Review

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Immunoediting in pregnancy: a new paradigm for understanding fetal tolerance and obstetric disease

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Abstract

Introduction: Pregnancy poses an immunological paradox: the maternal immune system must tolerate a semi-allogeneic fetus while maintaining defense against infections. Rather than being an immunosuppressed state, gestation is now recognized as a dynamic, highly regulated immune condition.

Content: This review applies the cancer-derived immunoediting framework – elimination, equilibrium, and escape – to maternal–fetal immune tolerance. We examine how immune checkpoints, regulatory T cells, non-classical MHC molecules, and placental exosomes coordinate to create a localized tolerant environment. Integrating knowledge from oncology and reproductive immunology, this perspective provides a unifying concept for pregnancy immune regulation.

Summary: The immunoediting framework reinterprets obstetric disorders such as preeclampsia, recurrent pregnancy loss, and preterm birth as failures of distinct immune phases rather than isolated pathologies. This conceptual shift allows for a broader understanding of how immune balance influences implantation, placental development, and fetal growth.

Outlook: Adopting an immunoediting perspective highlights potential clinical advances, including immune checkpoint modulation, regulatory T-cell therapies, and exosome-based biomarkers, paving the way for innovative diagnostic and therapeutic strategies in pregnancy care.

Keywords: immunoediting; pregnancy immunology; regulatory T cells; maternal-fetal interface; pre-eclampsia; exosomes

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Introduction

Pregnancy presents one of the most intriguing immunological paradoxes: the maternal immune system must tolerate a genetically distinct fetus while maintaining effective defense against infections and preserving systemic balance [1–3]. While previously viewed as a state of immunosuppression, it is now recognized as a dynamic and tightly regulated process of immune adaptation and surveillance [2, 4, 5].

This immune balance is maintained through several specialized mechanisms. Extravillous trophoblasts express

non-classical major histocompatibility complex (MHC) class I molecules such as human leukocyte antigen G (HLA-G), which bind to inhibitory receptors on uterine natural killer (uNK) cells and antigen-presenting cells, promoting localized immune tolerance [4, 6–8]. Regulatory T cells (Tregs), which expand during early gestation, suppress inflammatory responses through cytokines like interleukin 10 (IL-10) and transforming growth factor beta (TGF-β), and through inhibitory molecules such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [5, 9–12]. Immune checkpoints – especially the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis – play a key role by downregulating maternal cytotoxic responses. These checkpoints are expressed by trophoblasts and conveyed through placental exosomes [13–18] (Table 1; Figure 1).

Interestingly, these immune adaptations mirror those used by tumors to escape immune surveillance [19–24]. Both cancer and pregnancy create immune-privileged environments through tightly regulated suppression mechanisms [25–28]. This similarity forms the basis of applying the immunoediting model to gestation – comprising three phases: elimination, equilibrium, and escape [19, 20, 22, 24] (Figure 2; Table 2).

In pregnancy, elimination refers to early recognition of fetal antigens; equilibrium represents sustained tolerance through immune regulation; and escape involves breakdowns in tolerance, manifesting as complications like miscarriage or preeclampsia [12, 29–33] (Table 3). These phases map onto shifting immune landscapes across trimesters.

This review is the first to comprehensively apply the immunoediting framework to pregnancy by synthesizing insights from reproductive immunology, oncology, and exosome biology. We explore how immune checkpoints [13, 15, 17, 34–36], Tregs [5, 10–37, 37, 38] (Table 4), HLA-G [4, 39, 40], and placenta-derived exosomes [41–45] (Figure 3) collectively shape maternal-fetal tolerance. Ultimately, we propose reclassifying common obstetric disorders – not as distinct pathologies – but as failures of immune editing. This shift opens new possibilities for diagnostics and therapies inspired by oncology, such as checkpoint modulators, Treg-based strategies, and exosome-targeted interventions [14, 46–49] (Table 5).

