DELETERIOUS EFFECTS OF INFLAMMATION ON PARTURITION AND FETAL DEVELOPMENT

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ABSTRACT

Preterm birth is a major determinant of neonatal mortality and morbidity worldwide. One of the main causes of preterm parturition is maternal infection Dissemination of microorganisms from the vagina and cervix via the ascending route is the preponderant way of infection, although microorganisms may also access the amniotic cavity and the fetus via other pathways.

The pathophysiological processes that are set in motion during maternal infection lead to preterm labor and fetal damage with severe consequences both for the mother as well as the offspring. During inflammation associated to infection, a plethora of pro-inflammatory agents are produced in high levels. Thus, prostaglandins are released simultaneously with nitric oxide and their overproduction promotes uterine contractions contributing to embryonic and fetal expulsion. Oxygen and nitrogen reactive species and pro-inflammatory cytokines have been associated with preterm birth as well as fetal damage and they might contribute to the high mortality and morbidity associated with preterm labor.

The study of these pathophysiological processes is necessary to develop better tocolytic agents. Therefore, it is essential to establish good animal models of infection-induced preterm labor that would mimic the human parturition biology.

Keywords: pregnancy; preterm birth; infection; inflammation; fetal damage.

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Introduction

Preterm birth is defined as childbirth occurring before week 37 of gestation is completed and is a major determinant of neonatal mortality and morbidity worldwide [1]. According to the World Health Organization (WHO), an estimated 15 million babies are born prematurely every year. Preterm birth (PTB) affects mainly Sub-Saharan Africa and South Asia, accounting for over 60% of the cases worldwide. In Latin America and the Caribbean region, PTB occurs in 8.1% of all pregnancies [2]. This is not, however, a problem only of the low- to middle-income countries, since it has been documented an increase in PTB rates over the past 20 years in industrialized countries [2].

Preterm birth may result from either spontaneous developments or medically indicated interventions. Known causes of spontaneous preterm labor include infection (intrauterine or extrauterine), multiple gestation, placental abruption, hormonal disruptions and other factors, though a large proportion of preterm births are 'idiopathic', or without known cause [3].

The risk of death of a premature newborn is 120 times folds higher that of a baby born at term [4]. Excluding congenital malformations, premature birth accounts for approximately 70% of all neonatal deaths and results in nearly 50 percent of long-term neurological problems [5]. Sequelae of preterm birth are common in the neonatal period, may persist into adulthood and are inversely related to gestational age. Preterm babies are at risk of short-term morbidity due to various causes (diseases of the respiratory syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, retinopathy of prematurity) and long term morbidity, for conditions such as cerebral palsy, learning disabilities, blindness and respiratory diseases [6].

Maternal intrauterine inflammation has been strongly associated with preterm parturition [7]. Intrauterine inflammation/infection leads to a systemic inflammatory condition in the fetus called fetal inflammatory response syndrome (FIRS), characterized by an increase in pro-inflammatory cytokine levels [8] with maternal infection accounting for at least 25-40% of spontaneous PTB [3]. Intrauterine inflammation associated with premature birth, premature rupture of fetal membranes or placental inflammation has been linked to adverse neurological outcomes for ex-preterm children; like periventricular leukomalacia or cerebral palsy [9] as well as with other neuropsychiatric conditions such as cognitive dysfunction and behavioral deficits, schizophrenia and even autism [10-12]. However, it remains unclear whether these adverse neonatal outcomes are due to preterm birth or to prenatal inflammation.

Although survival rates of premature babies have improved in the last decades, the rates of morbidity are still high. Approximately 90% of infants born before week 30 of gestation show abnormalities in brain magnetic resonance which might be translated later in life in adverse cognitive and behavioral outcomes. Moreover, the risk of cerebral palsy is 70 times higher in these newborns than those born at term [13]. In addition to this enormous waste of human potential, the monetary cost is estimated at tens of billions of dollars annually, including the impact of neonatal intensive care, long-term cost recovery,

educational programs, special social assistance, institutional care and other services for survivors with disabilities and their families.

