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Review Article

The Role of the Immune System on Fetal Development: A Scientific Review

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Abstract

Fetal development is profoundly influenced by complex immunological interactions occurring at the maternal-fetal interface and within the developing fetus itself. The immune system plays dual roles during pregnancy: maintaining maternal-fetal tolerance while protecting against pathogens, and directly participating in organogenesis and tissue development.

This review examines the establishment of fetal immune populations, mechanisms of maternal-fetal immune tolerance, the role of immune factors in normal development, and the consequences of immune dysregulation. Maternal immune activation (MIA) can disrupt these finely balanced processes, leading to long-term neurodevelopmental, metabolic, and immune alterations in offspring. Understanding these immunological mechanisms is crucial for developing preventive and therapeutic strategies for pregnancy complications and offspring health outcomes.

Keywords: *Maternal Immune Activation (MIA); Fetal Development; Maternal-Fetal Immune*

Introduction

The immunological relationship between mother and fetus represents one of the most remarkable biological phenomena, requiring a delicate balance between tolerance and protection [1]. The developing fetus expresses paternal antigens, making it semi-allogeneic to the maternal immune system, yet pregnancy typically proceeds without rejection [2]. This paradox is resolved through sophisticated immune regulatory mechanisms at the maternal-fetal interface [3].

Recent evidence demonstrates that immune factors serve pathogen-independent developmental functions in the embryo and fetus, particularly in neurodevelopment [1]. The fetal immune system is not merely immature or deficient but possesses unique functional characteristics tailored to support growth and prepare for postnatal life [4]. Perturbations of maternal immunity during critical developmental windows can have profound and lasting effects on offspring health, influencing susceptibility to neurodevelopmental disorders, allergies, and metabolic diseases [5,6].

Development of the fetal immune system

Hematopoietic waves and immune cell origins

The fetal immune system develops through spatiotemporally coordinated waves of hematopoiesis [4]. In humans, early hematopoietic cells emerge in the extraembryonic yolk sac around 4 weeks post-conception, giving rise to primitive macrophages, mast cells, natural

killer (NK) cells, and innate lymphoid cell (ILC) progenitors [4]. Concomitantly, definitive hematopoietic stem cells (HSC) capable of lifelong blood cell production are generated in the intraembryonic aorta-gonad-mesonephros region [4].

Developmental stage	Hematopoietic site	Key cell types
4 weeks post-conception	Yolk sac	Macrophages, mast cells, NK cells
6-9 weeks	Fetal liver	HSC expansion, erythromyeloid cells
11-12 weeks	Bone marrow	Long-term HSC, B cells, neutrophils
6-9 weeks onward	Thymus	T cell development

Table 1: *Timeline of fetal hematopoietic development in humans [4].*

Between 6 - 9 weeks, yolk sac and AGM-derived progenitors seed the fetal liver, which becomes the major hematopoietic organ during fetal development [4]. The fetal liver supports active erythromyeloid hematopoiesis and HSC expansion throughout gestation. Subsequently, fetal liver-derived HSC colonize the bone marrow at 11 - 12 weeks, establishing it as the site of lifelong postnatal hematopoiesis [4].

Establishment of tissue-resident immune populations

A critical feature of fetal immune development is the establishment of tissue-resident immune populations that persist throughout life [4]. Tissue-resident macrophages, including brain microglia, epidermal Langerhans cells, and alveolar macrophages, originate from embryonic precursors and exhibit self-renewal capacity independent of bone marrow-derived monocytes [4].

Microglia, the resident macrophages of the central nervous system, colonize the developing brain early in gestation [1]. In humans, microglia are detected near neural tissue by 4.5 weeks gestation and within neural tissue by 5.5 weeks [4]. These cells derive from yolk sac erythromyeloid progenitors and establish themselves before maturation of the blood-brain barrier, which becomes impermeable to further immune cell seeding around 8 weeks in humans [4].

Fetal lymphoid populations also display unique characteristics. B-1 B cells, considered part of the innate immune system, spontaneously secrete antibodies with limited specificity, conferring immediate but nonspecific immune protection [4]. Fetal T cells appear in peripheral tissues during the second trimester with memory phenotypes and clonal diversity, particularly in mucosal sites like the intestine [4].

