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PRETERM BIRTH – NEW INSIGHTS ON AN OLD PROBLEM

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Abstract. Preterm labor is the final common pathway after several potential insults to the feto-maternal unit. As a common cause, intrauterine infections (both clinically evident and subclinical) are associated with increased proinflammatory cytokine concentrations in the amniotic fluid and the gestational tissues. This fact represents the trigger for "the intrauterine inflammatory response syndrome" as an abnormal maternal immune response.
Key words: preterm birth, preterm labor, maternal immune response, cytokines

Rezumat. Naşterea prematură este modalitatea finală şi comună de răspuns a unităţii feto-materne faţă de multiple posibile injurii. Infecţiile intrauterine (clinice şi subclinice) sunt o cauză frecventă şi se asociază cu creşterea concentraţiilor citokinelor proinflamatorii în lichidul amniotic şi ţesuturile gestaţionale. Aceasta reprezintă mecanismul declanşator al "sindromului reacţional inflamator intrauterin" ca manifestare a unui răspuns imun matern anormal.
Cuvinte cheie: naştere prematură, travaliu prematur, răspuns imun matern, citokine

INTRODUCTION

Although ongoing advances in the fields of obstetrics and neonatology have resulted in significant improvements in pregnancy outcomes, solutions to the problem of preterm labor and preterm birth remain frustratingly unsolved.

The high incidence of preterm birth, that continues unabated all over the world (1) and in our country, still represents a problem for the health cares.

Another facet of the problem is that the prematurity represents the most frequent cause of death in infancy, nowadays when infant mortality has become a benchmark for international comparisons of health-care systems. The countries with large urban population or where poverty is common have higher rates of preterm delivery and consequently higher rates of infant mortality.

Beside that, there is an important economic impact of prematurity upon the costs of the resources used to care for the newborn children, because a proportionally small number of births consume more than one third of health-care expenditures during the first year of life. Moreover, due to the sometimes- unfavorable long-term outcomes, additional expenditures for developmental handicaps are necessary during the remainder of childhood for many infants.

Despite of all medical advances and social efforts, the incidence of preterm birth in the United States (e.g.) has risen from 9.4% of all deliveries in 1981 to 11% in 1993, with 83% of all neonatal deaths associated with delivery at less than 37 weeks and two

thirds occurring in the newborns delivered at less than 29 weeks (2).
In Iaşi county, at the "Cuza-Vodă" Maternity Hospital, the frequency of preterm deliveries decreased from 11.6% (1992) to 6.98% (1998) increasing again to about 9 percent in the last three years. The mortality rate for the premature newborns has fluctuated between a minimum of 51.61% (1999) and a maximum of 81.8% (2000) from the total number of neonatal deaths.
Considering these arguments, it becomes evident that the main goal of management is to prevent or arrest the preterm labor, but despite the introduction of tocolytic drugs, little progress has been made in this respect over the past 30 years (3). This lack of progress actually reflects a poor understanding of its pathophysiology and the need of a new approach.
The preterm parturition may be considered as a response of the feto-maternal unit to a variety of insults such as: chorioamnionitis, ischemia (as in placenta praevia or abruptio, placental insufficiency), uterine abnormalities (malformations, myomata, cervical incompetence), certain pregnancy complications (overdistention due to multiple gestation, polyhydramnios) or individual conditions (age, systemic diseases, unfavorable environmental or socio-economic state).
An important and more recently achieved concept is that preterm birth represents a heterogeneous syndrome (4) with many possible etiological aspects, which is determined by certain abnormalities in the maternal immune response, leading to a single final common expression that being uterine contractility.
This review focuses on the role of the immune system as mediated by inflammatory cytokines in preterm labor in its interdependence with endocrine and paracrine systems.

CYTOKINES AT THE FETO-MATERNAL INTERFACE AND THEIR ROLE IN PRETERM LABOR

The traditional explanation for the onset of parturition in the presence of infection has been that the microorganisms or their endotoxins directly stimulate prostaglandin biosynthesis. However, because only few cases of preterm labor may be attributed to clinically evident intrauterine infection and there is an overlap of endotoxin concentrations among groups with and without labor, the involvement of other factors was suggested. It has now been established that endogenous cytokines mediate in the triggering the onset of preterm birth.
Defined as regulatory proteins secreted by nucleated cells, the cytokines act as communication signals between different types of leukocytes and as modulators of inflammatory responses (4). Their main characteristics are:
- cytokines are simple polypeptides or glycoproteins with a molecular weight < 30 Kd;
- basal production of cytokines is usually low or absent, being induced by various stimuli at the level of transcription or translation;
-cytokine production is transient and typically autocrine or paracrine;
- most of their actions are the result of an altered pattern of gene expression in the target cells, leading to a modulation in

the rate of cell proliferation, a change in cell differentiation status and/or change in the expression of some differentiated functions;
-although an individual cytokine may present a broad and diverse category of actions, at least part of these manifests towards the immune cells.
One of the main sources of cytokine production is represented by the macrophages that are present in the maternal, fetal and placental compartments. Once activated by microorganisms, bacterial products or a dysregulation of the maternal immune response, they secrete a wide range of inflammatory cytokines.
The cytokines, which play a key role in mediating the inflammatory process, may be classified by their general activity (5), as it is shown in Table 1.

