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*Published in:*  
Journal of Reproductive Immunology

*DOI:*  
[10.1016/j.jri.2018.01.004](https://doi.org/10.1016/j.jri.2018.01.004)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2018

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Prins, J. R., Eskandar, S., Eggen, B. J. L., & Scherjon, S. A. (2018). Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment? *Journal of Reproductive Immunology*, 126, 18-22. DOI: 10.1016/j.jri.2018.01.004

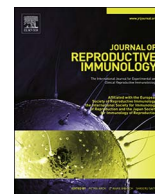
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# Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment? ☆

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## ARTICLE INFO

### Keywords:

Microglia  
Macrophages  
Pregnancy  
Preeclampsia  
Maternal immune activation (MIA)

## ABSTRACT

Disturbances in fetal neurodevelopment have extensively been related to neurodevelopmental disorders in early and later life. Fetal neurodevelopment is dependent on adequate functioning of the fetal immune system. During pregnancy, the maternal immune system is challenged to both tolerate the semi-allogenic fetus and to protect the mother and fetus from microbes. The fetal immune system is influenced by maternal immune disturbances; therefore, perturbations in maternal immunity likely do not only alter pregnancy outcome but also alter fetal neurodevelopment. A possible common pathway could be modulating the functioning of tissue macrophages in the placenta and brain.

Maternal immune tolerance towards the fetus involves several complex adaptations. In this active maternal immune state, the fetus develops its own immunity. As cytokines and other players of the immune system -which can pass the placenta- are involved in neurodevelopment, disruptions in immune balance influence fetal neurodevelopment. Several studies reported an association between maternal immune activation, complications of pregnancy as preeclampsia, and altered neonatal neurodevelopment. A possible pathway involves dysfunctioning of microglia cells, the immune cells of the brain. Functionality of microglia cells during normal pregnancy is, however, poorly understood. The recent outbreak of ZIKA virus (ZKV), but also the literature on virus infections in general and its consequences on microglial cell function and fetal neurodevelopment show the devastating effects a virus infection during pregnancy can have.

## 1. Introduction

Appropriate neurodevelopment is dependent on adequate and timely functioning of fetal immune cells within the central nervous system (CNS). Ample evidence suggests that an appropriate interaction between the maternal and fetal immune systems influences embryonic and fetal neuroimmunology, fetal neurodevelopment, and thereby postnatal neurodevelopment and cognitive function.

During pregnancy, the maternal immune system is carefully regulated to tolerate the semi-allogenic fetus. Factors known to influence the maternal immune response during pregnancy are direct factors as infections and environmental circumstances (smoking, nutrition, stress), characteristics of the mother such as obesity, and specific pregnancy related pathology as pre-eclampsia and placental

insufficiency. Collectively, these factors occur frequently in pregnant women and they have been extensively linked to neurodevelopmental disorders. For example, maternal viral infection during pregnancy has been implicated in the occurrence of neurodevelopmental problems (Atladdottir et al., 2009; Patterson, 2009; Atladdottir et al., 2010; Brown et al., 2014; Lee et al., 2015). Similarly, systemic inflammatory responses related to preeclampsia (Walker et al., 2015) or related to maternal body mass index (Gardner et al., 2015) have also been implicated in abnormal neurodevelopment.

The resident immune cells of CNS are microglia, which besides their roles in tissue inflammation and clearance of debris are key players in the orchestration of synaptic connections. Specifically, they are involved in removing faulty and unnecessary synapses, and this synaptic pruning is relevant both during fetal development (Paolicelli et al.,

☆ This review is partly based on a presentation given at the 10th Reunion International Workshop on Reproductive immunology: 5–8 December, 2016.

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2011) and in postnatal life (Schafer et al., 2012). Their role in pruning and synaptic network formation is more prevalent during late gestation and early postnatal development, whereas the immune function of microglia -their CNS macrophage phenotype- is acquired later during life (Matcovitch-Natan et al., 2016). As a result, microglia dysfunctioning has been suggested to contribute to neurodevelopmental disorders including schizophrenia (Matcovitch-Natan et al., 2016; Sekar et al., 2016) and autism spectrum disorder (ASD, reviewed in Koyama and Ikegaya (2015)). The exact mechanisms and maternal-fetal interactions contributing to neurodevelopment are unclear.