Functional maturity of fetal immune cells

Contrary to traditional views of fetal immune deficiency, recent evidence reveals surprising functional maturity in specific tissue compartments [4]. In the fetal intestine at 13 - 23 weeks gestation, clonally expanded CD4+ T cells with memory phenotypes are present and capable of producing pro-inflammatory cytokines upon stimulation [4]. These cells support intestinal stem cell growth and epithelial development through TNFα production [4].

Fetal lung NK cells, though less differentiated than adult peripheral NK cells, express multiple killer immunoglobulin-like receptors and intracellular perforin and granzyme B [4]. They demonstrate strong cytokine- and antibody-mediated immune responses while remaining hyporesponsive to HLA-negative target cells, balancing fetal-maternal tolerance with infection defense capacity [4].

Maternal-fetal immune tolerance

Cellular mechanisms at the decidual interface

The maternal decidua undergoes dramatic immunological remodeling during pregnancy, with leukocytes comprising 30 - 40% of all decidual cells in the first trimester [1]. Decidual natural killer (dNK) cells predominate, making up approximately 70% of decidual leukocytes, while macrophages constitute 20%, and T cells 3 - 10% [1].

- Decidual NK cells promote trophoblast invasion and vascular remodeling essential for placentation [7].
- Regulatory T cells (Tregs) suppress maternal immune responses against fetal antigens [2].
- Decidual macrophages support tissue remodeling and produce immunomodulatory cytokines [3].
- Dendritic cells at the interface present fetal antigens in tolerogenic contexts [4].

These cellular populations shift dramatically as pregnancy progresses, with NK cell and macrophage numbers decreasing and T cells becoming predominant by the third trimester [1]. This temporal regulation ensures appropriate immune support for implantation, placentation, and fetal development while maintaining protection against infections.

Molecular mediators of tolerance

Multiple molecular mechanisms contribute to maternal-fetal tolerance [2,3]. Cytokines play central roles, with anti-inflammatory cytokines like IL-10 and TGF-β suppressing proinflammatory responses at the interface [2]. Progesterone, elevated throughout pregnancy, promotes Treg expansion and inhibits NK cell cytotoxicity [2].

The enzyme indoleamine 2,3-dioxygenase (IDO) degrades tryptophan at the maternal-fetal interface, creating a local environment that suppresses T cell proliferation and promotes Treg differentiation [2]. Placental exosomes carry immunosuppressive molecules including FasL, TRAIL, PD-L1, and TGF-β, which impair T cell signaling, downregulate NK cell receptors, and promote apoptosis of activated immune cells [3].

Human leukocyte antigen (HLA) expression patterns on trophoblasts further facilitate tolerance. Invasive extravillous trophoblasts express HLA-C, HLA-E, and HLA-G but lack classical HLA-A and HLA-B molecules, reducing recognition by maternal cytotoxic T cells while engaging inhibitory receptors on dNK cells [2].

Immune factors in normal fetal development

Cytokines in organogenesis

Immune factors serve critical developmental functions beyond pathogen defense [1,8]. Cytokines influence hematopoiesis, angiogenesis, neurogenesis, and tissue remodeling throughout fetal development. IL-6, commonly known for its inflammatory roles, participates in normal neuronal migration and cortical development at physiological concentrations [1].

Interferons shape fetal immune cell development and function. Maternal IFN-γ exposure in utero can bias offspring immunity toward Th1 responses, reducing susceptibility to allergic diseases [5]. This protective effect is most potent when exposure occurs prenatally rather than postnatally, highlighting critical windows of immune programming [5].

Chemokines direct spatial organization of developing organs. For example, epithelial cells in the fetal intestine produce chemerin to attract macrophages from circulation into the gut mucosa, where they support mucosal barrier development [4]. These orchestrated cell migrations establish tissue architecture and immune surveillance capacity.

