, ≤ 32 week | Torricelli M. and al [2]<br>Conti N. and al. [25] |
| **Chronic histological** | Lymphocyte infiltration (CD8 TLy) with/without macrophages and plasma cells | preterm (34-70%) and term | Kim CJ and al. [19]<br>Murphy HS [44] |
| In narrow sence | Chorioamniotic membranes | term/preterm | Kim CJ and al. [20] |
| In wider sense | + decidua и chorionic villi | term/preterm | Reyes L and al. [53]<br>Khong TY and al. [71] |
| **Infectious** | pathogens –<br>bacteria, viruses, fungi | Term, ≥ 37 week (10%)<br>Preterm, 32 -36 week (18%)<br>Preterm, ≤ 32 week (39%) | Torricelli M. and al [2] |
| bacterial | Ureaplasma urealiticum (47%)<br>Gram negative anaerobes (38.4%)<br>Micoplasma hominis (30.4%)<br>Bacteroides bivius (29.5%)<br>Gardnerella vaginalis (24.5%)<br>Streptococcus agalactiae (15%)<br>Escherichia coli (8%) | preterm (39%)<br>term (10%) | Torricelli M. and al [2]<br>Czikk MJ and al [15]<br>Redline RW and al [18]<br>Hecht JL and al [103] |
| viral | Predominantly adeno viruses | preterm (41%) | Czikk MJ and al [15]<br>Spiegel AM and al [104] |
| fungal | Candida sp. | term/preterm<br>(<0.8%) | Stock SJ and al [105] |
| **Clinical** | Maternal hyperthermia<br>(>37.8$^0$C) (95-100%)<br>Maternal tachicardia (>100 beat per minute) (91.1%)<br>Fetal tachicardia (>160 beat per minute) (66%)<br>Maternal leucocytosis (>15000/mm$^3$) (33%)<br>increased tenderness of the uterus (9%)<br>unpleasant smell of amniotic fluid (3%) | preterm (20%)<br>term (5-12%) | Tita AT and al [14]<br>Romero R and al [29]<br>Martinelli P and al [109]<br>Burke C and al [113]<br>Romero R and al [117] |
| **Biochemical** | Increase in IL6 and IL8 concentration | Preterm and term | Romero R and al [29]<br>Burke C and al [113]<br>Evers AC and al [114] |

## INFECTIOUS CHORIOAMNIONITIS

Positive bacterial cultures were found in 10% of placenta from term, 18% of placenta from preterm births (between 32-36. weeks of pregnancy), while the highest percentage (39%) of placenta with positive bacterial cultures was obtained from childbirth before the 32nd week of pregnancy [2]. Histologically confirmed chorioamnionitis is found in 72% of cases of preterm births in which microbiological invasion of amniotic fluid was detected by amniocentesis [9]. Interestingly, in 40-60% of cases, aseptic intraamniotic inflammation was found in verified histological chorioamnionitis [72-75].

Although the etiology of chorioamnionitis remains elusive, the role of microorganisms, especially bacteria, cannot be disputed. It is considered that the development of infectious (microbiological) chorioamnionitis is only one of the stages in the development of intraamniotic infection. The dilemma remains whether intraamniotic infection is the cause or consequence of chorioamnionitis [9]. Also, it is not entirely clear whether chorioamnionitis is a cause or a consequence of preterm premature rupture of membrane (PPROM) and premature birth [9,76].

However, the presence of microorganisms in amniotic fluid is not always the indicator of microorganisms in the placenta. Also, it does not mean the development of chorioamnionitis. There are a number of reasonable explanations for these claims: the critical concentration of microorganisms as inducers of preterm birth or chorioamnionitis in the intrauterine compartments cannot be defined [77-81]. Secondly, the enzymes of almost all microorganisms are not sufficient/enough, to solely cause chorioamnionitis and premature birth. Therefore, it is considered that the host immune system triggered by microorganisms (or their particles) is responsible for the occurrence of the above conditions [82-84].

An interesting fact is that acute histological chorioamnionitis was found in 37% of cases with a negative finding of microorganisms in amniotic fluid [85]. In that study, sample of amniotic fluid was collected by amniocentesis, just before delivery (up to 48 h). The transcervical approach was excluded because it increases the possibility of secondary contamination, as well as the number of false-positive results.