## 2. Methods

A literature search was performed in PubMed for the published literature on immunology during pregnancy, fetal immune priming, neuro development, microglia, macrophages, and neuro-immunity. Relevant articles were identified by searching for keywords as; immune system, fetal programming, fetal immune programming, fetal immunity, immune function, placenta, priming, neurodevelopment(al), neuro-immune, preeclampsia, and pregnancy. Additional studies were identified by the analysis of reference lists. Data from these studies were analyzed, interpreted and were presented in this review.

## 3. Results

### 3.1. The maternal immune system during pregnancy is well orchestrated to optimize pregnancy outcome

The exact mechanisms that regulate the maternal immune system during pregnancy are complex and not within the scope of this review. In short, maternal immune regulation is influenced by genetic, environmental, paternal and fetal factors, all of which potentially modulate the maternal immune system and affect the susceptibility for pregnancy complications. Preparation for a pregnancy already start before conception including maternal immune changes, with alterations in maternal immune cells in peripheral blood and locally in the endometrial lining of the uterus during the menstrual cycle (Arruvito et al., 2007; Kallikourdis and Betz, 2007). In response to the exposure to fetal antigens via paternal semen further preparation for pregnancy is achieved (Robertson, 2005; Sharkey et al., 2007). During pregnancy many (if not all) immune cells are involved in fetal tolerance. It has been shown that regulatory T (Treg) cells are essential for the induction of maternal tolerance to fetal tissues, that these Treg are likely fetus specific (Tilburgs et al., 2008), and that depletion of Treg cells during early pregnancy in mice caused higher rates of fetal resorptions and lower implantation rates. Inadequate numbers and function of Treg cells are associated with human reproductive disorders as infertility, miscarriage and preeclampsia (Sasaki et al., 2004; Sasaki et al., 2007; Guerin et al., 2009). Also other immune cells, as dendritic cells, (uterine) NK cells, B cells, monocytes, and macrophages are all involved in fetal tolerance. Especially the latter one, macrophages might be relevant in the link between pregnancy and neurodevelopmental complications.

### 3.2. Possible vulnerability of placental and CNS macrophages for inflammatory stimuli

Different subsets of macrophages are known, which have specific roles in inflammation, infection, tissue remodelling and vascularisation (Mcgrath et al., 2015; Franken et al., 2016). Macrophages are classified by a physiological definition of macrophage subsets (Murray et al., 2014), and are implied in many diseases. After an inflammatory stimulus, macrophages switch to an inflammatory functional subset; although this switching of macrophages has beneficial short term effects, its long term tissue destructing effects are implicated in many diseases, as autoimmune diseases, cancer, heart diseases, and metabolic diseases

(Hamidzadeh et al., 2016). During pregnancy, both maternal and fetal macrophages are important. Mostly, maternal macrophages are decidua and fetal macrophages placental. Maternal macrophages are involved in placental development and have roles in placentation and vascularisation processes (Svensson-Arvelund and Ernerudh, 2015; Mori et al., 2016). There is some evidence that the balance of macrophage subsets is important for pregnancy success, and that a misbalance in maternal macrophages is involved in pregnancy complications (Schonkeren et al., 2011). Whether, this misbalance is caused by an inflammatory stimulus is not known.

Within the fetal brain, the local macrophages, or microglia, are important for synaptic plasticity by remodelling synaptic connections, tissue inflammation and clearance of debris. Especially, synaptic pruning is relevant during development and in postnatal life (Paolicelli et al., 2011; Schafer et al., 2012). Similar to other macrophages, microglia can be divided into functional subsets according to their phenotype (Kigerl et al., 2009), with the more inflammatory functional subset contributing to neurodevelopmental disorders (Hong et al., 2015; Sekar et al., 2016).

It is very interesting that contrary to other tissue macrophages, placental (fetal) and CNS macrophages develop from the embryo yolk sac directly and not through erythro-myeloid progenitors (Adhyatmika et al., 2015), this could explain the vulnerability of these macrophages for inflammatory stimuli.