Complement system in neurodevelopment

The complement system, traditionally associated with pathogen clearance, plays essential roles in fetal brain development [1]. Complement components C1q, C3, and their receptors are expressed in the developing central nervous system with precise spatiotemporal patterns [1]. Microglia utilize complement-mediated pathways for synaptic pruning during late gestation and early postnatal periods, eliminating excess synaptic connections to refine neural circuits [1].

Dysregulation of complement-mediated synaptic pruning has been implicated in neurodevelopmental disorders. Excessive complement activation leads to aberrant synapse elimination, potentially contributing to schizophrenia pathogenesis [1]. Conversely, insufficient pruning may result in excess connectivity characteristic of certain autism spectrum disorder subtypes [1].

Microglia in brain development

Fetal microglia actively participate in multiple neurodevelopmental processes beyond immune surveillance [1,4]. They support neurogenesis in the developing cortex, regulate the survival and death of neural progenitor cells, and facilitate angiogenesis in the expanding brain [4]. During synaptogenesis, microglia secrete factors that promote synapse formation and maturation [1].

The morphology and transcriptional profile of fetal microglia differ markedly from adult microglia [4]. Developmental microglia display an amoeboid shape resembling activated adult microglia and undergo dynamic maturation processes to acquire homeostatic profiles [4]. Their functions depend critically on temporal and spatial context, with different brain regions receiving microglial colonization in coordinated waves [4].

Maternal immune activation and fetal consequences

Mechanisms of MIA-induced developmental disruption

Maternal immune activation during pregnancy, whether from infection or inflammatory stimuli, can profoundly disrupt fetal development [9-11]. The mechanism involves elevation of maternal cytokines, particularly IL-6 and IL-17A, which cross the placenta and activate inflammatory cascades in fetal tissues [9,10].

In experimental models, a single maternal injection of IL-6 on embryonic day 12.5 in mice causes behavioral abnormalities in adult offspring, including prepulse inhibition and latent inhibition deficits reminiscent of schizophrenia [9]. Blocking IL-6 with antibodies prevents these behavioral changes, demonstrating the cytokine's critical role in mediating MIA effects [9].

IL-17A similarly disrupts cortical development [12]. Exposure to IL-17A increases cortical thickness, induces premature cortical folding, and accelerates neurogenesis and neuronal maturation [12]. These structural alterations are accompanied by dysregulation of extracellular matrix pathways, including upregulation of proteoglycans like brevican and versican [12].

Placental responses to MIA

The placenta serves as a critical checkpoint in maternal-fetal immune communication [13]. During maternal pulmonary inflammation, the placenta upregulates immunomodulatory genes, particularly the IL-6 signaling suppressor SOCS3, limiting inflammatory signal transduction to the fetus [13]. However, this protective barrier is incomplete, as metabolic alterations still occur in fetal tissues [13].

MIA induces placental cytokine expression changes and alters gene expression profiles in sex-specific patterns [14]. Male offspring from poly(I:C)-exposed dams exhibit higher placental levels of GM-CSF, IL-6, TNFα, and LT-α compared to controls, while female offspring show less pronounced changes [14]. Placental genes differentially expressed after MIA are enriched in pathways related to synaptic vesicles and neuronal development [14].

Impact on fetal immune system development

MIA has lasting effects on offspring immune system development beyond neurological changes [5,6]. Maternal inflammation induced by poly(I:C) at mid-gestation affects fetal hematopoietic stem cell development, leading to sustained expansion of lymphoid-biased progenitors and elevated lymphoid cell output postnatally [5].

- Altered hematopoietic stem cell balance favoring lymphoid over myeloid lineages [5].
- Hyperactivation of ILC2 populations in the lung, increasing allergy susceptibility [5].
- Dysregulated bone marrow immune cell populations persisting into adulthood [5].
- Modified responses to allergens and immune challenges in offspring [6].

The fetal lung is particularly susceptible to MIA effects. Prenatal immune activation leads to ILC2 hyperactivation, which persists postnatally and enhances susceptibility to allergic diseases [5]. These changes reflect fetal immune programming, where prenatal inflammatory exposures establish long-term alterations in immune cell function and distribution.