Bacteria are the most common cause of infectious chorioamnionitis. Bacterial DNA was detected in 50% of cases, and the microbiome ranged from vaginal to oral [86]. Regarding to gestational age, gram-positive bacteria were detected in 17% of placenta, while gram-negative bacteria were found in 10% of placenta in births before 32 weeks of age. In 11% of placentas, presence of gram positive, and in 8% gram negative bacteria were registered in childbirth between the 32nd and 36th week of pregnancy. In term, the placenta contained gram positive bacteria in 5%, and gram negative bacteria in 4% of cases [2].

Under normal conditions, the amniotic cavity is sterile [4]. The most common pathway for infection spreading is ascending from the lower genital tract. However, the mucus plug is an anatomical and functional barrier, which normally prevents infection spreading [87-93]. Furthermore, the invasion of bacteria into amniotic cavity is not exclusively dependent from membranes rupture. Fetal membranes have similar function, although they not represent an absolute barrier. There is no need for rupture of membranes for bacteria to be present in the amniotic cavity. In favor of that goes the finding of the initial infection of decidua in the supracervical region. Subsequently, bacteria multiply and pass through the chorioamnion membranes [94,95].

Bacteria are more often detected in amniotic fluid than in chorioamniotic membranes (100% and 33%, respectively) [96]. Moreover, it can be found in chorioamniotic membranes (probably as the initial stage of invasion), although in that case bacteria cannot be isolated from amniotic fluid [97]. It was not considered for the initiation of premature birth, except in the case of bacteria introduced into amniotic cavity [98]. In such a case, a strong inflammatory reaction is activated with an increase in the concentration of proinflammatory cytokines and chemokines [4].

Hematogenous dissemination of microorganisms is one of the pathway of spreading infection from primary focus to gravid uterus. The fact of more frequent intraamniotic infections and more frequent chorioamnionitis in women with periodontal diseases speaks in favor of this circumstance [99,100]. Microorganisms reach the intervillous spaces, invade chorionic villi and enter the fetal circulation [101]. Iatrogenic infection can be introduced into the amniotic cavity during diagnostic or therapeutic procedures, while the retrograde route of infection spreading from the abdominal cavity through the fallopian tubes cavity remains debatable [102].

The percentage of confirmed positive bacterial cultures is directly proportional to the severity of histological chorioamnionitis. Bacteria were isolated in 18% of AHCA 3 cases, 12% of AHCA 2 cases and only 4% of AHCA 1 cases [2]. Also, positive bacterial cultures in placentas was positive in 39% of preterm births and 10% of term deliveries [2].

The most commonly isolated bacteria in amniotic fluid are *Ureaplasma urealiticum* (47%), gram negative anaerobes (38.4%), *Mycoplasma hominis* (30.4%), *Bacteroides bivius* (29.5%), *Gardnerella vaginalis* (24.5%), and *Streptococcus agalactiae* (15%) [15]. Microbiological analysis of the placenta revealed *Ureaplasma urealiticum* (47%), *Gardnerella vaginalis* (26%), while *Escherichia coli* was present in about 8% of cases [18,103]. In 65% of cases, the isolated flora was polymicrobial [14]. Isolation of the virus from amniotic fluid is less frequent than the isolation of bacteria, although as the most dominant among viral represent adenoviral infection of the placenta (41% of premature births and 75% of histologically proven chorioamnionitis) [15,104]. Fungal infections were found to complicate less than 0.8% of pregnancies [105].

The concept of "TRIPLE I". In the light of etiological considerations, chorioamnionitis was observed as heterogeneous entity. Several American health associations have suggested that the term chorioamnionitis could be replaced by the term "triple I" - infection, inflammation and both [8,12]. Although this term can be used in clinical infectious chorioamnionitis, and confirmed by bacteriological examinations, it still remains reserved for the histological form of chorioamnionitis [8,12].

"Triple I" encompasses the two most important pathophysiological processes; infection - which is found in a significant percentage of chorioamnionitis, and inflammation that can be aseptic or triggered by microbiological invasion. It also refers to any of these two terms isolated: infection (proven microbiological agents, their particles or DNA) of placental tissue, fetal membranes, amniotic fluid and umbilical cord, without consequent inflammation [9], or aseptic inflammation without proven microorganisms [27].

"Triple I" is interpreted in terms of clinical manifestations of chorioamnionitis, and confirmed by microbiological, histopathological and laboratory analyzes [10,106,107]. However, a recent Cochrane review concluded that the quality of the evidence in favor of the broader application of the “triple I” concept is poor [8,108].