### 3.3. Maternal immune disturbances influence neuro-immune development

A specific field of fetal immune development is neuro-immunity. During and after pregnancy, fetal and neonatal immunity is developing. The development of myeloid cells (macrophages, dendritic cells and microglia) is between week 4–7 of pregnancy while for lymphoid cells this is somewhat later: between 8 and 18 weeks of gestation (Vieau et al., 2007; Marques et al., 2013; Adhyatmika et al., 2015). During early pregnancy, myeloid progenitors from the primitive yolk sac colonize the neuro-epithelium and differentiate into microglia, the CNS-resident immune cells. M-CSF and CSF-1 receptors recruit microglial cells to the central nervous system (Bilbo and Schwarz, 2012). Microglia are involved in orchestration of synaptic connections, and also have an immune function, producing cytokines and express immune related (cytokine) receptors: CD11b, TNF, CCL2, MHC molecules, TLRs, ICAM, Nestin. They also produce M-CSF, CSF-1, MCP-1, CCL3, CCL6, CCL7, CX3CR1, CXCL6 (Bilbo and Schwarz, 2012). Microglial cells are especially important in the hippocampus, a region with extensive neurogenesis, which is a critical region for learning, cognition, memory and behavior. Neuronal migration of new neurons in the brain is further guided by CXCL 12 and its receptor CXCR4. NCH1 affects activity-dependent synapse formation, while TNF promotes synaptic transformation (Bilbo and Schwarz, 2012). The complement factors C1q and C3 have a role in synapse pruning by the microglia cells (Hong et al., 2015).

As it is known that cytokines affect neuronal function (reviewed in Filiano et al. (2014)), alterations in the maternal immune system most likely affect neurodevelopment of the fetus. The fetal blood brain barrier (fBBB) might be permissive for these cytokines and even for immune cells coming from the mother and passing the placenta as this fBBB is not completely functional until late in gestation or early childhood. This suggests that immune molecules are involved in behavioral outcomes, including cognition, mood, and social interactions. Indeed, there is literature, showing the involvement of diverse immune challenges during early development in neurodevelopmental and neuropsychiatric disorders (Bilbo and Schwarz, 2012). A well-known example of this is the association between maternal infection and autism in the progeny (Knuesel et al., 2014; Mattei et al., 2017). Disturbances in early fetal and neonatal neurodevelopment are related to maternal immune activation (MIA) during pregnancy (as viral and bacterial infection), both of peripheral immune cells and local immune cells in the

placenta (Estes and Mcallister, 2016). These neurodevelopmental disturbances can be both a consequence of the maternal immune activation itself, or by the pathogen directly (Estes and Mcallister, 2016).

The sometimes long latent period between the maternal immune activation and altered neurodevelopmental outcomes is not clear. A possible pathway could be through epigenetic modifications of the microglia, which could have persistent influence on their phenotype and with that on their functional development (Nardone and Elliott, 2016). Indeed a recent mouse study has shown alterations in the epigenome of microglia after maternal immune activation in a mouse asthma model (Vogel Ciernia et al., 2018). Another possible long term pathway might be via maternal microchimeric cells to the fetal brain as described below.

A possible pathway might be the role of leukemia inhibitory factor (LIF) in neurodevelopment and inflammation. It is known that LIF is involved in fetal neurogenesis (Simamura et al., 2010). LIF itself is a cytokine of the IL6 cytokine family and has some roles in inflammation (Yue et al., 2015), but more interestingly it is also blocked by other cytokines. Interestingly, in a mice model it has been shown that maternal immune activation causes a reduction in fetal LIF, and this was associated with decreased fetal neurogenesis (Tsukada et al., 2015).

Early brain development -even up to early adulthood- and in more detail neurogenesis, is characterized by extensive elimination of synapses, “pruning”, especially in the cerebral cortex. Mechanistically in these pathways the important role of (CNS) microglia cells is well established. As described above microglia cells are key immune cells in the CNS which have, besides an involvement in immune modulation and damage sensing, important functions in brain development processes, such as synapse formation and removal of cellular debris in the CNS (Wu 2016). TAM receptors (tyrosine kinases) such as (Tyro3 in neurons), Mer and Axl2 (in microglia cells) and the ligands Gas6 and protein S, are important in these, driving these crucial functions during neurogenesis (Fourgeaud et al., 2016). Direct evidence for the activation of fetal microglia after intra-uterine infection has been given by a recent paper (Mattei et al., 2017; Schaafsma et al., 2017). Pregnant mice were challenged with LPS, microglia of mice that were exposed to LPS during embryonic development displayed altered activation (Schaafsma et al., 2017), with whole brain microglia displaying a persistent reduction in pro-inflammatory activation, whereas hippocampal microglia of these mice displayed an increased inflammatory response to a LPS re-challenge (Schaafsma et al., 2017). Moreover, this paper showed that this LPS exposure negatively affects learning and behavior in the offspring.