Neurodevelopmental consequences

MIA is associated with increased risk of neurodevelopmental and psychiatric disorders in offspring, including autism spectrum disorder, schizophrenia, and cerebral palsy [9,10,15]. Epidemiological studies have linked maternal infections during pregnancy to these outcomes, and animal models have provided mechanistic insights [9,10].

Poly(I:C)-induced MIA in pregnant rodents produces offspring with behavioral abnormalities, histological changes, and altered gene expression in brain regions involved in social behavior, cognition, and sensory processing [9,10]. At mid-gestation, MIA increases cortical thickness in developing fetuses, with females showing thicker ventricular zones and males thicker cortical mantles [10]. Neural precursor cells isolated from MIA-exposed fetal brains exhibit higher self-renewal rates and altered expression of Notch signaling components [10].

Transcriptomic analyses reveal that MIA induces robust increases in antiviral and inflammatory gene expression in the conceptus, accompanied by decreased expression of genes associated with nervous system development, including central nervous system development, axon guidance, and neuronal action potential pathways [10].

Sex-specific effects

MIA effects often display sexual dimorphism, with males typically more severely affected than females [14,16]. This pattern mirrors the male bias observed in neurodevelopmental disorders like autism and schizophrenia. Sex differences in placental responses to MIA may contribute to these disparate outcomes [14].

Male placentas show more pronounced cytokine elevation following MIA, while fetal brain gene expression changes also differ by sex [14]. Female fetal brains exhibit more differentially expressed genes related to excitatory and inhibitory signaling following MIA, whereas male brains show fewer stable gene expression changes [14]. These sex-specific responses may reflect differential vulnerability or distinct compensatory mechanisms.

Gut microbiota and maternal-fetal immune programming

Microbiota-immune axis in pregnancy

Maternal gut microbiota influences immune function at the maternal-fetal interface and shapes fetal immune development [17,18]. Gut dysbiosis in pregnant mice leads to increased fetal resorption, impaired placental development, and altered vascularization [17]. These adverse outcomes are associated with hypoxia, endoplasmic reticulum stress, and reduced uterine natural killer cell numbers at the maternal-fetal interface [17].

Gut dysbiosis significantly perturbs placental carbohydrate metabolism, impairing NK cell IFN-γ secretion [17]. Glucose supplementation restores placental NK cell function and reduces fetal resorption, demonstrating that metabolic alterations underlie immune dysfunction in this context [17]. This highlights the gut microbiota as a key regulator of placental immunity and pregnancy outcomes.

Microbial metabolites and immune programming

Maternal gut microbiota produces metabolites that cross the placenta and influence fetal development [18]. Short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate possess immunomodulatory properties and affect gene expression through histone deacetylase inhibition [18]. Maternal SCFA levels correlate with fetal immune cell development and postnatal immune function.

The „hygiene hypothesis" has been extended to prenatal life, proposing that maternal microbial exposures train the fetal immune system [19]. Reduced microbial diversity and altered maternal microbiota composition during pregnancy may contribute to increased offspring susceptibility to allergies and autoimmune diseases [19]. This „layered hygiene hypothesis" suggests that immune training occurs through multiple waves of microbial education, beginning in utero [19].

Clinical implications and pregnancy complications

Preeclampsia and immune dysfunction

Preeclampsia, characterized by hypertension and organ dysfunction during pregnancy, involves aberrant maternal-fetal immune interactions [17]. Defective placentation results from inadequate trophoblast invasion and spiral artery remodeling, processes that depend on proper dNK cell and macrophage function [7]. Excessive inflammatory responses and insufficient Treg populations contribute to endothelial dysfunction and systemic inflammation in preeclampsia [7].

Maternal gut dysbiosis is implicated in preeclampsia pathogenesis through its effects on placental immunity and metabolism [17]. Interventions targeting the gut microbiota, such as probiotics or prebiotics, represent potential preventive strategies, though clinical evidence remains limited [17].

Recurrent pregnancy loss

Recurrent pregnancy loss often involves immune-mediated rejection of the conceptus [2]. Inadequate Treg responses, excessive NK cell cytotoxicity, or proinflammatory cytokine dominance can disrupt maternal-fetal tolerance [2]. Elevated Th17 responses and reduced IL-10 production have been observed in women with recurrent miscarriages [2].