Parturition is the process involving changes in gestational tissues that results in birth as well as the events in the maternal, placental and fetal compartments that lead to these changes. The precise biomolecular mechanisms, by which human parturition is initiated spontaneously, either at term or preterm, are not well understood.

The current therapeutic approaches are directed toward stopping premature labor when it is started and they have generally been unsuccessful.

A better understanding of the mechanisms that regulate the onset of labor may enable the development of new strategies for early diagnosis, treatment or even prevention of preterm birth and neurological consequences.

Maternal immune system and pregnancy

Mammalian pregnancy represents a singular challenge for the maternal immune system: it must ensure tolerance to accept the semi-allogeneic embryo while maintaining immune reactivity against potential infections in order to protect both the mother and the fetus [14]. Several changes take place at the feto-maternal interface, particularly a shift in cytokine pattern. Pregnancy has been associated with a Th2 phenomenon. This shift from type 1 to type 2 cytokine production during pregnancy is necessary since type 1 cytokines (e.g. IL-1β, IFN-γ and TNF-α) are potentially harmful because they inhibit embryonic and fetal development [36].

Interestingly, it has been shown that the innate immune system is activated during pregnancy.

In spite of the mechanisms present in the feto-maternal interface to prevent infection, some microorganisms are able to breach the placental barrier and/or reach the amniotic cavity leading to an intense inflammatory response in the fetus (FIRS) which has been associated with PTB [3, 8, 14].

Bacterial infections of pregnant women, fetus and newborn represent major problems in obstetric and perinatal care. Maternal infection is strongly related to the loss of pregnancy, including fetal abnormalities, stillbirth, premature labor, premature rupture of membranes and miscarriage. Infectious agents can reach the feto-placental compartment via five different pathways **(Figure 1)**: 1) ascending from the vagina and the cervix; 2) hematogenous dissemination through the placenta (transplacental infection); 3) retrograde seeding from the peritoneal cavity through the fallopian tubes; and 4) accidental introduction at the time of invasive procedures such as amniocentesis, percutaneous fetal blood sampling, chorionic villous sampling, or shunting; 5) contaminated food or mouth infections [15]. The most frequently way of microorganisms to access the uterus is ascending from the vagina and cervix. Ascending infections extends to the choriodecidual space and may ultimately invade the membranes, amniotic fluid, and fetus [12].