Methods

This review employed a multi-phase, integrative approach aimed at developing a comprehensive and theory-driven framework for understanding maternal-fetal immune tolerance through the lens of immunoediting. Rather than following a rigid systematic review or meta-analysis structure, this methodology draws upon elements of concept synthesis, scoping review, and translational modeling to capture the complexity and interdisciplinary nature of the topic [50–55].

The development of the conceptual framework was guided by the hypothesis that the immunoediting model – originally proposed to describe tumor evolution under immune pressure [19, 20] – can be applied to pregnancy to reinterpret the immunological events governing fetal tolerance [51]. To construct this framework, the review integrated mechanistic, clinical, and theoretical findings from reproductive immunology [2, 3], placental exosome biology [41], immune checkpoint regulation [13, 15, 16], and oncology. This triangulated synthesis aimed to identify common immune mechanisms that contribute to either immune equilibrium or immune escape, depending on physiological or pathological context.

A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science databases for peer-reviewed publications from January 2000 to March 2025 [52]. Search terms included combinations of “maternal-fetal immune tolerance,” “programmed death-ligand 1 (PD-L1) and placenta,” “regulatory T cells (Tregs) in pregnancy,” “immune checkpoint expression in trophoblasts,” “human leukocyte antigen-G (HLA-G),” “tumor immune escape,” and “immunoediting.” Boolean logic was used to refine the search scope, and results were limited to full-text articles published in English. Both human and murine model studies were included, provided they offered mechanistic insight relevant to pregnancy or tumor immune regulation.

The inclusion criteria consisted of articles that demonstrated immunological relevance to maternal-fetal interaction, immune modulation, checkpoint biology, or clinical outcomes such as preeclampsia, recurrent pregnancy loss, or preterm labor [29–32, 53]. Articles focusing solely on infectious disease, unrelated autoimmunity, or with inadequate experimental rigor were excluded. Additionally, non-English articles, abstracts without full data, and conference proceedings were omitted from final consideration.

The study selection process followed a three-tiered screening method. Titles and abstracts of all search results were first reviewed for relevance to the review’s objectives. Studies passing this initial screen were read in full and appraised for scientific quality, experimental depth, and alignment with the proposed immunoediting framework. Discrepancies in selection were resolved through discussion among the reviewing authors. A total of 110 articles meeting the criteria were retained for detailed thematic analysis (Figure 4 outlines this PRISMA-guided selection process).

Table 1: Summary of key literature on maternal-fetal immune tolerance.[a]