Although microglia cells are thought to be protected by two separate barriers, both the placental and the blood-brain barrier, there are many examples, as viruses, which are able to cross one or both of these barriers, some well-known are CMV, Zika virus (ZKV), and Rubella.

In contrast to adults, the fetal blood-brain barrier might be less functional, leaving fetal brains less protected for e.g. immune cells and cytokines. In autopsy studies in adults, fetal cells have been found in maternal brains (Chan et al., 2012; Rijnink et al., 2015), suggesting that maternal cells can home into the fetal brain, we are however not aware of maternal cells found in fetal brain tissue. However homing of competent maternal immune cells in fetal tissue, other than fetal brain is well demonstrated (Aractingi et al., 1998). More in detail; it has been shown that in mice not before late pregnancy the blood brain barrier is fully restrictive to for example maternal antibodies, which potentially could cause fetal brain injury (Kowal et al., 2015). Moreover, a recent animal study provides evidence that viral infections in itself are sufficient to modulate the function of the blood brain barrier in developing fetuses (Bloise et al., 2017). Moreover, it is known that several cytokines, as well as maternal leukocytes can cross the placental barrier (Kinder et al., 2017). Therefore, it is reasonable to believe that any maternal inflammatory response, leading to altered cytokine levels and leukocyte populations will influence fetal immune cells as well both having a systemic effect on fetal immune cells and possible local effect

on brain immune cells. Especially maternal cells which are primed by an infection in a more inflammatory phenotype could have fetal consequences. Once crossing the placenta, maternal microchimeric cells, have been linked to immune development in offspring (reviewed in Kinder et al. (2017)).

In a mice model it was recently shown that maternal challenge with LPS (an inflammation model) causes altered activation of fetal microglia (Schaafsma et al., 2017). So taken together we postulate that during maternal infection fetal microglia can be activated either directly (as by some viruses), or indirectly through cytokines or maternal microchimeric cells (Kinder et al., 2017).

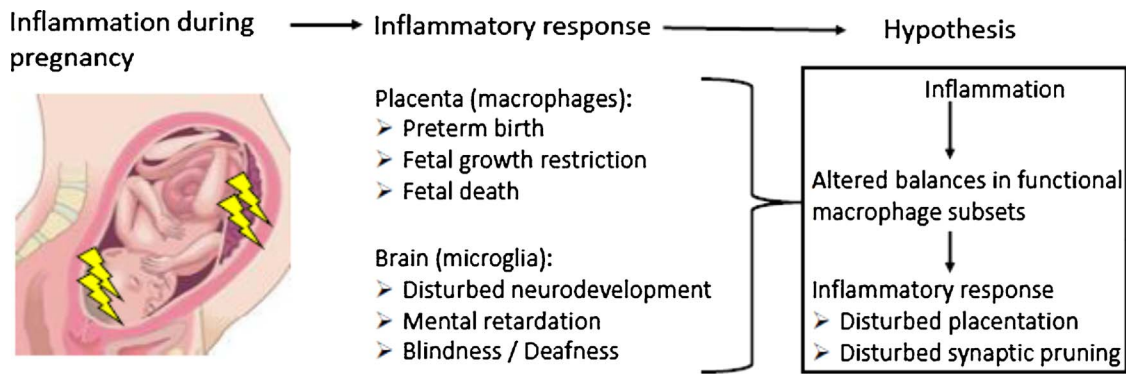
Both prenatal and postnatal influence on the function of microglia cells might be crucial to these developments, whereby microglia surveillance and thereby immune related pathways probably have important effects on synaptic function and plasticity. Acute interference with e.g. the CX3CR1- CX3CL1 pathway will stimulate microglia cells and reduces neuronal activity, while chronic reduction of the CX3CR1- CX3CL1 pathway leads to an increase in IL1 in the CNS (associated with an increase in long-term potentiation (LTP)). Also, TNF can modify synaptic strengths having opposite effects, depending on the brain region (e.g. the hippocampus and the stratum behave differently). Increase in TNF (and of TLR2 or TLR4) -and a decrease in CD200- (a more inflammatory phenotype) is associated with decreased LTP. Microglia cells that transiently express DAP12 also determine replacement during early development of NMDA receptor subunits.

The combined influence of prenatal and postnatal influence on microglia cell function has been further elaborated by the two-hit theory (Estes and Mcallister, 2016). Possibly maternal immune activation increases the susceptibility for later in life neurodevelopmental disorders (Estes and Mcallister, 2016), with a second post natal event leading to the disorder. This has been show to be involved in schizophrenia in a recent study, which showed that prenatal infection and psychological trauma in peripubertal life can act in synergy to increase the risk of schizophrenia (Debost et al., 2017).