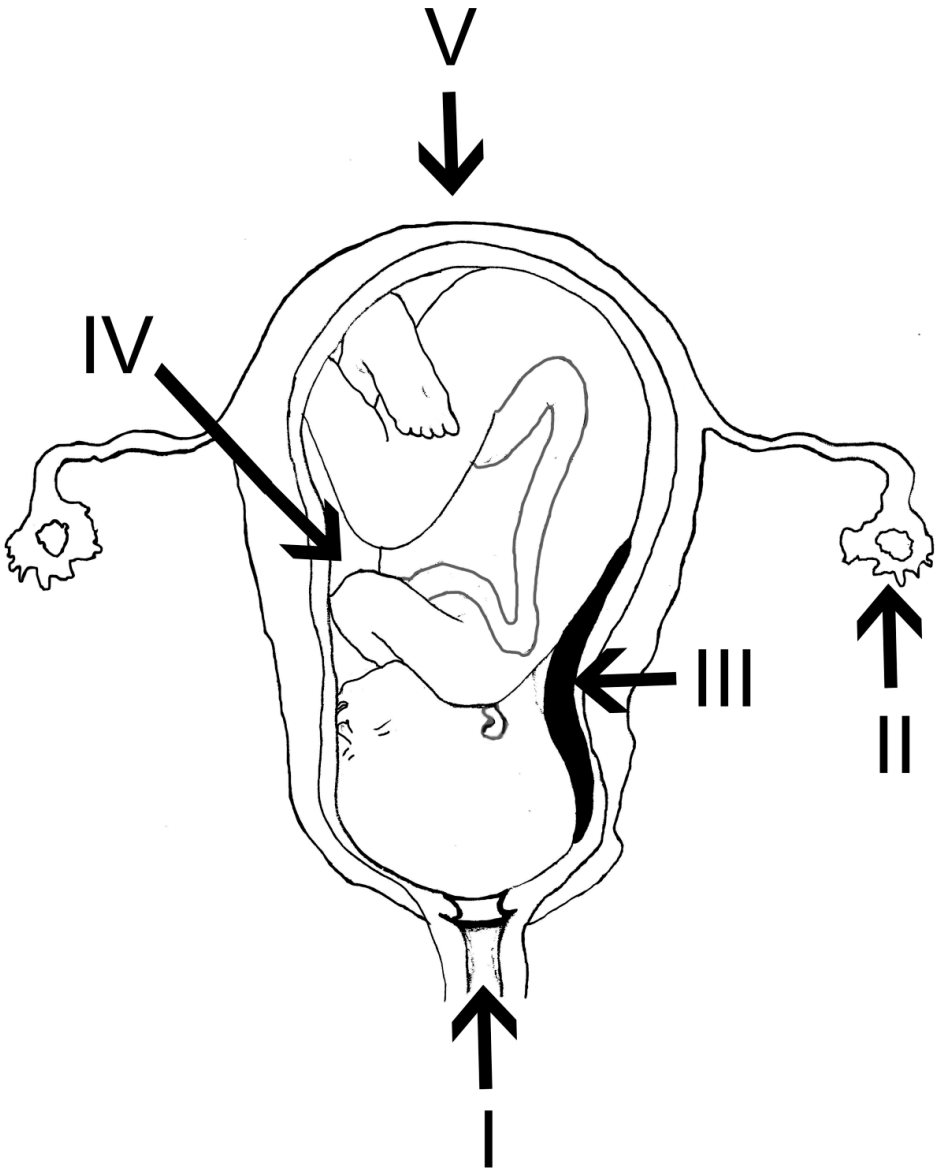

Figure 1. Pathways via which infectious agents can reach the feto-placental compartment: I) ascending from the vagina and the cervix; II) retrograde seeding from the peritoneal cavity through the fallopian tubes; III) hematogenous dissemination through the placenta (transplacental infection); IV) accidental introduction at the time of invasive procedures such as amniocentesis, percutaneous fetal blood sampling, chorionic villous sampling, or shunting; and V) contaminated food or mouth infections.

Several studies support the notion that bacterial vaginosis, the abnormal bacterial colonization of the vagina, is strongly associated with preterm delivery. Due to an interruption in normal vaginal flora, there is an imbalance in the normal vaginal flora, with a reduction in lactobacillus and an overgrowth of other anaerobic bacteria such as gardenerella, bacteroides, and mobiluncus, all vaginal organisms of relatively low virulence [16].

After changes in vaginal and/or cervix flora, microorganisms ascend into the choriodecidual space. From there, microorganisms are able to migrate between the chorion and amnion and infect the intrauterine cavity with some of the fetuses ultimately becoming infected. However, only a small number of the preterm-delivered fetuses have positive blood or cerebrospinal fluid cultures at delivery, being this condition the most advanced and serious stage of ascending intrauterine infection [3].

As mentioned earlier, prenatal infection and inflammation are the main causes of preterm labor and constitute a risk factor for the later development of cerebral palsy and neonatal sepsis [17]. Exposure to lipopolysaccharide (LPS) has been associated with a variety of lesions in the white matter of the developing brain of the newborn [18], such as periventricular leukomalacia, a condition associated with the development of cerebral palsy, and diffuse lesions in the white matter, the most common brain abnormality associated with adverse neurological development [19]. Even the exposure to low doses of LPS, insufficient to induce parturition, has been shown to induce white matter damage in the developing brain, with adverse long-term outcomes [9].