## CLINICAL CHORIOAMNIONITIS

The prevalence of clinical chorioamnionitis ranges from 5-12% of term pregnancies, and 20% of preterm pregnancies with premature rupture of the fetal membranes [14,29,109]. Microorganisms in amniotic fluid are present in 61% of patients with clinical chorioamnionitis at the term gestations, but the diagnosis is rarely confirmed by microbiological tests [29,110]. However, in about 24% of cases of clinical chorioamnionitis, no microorganisms were detected, despite presence of intraamniotic inflammation [29]. Overlap of clinical and histological chorioamnionitis was found in 51-62% of cases [111].

Clinical chorioamnionitis is an entity characterized by maternal temperature of 38°C or higher and, at least two of the following signs:

- maternal tachycardia (> 100 beats per minute);
- fetal tachycardia (≥ 160 beats per minute);
- maternal leukocytosis (≥ 15000 leukocytes / $mm^3$);
- increased tenderness of the uterus;
- unpleasant smell of amniotic fluid [12,112].

Maternal hyperthermia almost always exists in clinical chorioamnionitis (95-100%) and represents the most important clinical sign. However, it is an accurate indicator of a proven infection in the microbiological form in only 30% of cases [113,114]. This finding indicates that not every hyperthermia is of infectious etiology, although the perinatologist can start the treatment with antibiotics in presence of hyperthermia [113].

The reason for the hyperthermia during delivery may be a consequence of the applied epidural anesthesia. In these circumstances, there is an increase in vaginal temperature at a rate of 10°C every 7 hours [113,115]. The exact mechanism of epidural anesthesia on hyperthermia occurrence remains unknown, but it is assumed that sympathetic blockade of thermoregulatory processes underlied it [14]. However, there is no reliable way to distinguish the hyperthermia of infectious etiology and hyperthermia caused by epidural anesthesia [113,116].

Maternal tachycardia (present in 91.1% of patients with chorioamnionitis) may not always be an indicator for pathological condition [117]. It may occure due to significant maternal hemodynamic needs, increased heart rate and cardiac output [113,118]. Also the use of medications (sympathomimetics), as well as psychosomatic stimuli that activate the sympathetic nervous system may be the cause of maternal tachycardia.

Fetal tachycardia occurs in 66% of chorioamnionitis [113,117]. It is a consequence of increased fetal metabolism in conditions of maternal hyperthermia, while it also occurs isolated in presence of fetal hypoxia due to compensatory stimulation of the sympathetic nervous system [113,119]. Diagnostic accuracy of fetal tachycardia in chorioamnionitis is partial because it is not always a reflection of infectious etiology (as evidenced by the previous statements).

Leukocytosis is considered to be a number of leukocytes in the mother's blood higher than 15000 leukocytes / $mm^3$ and represents a non-specific biochemical indicator. It can be registered during delivery, even without evidence of infection. It occurs in 33% of cases of clinical and histologically proven chorioamnionitis [113,117]. Tita and Andrews [14] found a higher frequency of leukocytosis in clinical chorioamnionitis (70-90%), but they defined leucocytosis as higher then 12000 of leukocytes in $mm^3$ of blood.

Increased uterine tenderness occurs in 9% of chorioamnionitis, but it is accurate indicator in predicting clinical chorioamnionitis in 48.9% of cases [113,117]. It occurs due to prostaglandins release as well as secretion of bacterial exo- and endotoxins, and thus increased uterine contractility [113,120]. Moreover, decreased uterine perfusion and consequent muscle hypoxia may cause increased uterine tenderness as well as blood in the decidua [113,120].

Unpleasant malodour of amniotic fluid is found only in 3% of chorioamnionitis, while its diagnostic accuracy was 46.3%. It is most commonly associated with intraamniotic bacterial infection [113,117].

Signs and symptoms of clinical chorioamnionitis have low sensitivity and specificity, poor prediction, are not reliable and usually appear late. They may be absent, despite proven histological confirmation of chorioamnionitis, but also present in cases of histologically unconfirmed chorioamnionitis. Nevertheless, they represent an empirical guideline

for the dilemma in the application of therapy during pregnancy.

## BIOCHEMICAL CHORIOAMNIONITIS

This form of chorioamnionitis is the most controversial and debatable. Literature data do not provide enough information about biochemical chorioamnionitis. It is difficult to even define this term. Simply, we could state that biochemical chorioamnionitis is found with more or less share in all the previously mentioned forms.