The recent ZIKA virus (ZKV) outbreak underscored the devastating effects of a virus infection during pregnancy on neurodevelopment (Petersen et al., 2016). The worldwide presence (urban or peri-urban cycle) of Aedes as a vector makes that the disease can be spread worldwide relatively rapidly (Musso, 2015). Besides diffuse astrocytosis and activated microglia cells (and macrophages), clusters of viral like particles, morphologically consistent with characteristics of the Flaviviridae virus family, were demonstrated using electron microscopy (Makar et al., 2016). There is strong neurotropism (neuroinvasiveness and neurovirulence) as no virus was detected in other organs. The viral persistence in the brain might be because of an immunological “secure” milieu for the virus. Human embryonic neuronal progenitor cells (hNPCs) are a direct target of ZKV infection. Moreover, it has been shown that ZKV itself has an effect on microglia cells (Nowakowski et al., 2016; Lum et al., 2017; Meertens et al., 2017). In neurospheres and brain organoid models for first trimester brain development, a reduction in the growth rate and viability (30% reduction) of human brain cells was found, explaining stunted NPC growth after ZKV infection resulting e.g. in microcephaly (Garcez et al., 2016). Most important is that microcephaly might be the tip of the iceberg with possible other less severe complications affecting the (fetal/neonatal) brain development, having important effects on e.g. cognitive function. Since a direct effect of ZKV on microglia has been found, in case of ZKV both the effect of ZKV itself as well as possibly the maternal immune activation could cause the disturbances in neurodevelopment.

#### 3.4. Immune based complications of pregnancy, as preeclampsia, and neurodevelopment

The maternal immune system is involved in several complications of pregnancy as preterm birth, fetal growth restriction and preeclampsia. Interestingly, especially the latter one, preeclampsia, has been linked to



**Fig. 1.** During inflammation in pregnancy both placental and CNS macrophages switch to an inflammatory functional subset; although this switching of macrophages has beneficial short term effects, its long term tissue destructing effects lead to disturbed placentation and disturbed synaptic pruning.

neurodevelopmental problems as neurodevelopmental delay and autism (Whitehouse et al., 2012; Walker et al., 2015; Warshafsky et al., 2016). The mechanisms between this correlation have not been clarified yet. However, it is tempting to speculate that the inflammatory immune response as seen in preeclamptic women have similar consequences on microglia as maternal immune activation as described above, and with that influence fetal microglia stability. Especially since an inflammatory response during pregnancy has been linked to altered microglia function (Schaafsma et al., 2017). Indirect evidence for the relation between preeclampsia and microglia fetal alteration comes from a rat study (Johnson et al., 2014). In this study a rat model was used combining the reduced uteroplacental perfusion pressure model of placental ischemia with a high cholesterol diet (Johnson et al., 2014). Although this study showed more activation of maternal microglia compared to control pregnant rats (Johnson et al., 2014), no data on fetal microglia was shown. This effect is preeclampsia specific and not pregnancy related, as an earlier study showed no effect from pregnancy itself on microglia activation (Johnson et al., 2015).

As preeclampsia is often accompanied by fetal growth restriction, and also (iatrogenic) preterm birth, it is difficult to fully clarify the pathways. Interestingly, any disturbance of fetal neurodevelopment due to preeclampsia could even further dysregulated by breastfeeding as, as studies have shown that women with preeclampsia have altered levels of milk neurotrophins, which have a role in neurodevelopment (Dangat et al., 2013). This is however hypothetical, and is (most possibly) by far outweighed by the beneficial effect of breastfeeding.

**4. Conclusions**

During pregnancy, fetal neurodevelopment is vulnerable for any disturbances, most possibly also for disturbances of the maternal immune regulation and environmental perturbations, disrupting fetal neurodevelopment. The recent outbreak of ZKV and its consequences on fetal neurodevelopment shows the devastating effects of an environmental influence -such as a viral infection- during pregnancy -most possibly via an effect on fetal immune development- can have. A possible link between both pregnancy complications and disturbed neurodevelopment could be caused by perturbed function of placental and CNS macrophages (microglia) (Fig. 1). However, more research is needed to delineate the causal underpinnings of neurodevelopmental disorders and neuroinflammation during fetal development.

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