Maternal innate immune system activation and premature cervical remodeling

Once microorganisms have colonized cervical, uterine and/or amniotic structures, several signaling pathways are initiated, which can either individually or collectively promote preterm parturition. First, bacteria or even bacterial by-products, such as LPS, are detected by immune system pattern recognition receptors, specifically the toll-like receptors (TLRs) [20].

Uterus, cervix, amniotic epithelium, and the decidua abundantly express TLRs, in particular TLR-2 and TLR-4 [14] **(Figure 2)**. When TLRs detects bacteria or bacteria products, they activate several immune pathways, triggering an inflammatory response mediated primarily by pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α) and IL-6, prostaglandins and nitric oxide (NO).

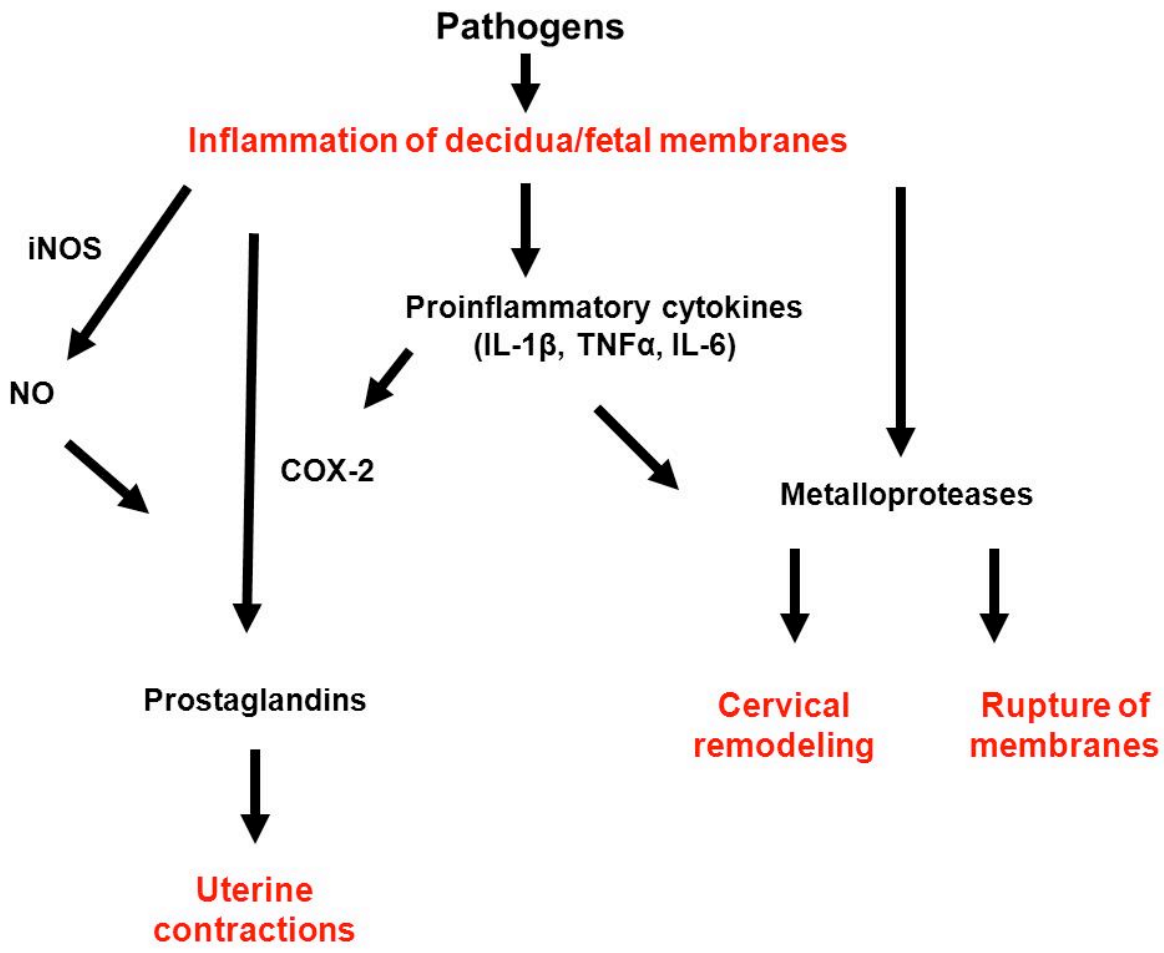

Figure 2. Molecular pathways involved in premature labor.