Complex biochemical processes represent the fundamental links in all pathophysiological processes, as well as in mechanisms underlie the chorioamnionitis. Beside various processes, apoptosis is one of the basic mechanism affecting and damaging the trophoblast cells [19,20]. Chemotaxis, as a basis for the attraction of inflammatory cells, is also mediated by complex biochemical processes. IL8 acts as a chemotactic factor for neutrophil infiltration in acute chorioamnionitis [4,37]. Chemokines such as CXCL9, CXCL10 and CXCL11 released from macrophages, endothelial cells and stromal cells attract cytotoxic CD8 TLy in complex immune and pathophysiological processes of development of chronic chorioamnionitis [19,46].

Determining the above-mentioned immune components in the blood of the mother, umbilical cord or fetal blood can be of help in a better understanding of chorioamnionitis. The specific analysis of biological tissues (samples of placental tissue, biopsies of decidua or umbilical cord) using sophisticated biochemical procedures represents very interesting and scientifically based procedures. Cervical smear for fibronectin is a decades-long test in assessing the risk of premature birth [9,121-124], followed by determination of salivary estradiol [125,126] or corticotropic hormones. Standard inflammatory markers such as fibrinogen, procalcitonin, and C-reactive protein are nonspecific when observed isolated, but they were commonly interpreted along with leukocytosis [9].

Traditional determination of proinflammatory cytokines (TNF, IL1 and IL6) in blood or amniotic fluid, as well as antiinflammatory cytokines (TGF, IL10), chemokines, their receptors and receptor agonists is less and less specific for chorioamnionitis [9]. Currently, IL8 is the most reliable diagnostic marker for the pathohistological confirmation of acute chorioamnionitis [113,114]. However, determination of the IL6 concentration in amniotic fluid is used to assess the extent of the inflammatory response [29]. The mean value of IL6 concentration in clinical, microbiologically confirmed chorioamnionitis is 14 ng / ml [29].

There is an urgent need for further investigations in order to detect a specific biochemical marker, while known biomarkers have not given the expected results so far [9]. Probablly, the future diagnosis will rely on determination of so-called "alarmins", a more sensitive and specific markers of cell damage, such as IL33 [29,127]. The rationale for such considerations are apoptotic processes of the placenta trophoblast cells that occur during chorioamnionitis. Studies concerning this theme are ongoing.

## CONCLUSION

Taking into consideration the above mentioned, it could be abslutely argumented, that chorioamnionitis represents a great enigma for perinatologists. Although significant progress has been made in understanding pathophysiological events, it turns out that the key "links" of this complex process are often missing or unclear. In support of that, there are constant dilemmas: is intraamniotic infection a cause or a consequence of chorioamnionitis? Even more, it is not entirely clear whether chorioamnionitis is a cause or a consequence of PPROM and premature birth?

The diversity of the chorioamnionitis prevalence is a consequence of insufficiently defined criteria, especially when it comes to clinical chorioamnionitis. However, there is less of a problem regarding the clinical signs (hyperthermia) than clinical symptoms (uterine tenderness). Generally, the sensitivity and specificity remains extremely low, so the diagnosing of chorioamnionitis in this way is certainly questionable.

A series of diagnostic procedures performed in order to confirm of chorioamnionitis did not give the expected results. Standard laboratory inflammatory markers are overcomed, and interpreted only in the context of clinical manifestations. Diagnostic procedures such as amniocentesis are more sensitive, but they are invasive and not routinely performed in purpose of diagnosing inflammation of amniotic fluid or placental tissue.

Definitive confirmation of chorioamnionitis is made by histopathological analysis which represents the gold standard. However, the incidence of histological chorioamnionitis is three times higher than clinical, which is an additional aggravating circumstance. Although, the histopathological diagnosis of chorioamnionitis remains the most reliable one, it can be performed only after delivery i.e. retrogradely. Nevertheless, after delivery, there is no further effect of the medications on the course of pregnancy, or on the potential complications of the newborn.

Further investigations regarding chorioamnionitis, could provide a deeper understanding of pathophysiological events and detection of specific and sensitive biomarkers. The detection of "alarmins", specific cytokines indicating cell damage, should also be taken into consideration. Furthermore, special attention should be paid into initial factors, the initiators of the aseptic inflammatory reaction, which is both clinical and scientific challenge.

All of the abovementioned should provide a more effective perinatological monitoring, prevent potential neonatological complications, decrease the time between diagnosis and therapeutic treatment, but also provide more precise evidence based facts and taxonomy.

## CONTRIBUTORS

All authors contributed to and have approved the final manuscript.

## CONFLICT OF INTEREST

The authors report no conflicts relevant to this paper.

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