Table 1. Inflammatory cytokines classified by activity

Class	Cytokine
Proinflammatory	IL-1
	TNF-α
Chemokines	IL-8
	MIP-1α
Immunomodulatory	IL-6
	LIF
	Oncostatin M
	IL-11
Anti-inflammatory	IL-10
	TGF-β
	IL-4

After stimulation, macrophages and other damaged cells secrete proinflammatory cytokines, which act to initiate the process. Interleukin-1 (IL-1) and tumor necrosis factor α (TNF α) are the representatives for these cytokines (6, 7). They stimulate prostaglandin production and have other systemic and local effects, one of these being induction of the chemokine or chemoattractant cytokine production. Among the over 20 characterized chemokines, the 2 best-described ones are IL-8 and macrophage inflammatory protein 1α (MIP-1α). IL-8 is the representative for the α-chemokines, a class of cytokines that attracts and activates mainly neutrophils, while MIP-1α represents the β-chemokines, that attract and activate predominantly monocytes and macrophages. Chemokines play together the role to attract the immune effector cells and to induce their activation (8).
After this phase of initiation of the inflammatory process, immuno-modulatory cytokines are produced. IL-6, as a representative, but also leukemia inhibitory factor (LIF), IL-11 and oncostatin M act through multimeric receptor complexes,

exerting a variety of effects which depends on the context of activity, amount of cytokine and the stage of differentiation of the target tissues (9). For example, IL-6 may enhance T and B cells maturation, mediates the acute phase response and enhances prostaglandin secretion and the effect of chemokines.

Anti-inflammatory cytokines, such as IL-4, IL-10 and transforming growth factor β (TGF β), with its many species, mediate the resolution of inflammation. Originally termed "cytokine synthesis inhibitory factor", IL-10 essentially acts by turning off the gene promoters for the most if not all of the proinflammatory cytokines, including IL-1, TNF-α, IL-6 and IL-8. IL-10 and TGF β are critical both to the normal healing and the normal evolution of pregnancy (10, 11).

The role of inflammatory cytokines in the pathogenesis of preterm labor is supported by the studies in the amniotic fluid, in vivo and in vitro gestational tissues and animal models.

Elevated amniotic fluid titers of many cytokines including IL-1β (12), TNF-α, IL-6, IL-8, MIP-1α, and IL-4 (13), have been associated with infection-induced preterm labor, while the findings about IL-10 concentration are controversial.

Gestational tissues are other important sources of cytokines at the feto-maternal interface level, producing a wide variety of cytokines after stimulation by bacterial products or pro-inflammatory cytokines.

Both explants and monolayer cultures of maternal decidua have been demonstrated to produce IL-1, TNF-α, IL-6, IL-8, and MIP-1α (14). Although it is difficult to extrapolate the in vitro data, it has been noted that decidual cells produce only relatively small amounts of IL-10 (15).

Similarly, fetal chorionic cells have been reported to produce important quantities of IL-6, IL-8, and MIP-1α, as a response to IL-1, TNF-α, and certain bacterial products as lipopolysaccharide. IL-10 is also produced in small amounts and only as a response elicited by the lipopolysaccharide. Conversely, amniotic cells supply only small amounts of IL-8 and other cytokines, but they have been demonstrated to produce more arachidonic acid metabolites than inflammatory cytokines.

The production of arachidonic acid metabolites by gestational tissues as a response to pro-inflammatory cytokines actually represents the key link from cytokine cascade to preterm labor and birth. IL-1β, TNF-α and IL-6 elicit production of the powerful uterotonic prostaglandin E_2 by the human gestational tissues, including decidua chorion and amnion, thus inducing the preterm birth.

Investigation of tissues obtained from women experiencing preterm labor and birth revealed that messenger ribonucleic acid of inflammatory cytokines including IL-1β, TNF-α, IL-6 and IL-8 could easily be isolated from chorion and decidua, regardless of the presence of infection (17), while IL-10 messenger ribonucleic acid was not found so universally (15).

Studies on animal models (mice, rabbits and primates) have demonstrated consistent results. Moreover, the

attempt to stop labor by using immunotherapeutic agents was with no effect, suggesting that after the cytokine cascade has been initiated the normal inhibitory influences on the inflammatory process are not efficient.

PRETERM LABOR AS AN INTRAUTERINE INFLAMMATORY RESPONSE SYNDROME

This concept suggests that certain cases of preterm labor represent an abnormally regulated maternal immune response to a bacterial stimulus, which otherwise may be relatively harmless in a normal host. When the normal regulation of the inflammatory process is aberrant or inadequate, pro-inflammatory cytokines are produced in excess and anti-inflammatory cytokines are not or insufficiently produced. Thus, the intrauterine inflammatory response syndrome encompasses the setting of preterm labor that may be caused by an undiagnosed intrauterine infection or a dysfunction of the maternal immune response.

Several aspects can be noticed from the above statements:

- Cytokines themselves do not cause preterm labor, but actively mediate the maternal response to an inflammatory stimulus;
- Human gestational tissues produce cytokines and they seem to be prone to make more pro-inflammatory than anti-inflammatory cytokines, but it is not known which are the adequate concentrations for the last ones to regulate the process;
- Maternal gestational tissues are constantly in contact with vaginal bacterial flora, but only few women have preterm birth, because the maternal immune response, rather than the infection, mediates the preterm labor.

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