LPS-induced production of NO has been associated with increased uterine prostaglandin (PG) synthesis in a murine model of preterm labor [21]. Interestingly, NO production was found to have a dual effect on PG synthesis, with low concentrations of NO downregulating PG synthesis and higher concentrations increasing PG levels [21]. The secretion of pro-inflammatory cytokines, such as IL-1β and TNF-α, by gestational tissues in response to bacterial products has been associated with the pathological process of infection-induced rupture of fetal membranes [22]. Moreover, these cytokines may stimulate the biosynthesis of IL-6 by decidual cells, which is considered a responsive indicator of intrauterine infection in pregnant women [23].

The increased expression of pro-inflammatory cytokines induces the augmentation of matrix metalloproteinases (MMP) production [24]. These changes contribute to increased enzymatic degradation of the extracellular matrix within the uterine cervix [25].

Furthermore, IL-1β and TNFα have been also shown to upregulate cyclooxygenase (COX)-2 activity, therefore increasing PGE2 production and promoting cervical maturation [26].

Considering that many cell types synthesize the inflammatory mediators, it becomes difficult to identify precisely their origin during preterm labor. It has been suggested that the infiltration of leukocytes such as neutrophils, macrophages, monocytes, and T and B lymphocytes to the choriodecidual tissue immediately before the initiation of labor is associated with increased the levels of cytokines IL-1β, IL-6, IL-8, and TNFα, leading to the establishment of the inflammatory microenvironment during parturition [27].

All these molecules acting in concert induce a complex response involving uterine contractions, placental detachment, infiltration of inflammatory cells into gestational tissues, a series of biochemical and structural changes in the cervix known as 'ripening' and weakening of the fetal membranes. Cervical remodeling can be considered as a continuous process divided in four overlapping phases: softening, ripening, dilation and labor and pospartum repair [28]. Cervical integrity and the correct timing of cervical remodeling are essential for maintaining pregnancy. It has been shown that pro-inflammatory cytokines disrupt the cervical epithelial barrier, thus inducing an earlier cervical remodeling that eventually leads to preterm birth [29]. Thus, it has been suggested that measurement of fetal fibronectin (as a parameter of membrane degradation) and surfactant protein-D (as measurement of intrauterine inflammation) could be used a potential markers of greater risk of preterm birth [30].

Hösli et al. [31] have recently reviewed the use of tocolysis to prevent preterm labor. According to these researchers, calcium antagonists and oxytocin receptor antagonists seem to have a better neonatal outcome than beta-sympathomimetics with yet not enough data regarding the potential usefulness of prostaglandin synthesis inhibitors and nitric oxide donor drugs as tocolytic agents [31]. An ideal tocolytic agent should prevent preterm birth; improve neonatal outcome with few or non maternal, fetal and neonatal side effects and without any long-term side effects [32]. Therefore, an ideal tocolytic agent should be able to modulate maternal innate immunity without suppressing it. Intriguingly, neither vaginal progesterone nor 17 α-hydroxyprogesterone caproate, two regularly used drugs to prevent preterm birth in high-risk populations, have been shown unable to upregulate mucosal immunity, collagen content or the number of immune cells in the cervix of treated mice, suggesting that these compounds prevent preterm birth by different and still unknown mechanisms [33]. Paradoxically, it has been recently shown that blocking IL-1 receptors might prevent fetal brain damage but not preterm parturition [34], suggesting that the mechanisms governing preterm labor are still not fully understood. A recent work by Domínguez-Rubio et al. [35] has shown that treatment with melatonin prevented preterm parturition in 50% of the cases in an LPS-induced murine model of preterm labor. Interestingly, melatonin treatment not only reduced TNFα, prostaglandin E2 and prostaglandin F2α levels, decreased COX-2 and iNOS protein expression and NOS activity but also protected the fetuses from LPS-induced damage even in the cases in which preterm labor was not prevented [35]. Therefore, there is still much to learn about the molecular mechanisms involved in inflammation-induced preterm labor in order to design the ideal tocolytic agent.

