

## Heterogeneity of the Intra-Amniotic Inflammatory Response during Pregnancy - FIRS Type I and II

Cornelia Amalinei\*

Department of Morphofunctional Sciences I, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania  
Department of Histopathology, Institute of Legal Medicine Iasi, Romania

\***Corresponding author:** Cornelia Amalinei, Department of Morphofunctional Sciences I, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, E-mail: cornelia\_amalinei@yahoo.com

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The Fetal Inflammatory Response Syndrome (FIRS) has a relatively high incidence in spontaneous preterm labor [1]. FIRS comprise the fetal component of Systemic Inflammatory Response Syndrome (SIRS) and it is related to intra-amniotic infection and/or inflammation [1]. Placental inflammation represents a major cause of perinatal mortality and morbidity, such as cerebral palsy, bronchopulmonary dysplasia, and necrotizing enterocolitis [2]. Supplementary, FIRS can develop into multiple organ dysfunctions, by involving the heart, the kidneys, the adrenals, the hematopoietic organs, and skin [1]. The histological markers of FIRS are the inflammation of the umbilical cord (funisitis), acute chorioamnionitis [3] (Yoon et al., 2001) or chorionic villi vasculitis [4].

The placental components inflammation is a routine and important histological finding and the feature and the distribution pattern of the inflammatory infiltrate may be useful in determining the etiology. There are two large categories of placental inflammations: acute chorioamnionitis, comprising an acute inflammatory reaction involving the fetal membranes and the umbilical cord, graded into three stages, according to the extent of the disease, and villitis, comprising a chronic inflammatory infiltrate restricted to the chorial villi parenchyma.

The acute chorioamnionitis has an infectious etiology, different microorganisms being responsible for ascendant infection originating from vaginal or cervical infections. Villitis has an idiopathic feature, being rarely infectious, attributed to microorganisms, by hematogenous spread, such as bacterias (Group B Streptococcus, Peptostreptococcus, *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus*, *Bacteroides fragilis*, *Fusobacterium necrophorum* and *nucleatum*, *Clostridium perfringens*, *Mycoplasma hominis*, *Haemophilus influenzae*, *Ureaplasma urealyticum*, *Chlamydia trachomatis* and *psittaci*, *Campylobacter fetus*, *Bacteroides*

*fragilis*, *Proteus mirabilis*, *Gardnerella vaginalis*, *Mycobacterium leprae* and tuberculosis, *Morganella morganii*), viruses (Cytomegalovirus, Herpes simplex virus-2, Parvovirus B19, Varicella/ Zoster, Rubella, human immunodeficiency virus-1/ HIV-1), fungi (*Candida albicans*, parapsilosis, and tropicalis), or protozoans (*Treponema pallidum*, *Toxoplasma gondii*, *Plasmodia*, *Trichomonas*), originating from maternal blood (hematogenous infection), being considered as a transplacental infection [5,6]. The specific serological marker of FIRS is increased IL-6 in the umbilical cord blood [7].

Research of the pregnancy immune particularities showed evidences that fetus is a semi allograft and needs a specific tolerogenic status of the maternal immune system [8]. Relatively recent studies have demonstrated that T-cells chronic chorioamnionitis, plasma cells deciduitis, and Villitis of Unknown Etiology (VUE) can be in fact the expression of maternal anti-fetal rejection [9], due to graft-versus-host disease and alloimmune reactions [10]. The serological marker of this condition is the increased C-X-C motif chemokine 10 (CXCL10) [8,11]. CXCL10 is as a ligand for C-X-C motif chemokine receptor 3 (CXCR3), acting as a chemotactic factor for macrophages, activated T cells, and natural killer/NK cells in fetal plasma, being associated with seropositivity for Human Leukocyte Antigen (HLA) Panel Reactive Antibodies (PRA) in maternal serum [8,11]. These conditions are risk factors for preterm delivery after 32 weeks of gestation [11]. Moreover, maternal anti-fetal rejection shows analogous features with allograft reaction, and FIRS type II has been proposed as an appropriate term for this condition [8], as different from the fetal systemic inflammation in the context of intra-amniotic infection or FIRS type I, associated with interleukin-6/IL-6 plasma elevation.

Another key element in fetus and placenta immunology is represented by macrophages, as their dynamics within the maternal-fetal compartment is responsible for a successful pregnancy [12]. M1 and M2 macrophage polarity exhibit their divergent properties [12]. The activated status (M1 macrophages) shows the ability of antigen presenting cells, IL and reactive oxygen species production, while alternatively activated macrophages (M2 macrophages) are responsible for tissue

remodeling, immunosuppression, and T helper 2 (Th2) or antibody mediated immune reactions promoters [12]. M1 polarization is stimulated by Toll-Like Receptor (TLR4) agonists, such as lipopolysaccharides from *Escherichia coli*, Tumor Necrosis Factor-Alpha (TNF- $\alpha$ ), Interferon Gamma (IFN- $\gamma$ ), and Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) [12]. M2 polarization is promoted by IL-4, IL-13 (M2a) or by IL-10, glucocorticoids (M2c), IL-33, Transforming Growth Factor Beta (TGF- $\beta$ ), and Granulocyte Colony-Stimulating Factor (G-CSF) [12]. M2b promotes Th2 response and produces TNF- $\alpha$ , IL-1, IL-6, IL-10<sup>high</sup>, and IL-12<sup>low</sup> [12].

Hofbauer cells or fetal tissue macrophages have been described in the early 1900's [13] and are displayed in the chorionic villi prior to the establishment of a fetal circulation. Thus, their early origin in villous mesenchymal cells and later origin in fetal monocytes has been demonstrated [11]. Relatively recent findings of their activated macrophage status (M2), along with over expression of T cell chemokines, such as CXCL9, CXCL10, and CXCL11 resulting in infiltration of villi with T-cells, in VUE [14].

Another relatively recent finding is that the cytokines involved in inflammation regulation express an analogous profile in FIRS and adult sepsis/SIRS, due to gene expression differences detected by mRNA transcriptome of peripheral leukocytes [1].

## Conclusions

Relatively recent progresses in understanding fetus and placenta privileged status led to a different perspective on FIRS, adding to type I, correlated to intra-amniotic infection, another entity, FIRS type II, currently considered as an expression of maternal anti-fetal rejection and manifested by chronic chorioamnionitis or deciduitis and VUE.

Further research is necessary to find useful tools in refining FIRS type diagnosis and appropriate management in order to prevent perinatal mortality and morbidity.

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