Immune therapies, including intravenous immunoglobulin, lymphocyte immunization, and anti-TNFα antibodies, have been explored for recurrent pregnancy loss with variable success [2]. Personalized approaches based on specific immune abnormalities may improve outcomes.

Intrauterine growth restriction

Intrauterine growth restriction (IUGR) involves insufficient fetal growth due to placental insufficiency [20]. Inflammatory processes at the maternal-fetal interface contribute to impaired nutrient and oxygen transfer [20]. Elevated maternal inflammatory cytokines and reduced placental growth factor expression are associated with IUGR [20].

Long-term consequences of IUGR include increased susceptibility to metabolic syndrome, cardiovascular disease, and neurodevelopmental delays [20]. These outcomes reflect developmental programming, where adverse intrauterine conditions establish persistent physiological alterations

Protective immune interventions

Maternal immunization

Maternal immunization protects offspring through transplacental antibody transfer and may beneficially shape fetal immune development [5]. Maternal vaccination against influenza, pertussis, and tetanus is recommended during pregnancy and provides neonatal protection during the vulnerable early postnatal period [5].

Emerging evidence suggests maternal immunization may have broader immunomodulatory effects beyond pathogen-specific antibodies [5]. Maternal antigen exposure upregulates FcγRIIb on offspring splenic B cells, modulating B cell activation and cytokine production [5]. These effects contribute to reduced Th2/Th1 cytokine ratios, potentially decreasing allergy risk [5].

Nutritional interventions

Maternal nutrition profoundly influences fetal immune development through epigenetic mechanisms and metabolite provision [18,21]. Vitamin D supplementation during pregnancy reduces MIA-induced inflammation and prevents autism-related behaviors in offspring of immune-activated mice [21]. Vitamin D inhibits the IL-6/STAT3/SAA signaling pathway, reducing IL-17A expression and improving behavioral outcomes [21].

Omega-3 fatty acids, particularly docosahexaenoic acid (DHA), support fetal brain development and possess anti-inflammatory properties [13]. During maternal systemic inflammation, increases in placental and fetal DHA-containing lipids may represent compensatory responses to promote neurodevelopment despite inflammatory stress [13].

Anti-inflammatory therapeutics

Targeting inflammatory pathways during pregnancy holds promise for preventing MIA-associated developmental abnormalities [12]. Parthenolide, an inhibitor of NF-κB and HDAC1 pathways, reverses IL-17A-induced cortical abnormalities in *ex vivo* human fetal brain models, restoring normal cortical thickness, folding patterns, and neurogenesis [12].

However, anti-inflammatory interventions during pregnancy require careful evaluation given the essential roles of immune factors in normal development. Timing, dosage, and specificity of immunomodulation are critical considerations. Prenatal dexamethasone, for example, while beneficial for fetal lung maturation in preterm birth, can have adverse long-term metabolic and cardiovascular effects through developmental programming [22].

Future Directions and Conclusions

Understanding immunological effects on fetal development has profound implications for maternal-fetal medicine, neurodevelopmental research, and preventive health strategies. Several key areas warrant further investigation:

1. Precise mechanisms linking specific maternal immune perturbations to distinct offspring phenotypes.
2. Critical windows of vulnerability for immune-mediated developmental disruption.
3. Sex-specific differences in fetal responses to maternal immune activation.
4. Long-term consequences of prenatal immune programming across the lifespan.
5. Development of targeted interventions to prevent MIA-associated pathology without disrupting beneficial immune functions.
6. Integration of microbiome science with maternal-fetal immunology.
7. Clinical translation of experimental findings to improve pregnancy outcomes.

The fetal immune system is not merely an immature version of adult immunity but possesses specialized functions supporting development and preparing for postnatal life. Maternal immune activation can disrupt these finely orchestrated processes, with consequences extending from neurodevelopment to lifelong immune function. As our understanding deepens, opportunities emerge for interventions that optimize maternal-fetal immune interactions, promoting healthy pregnancy outcomes and reducing offspring disease risk.

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