Maternal inflammation and the developing brain

Several studies have shown that maternal exposition to LPS during late gestational stages lead to fetal death, growth restriction and preterm birth [19]. The central nervous system development is a fine tuned process in which each brain area develops at its own pace. Therefore, any perturbation at a given point will result in a functional deficit of a certain brain area with a concomitant development of a neuropsychiatric disorder later on in life. Thus, maternal infections during the second trimester have been suggested to alter the migration of post-mitotic neurons from the subventricular zone to the neocortex [36]. Both the inflammation-induced neuronal damage as well as the interference on the normal pattern of migration of the newly born neurons led to an aberrant cortical development [36]. In a similar fashion, it has been reported that maternal administration of LPS induces alteration in the developing brain cytoarchitecture of mice [37] and rabbits [38]. The increased expression of pro-inflammatory cytokines is critical during this developmental stage since it could provoke not only alterations in the cerebral cytoarchitecture, but damage in mature oligodendrocyte subpopulations (which are extremely sensitive to injuries) and activation of white matter ameboid microglia, thus propagating and perpetuating the inflammatory process [37, 38]. The perpetuation of the inflammatory response contributes to the brain damage observed in leukomalacia and affects behavioral and cognitive capacities later on in life. Meyer et al. [11] reported that maternal immune challenge exerts different effects on the fetal brain depending on the gestational stage of the pregnancy. Thus, maternal immune stress during midterm pregnancy led to an offspring with lesser exploratory activity; whereas a maternal immune challenge during late pregnancy was associated altered behavioral patterns related to schizophrenia, autistic spectrum disorders, obsessive-compulsive disorders and addictive behavior [11].

Local intrauterine inflammation is responsible for an overexpression of pro-inflammatory cytokines that causes significant fetal brain injury including reactive gliosis, loss of different subpopulations of olygodentrocytes and neuronal damage [8, 9]. Similarly, Sharangpani et al. [39] have reported an increased caspase activity and a higher number of apoptotic bodies in the fetal brain of rats exposed to an intrauterine inflammation model. In this model, the authors also showed a secondary damage in the white matter produced by the overexpression of cytokines and other pro-inflammatory factors by activated resident astrocytes and microglia, contributing to worsen the initial damage [39].

The molecular events that take place at the feto-maternal interface after LPS stimulation are not fully understood, but it has been shown that the excessive production of oxygen and nitrogen reactive species (reviewed in [40]) as well as the presence in the amniotic fluid of high levels of pro-inflammatory cytokines, such as TNFα, IL-1β or IL-6 are associated with higher risks of developing leukomalacia or cerebral palsy [41]. In this sense, Leitner et al. [34] have recently shown that blocking IL-1 receptor prevented fetal cortical brain injury but not preterm birth. As mentioned earlier, this intrauterine inflammation associated to preterm birth, placental inflammation or premature rupture of the fetal membranes can trigger a generalized inflammatory response in the fetus, known as Fetal

Inflammatory Response Syndrome or FIRS. FIRS has been associated with the development of periventricular leukomalacia in premature newborns which leads to motor and cognitive deficits in these children (reviewed in [19]). Moreover, it has been described the presence of hypertrophic astrocytes and activated microglia, considered markers of white matter damage, in the autopsies of premature newborns.

The neuroinflammatory events that initiate during fetal development could continue during the extrauterine life, as suggested by observation of necropsies of patients suffering from periventricular leukomalacia and austistic spectrum disorders [42]. This constant microglial activation perpetuates the damage by a series of mechanisms: continuous production of pro-inflammatory cytokines, cytotoxic metabolites such as glutamate and quinolinic acid (which are cytotoxic to olygodendrocytes), oxygen and nitrogen reactive species and arachidonic acid derivatives (reviewed in [19]). Since olygodendrocytes exhibit low tolerance to oxidative stress and they express calcium-permeable glutamate receptors, these cells are extremely susceptible to neuroinflammatory processes. Damaged olygodendrocytes are the main source of deposits of myelin and aberrant proteins which contribute to neuroinflammation and cognitive deficits observed in periventricular leukomalacia and cerebral palsy patients [19]. Similarly, intrauterine inflammation can affect the developing brain by other mechanisms such as cerebral hypoperfusion, which leads to a hypoxic-ischemic damage and the production of pro-inflammatory cytokines [43]. All these mechanisms contribute to development of periventricular leukomalacia which is characterized by multiple and small foci of necrosis.

As shown by Elovitz et al. [9], even lower levels of intrauterine inflammation, which do not induce parturition, are still able to produce fetal and neonatal brain damage. Several epidemiological studies have found a strong correlation between maternal infection during mid and late-term pregnancy and a higher risk for the offspring to suffer from schizophrenia or autistic spectrum disorders [42]. In this sense, preclinical studies using LPS as a model of bacterial infection or Poli I:C as a model of viral infection have been consistent in showing an association between maternal infection and development of mood disorders in the offspring. Thus, Lin et al. [44] reported that LPS-treated rats during midterm pregnancy induced in the offspring the development of anxiety disorders and an elevated response to stress in adulthood. In the same line, Hao et al., [45] found that maternal treatment with LPS produced an offspring with delayed cognitive maturity, altered hippocampal with augmented astrogliosis and reactive microglia. Similar studies have determined that maternal administration of LPS produced behavioral changes such as higher levels of anxiety and lower levels of social interaction [46], altered response to pre-pulse inhibition test [47], object recognition memory [48] and spatial memory [49] in adult mice. In fact, many of this deficits and disorders can be detected very early on, as shown by Baharnoori et al. [50], who have reported alterations in the neonatal behavior of the offspring of rats treated with LPS. These pups showed altered nest-searching behavior, olfactory memory and a lower ultrasonic vocalization [50]. These findings provide strong evidence that maternal inflammation induces important modifications in the normal nervous system development of their offspring and that these pathological changes can be detected as behavioral alterations very early on in life.

Conclusions

Preterm birth is a serious health issue with heterogeneous precipitating events that affects worldwide. Maternal infection is one of main causes of preterm labor with serious sequelae in the newborn and long-term disabilities in the adulthood of ex-preterm infants.

During inflammation associated to infection, the maternal immune system is over-activated and a large number of pro-inflammatory mediators are produced. Pro-inflammatory cytokines are expressed in high levels and they have been shown to damage the fetus and to be toxic for the normal nervous system development. Prostaglandins are released simultaneously with NO and their overproduction promotes uterine contractions contributing to embryonic and fetal expulsion. NO and other oxygen and nitrogen reactive species also contribute to the onset of preterm labor as well as fetal damage. Collectively, these pro-inflammatory mediators contribute to the high mortality and morbidity associated with preterm labor.

The search of better tocolytic agents should be a priority in preterm labor research, particularly ones that would not only prevent preterm parturition but would also protect the fetus. Therefore, it is essential to develop good animal models that would mimic human parturition biology, despite their limitations, in order to answer specific questions related to prematurity and to describe the pathophysiological events associated with preterm birth that will contribute to the development of rational and efficacious treatment and prevention strategies for preterm birth.

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Conflict of interest

The authors have declared that no conflict of interests exists.

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