Author/Year	Focus area	Model/ system	Key findings/insight	Strength	Limitation	Immunoediting phase
Dunn et al. 2004 [1]	Immunoediting concept	Cancer model (conceptual)	Introduced the elimination phase in immunoediting	Foundational concept	Not pregnancy-specific	Elimination
Moffett & Colucci, 2014 [12]	uNK cells	Human	Described the role of uNK cells in implantation and placental development	Human-focused and mechanistic	Focuses only on NK cells	Elimination
Zhou et al. 2016 [5]	Immune cell dynamics	Human	Linked dysregulated immune cells to recurrent miscarriage	Clinical relevance	Correlative, not mechanistic	Elimination
Vacca et al. 2011 [22]	NK precursors	Human decidua	Identified hematopoietic precursors differentiating into NK cells	Novel cellular source	Cell-specific focus	Elimination
Tilburgs et al. 2015 [3]	HLA-G	Human	Explains dual role of HLA-G in tolerance and immunity	Mechanistic depth	Focused on one molecule	Elimination
Aluvihare et al. 2004 [6]	Tregs	Murine	Tregs prevent fetal rejection	Experimental causality	Animal model	Equilibrium
Zenclussen et al. 2006 [9]	Tregs	Murine	Tregs promote fetal-maternal immune privilege	Model-based validation	Translational gap	Equilibrium
Samstein et al. 2012 [20]	Treg generation	Placental mammals	Describes extrathymic Treg development	Evolutionary and mechanistic insight	Requires further clinical correlation	Equilibrium
Mincheva-Nilsson & Baranov, 2014 [10]	Exosomes	Human	Exosomes carry immunosuppressive signals	Novel tolerance vector	*In vitro* bias	Equilibrium
Robertson et al. 2018 [56]	Tregs in implantation	Human/ murine	Links Tregs with successful implantation	Broad relevance	Complex interactions	Equilibrium
Zhang et al. 2023 [13]	PD-L1 in RM	Human	Reduced PD-L1 in recurrent miscarriage	Clinical tissue evidence	No functional tests	Escape
Rong et al. 2021 [15]	PD-L1 and PE	Human	Low PD-L1 suppresses GM-CSF and promotes preeclampsia	Mechanistic and clinical	Pathway-specific	Escape
Zhang et al. 2019 [18]	PD-1/PD-L1 and macrophages	Human	PD-L1 shapes macrophage polarization	Links checkpoints to immune environment	Model needs expansion	Escape
Qian et al. 2024 [57]	PD-1/OX40 in RPL	Human	Differential checkpoint expression in RSA tissue	Checkpoint profiling	Correlative	Escape
Tian et al. 2025 [58]	PD-L1 and JAK/STAT5	Human	Downregulated PD-L1 activates pro-inflammatory signaling	Pathway-level detail	Focused scope	Escape
Schreiber et al. 2011 [7]	Immunoediting phases	Cancer (conceptual)	Described elimination, equilibrium, escape	Cross-disciplinary insight	Not empirical in pregnancy	All
Mittal et al. 2014 [17]	Cancer immunoediting	Cancer	Refined immunoediting model	Established theoretical foundation	Requires obstetric translation	All
Costanzo et al. 2018 [11]	Onco-fetal immunology	Human (review)	Linked placental and tumor immune strategies	Conceptual synthesis	Theoretical	All
Zhu et al. 2022 [27]	TIM-3 checkpoint	Human	TIM-3 expression associated with maternal-fetal tolerance and RSA	Checkpoint relevance in human pathology	Primarily observational	Equilibrium
Zhang et al., 2021 [21]	Checkpoint therapy	Murine	Blocking CD28 prevents fetal rejection	Therapeutic intervention validated *in vivo*	Preclinical data only	Escape
Zhang et al. 2023 [59]	Memory Tregs	Human	Characterized $FOXP3^+$ memory Tregs during pregnancy	Defines new regulatory subset	Lacks functional assays	Equilibrium
Luo et al. 2025 [53]	$CD8^+FoxP3^+$ Tregs	Human/ Animal	Describes cytotoxic regulatory T cells with tolerogenic function	Expands Treg paradigm	Emerging topic	Equilibrium
Yin et al. 2025 [60]	Exosomal biomarkers	Human	Exosome content may serve as predictive biomarker in PE	Clinical utility	Validation needed	Escape

Table 1: (continued)

Author/Year	Focus area	Model/ system	Key findings/insight	Strength	Limitation	Immunoediting phase
Qian et al. 2024 [62]	Checkpoint profiles	Human	Differential PD-1/OX40 in RSA	Checkpoint mapping	Correlational	Escape
Li et al. 2024 [61]	Exosome therapy	Review/ Preclinical	Exosomes explored for immunotherapy delivery	Novel translational approach	Preclinical only	Escape
Green et al. 2021 [62]	Tregs in adverse outcomes	Systematic review	Lower Treg levels linked with miscarriage and PE	Meta-analysis support	No mechanistic data	Escape
Lu et al. 2025 [63]	Treg immunometabolism	Review	Metabolism affects Treg stability in inflammation	Molecular mechanism insight	Requires *in vivo* proof	Equilibrium
Zhao et al. 2025 [64]	Mitochondrial regulation	Review	Mitochondria control Treg suppressive capacity	Deep cellular mechanism	Conceptual only	Equilibrium
Zhao et al. 2022 [65]	Exosomes in cancer vs. Pregnancy	Review	Parallels in exosome-mediated immune editing	Cross-field insight	Theoretical	All

[a]This table summarizes key studies illustrating mechanisms of maternal-fetal immune tolerance, categorized by immunoediting phase and focus area, across both experimental and clinical models.

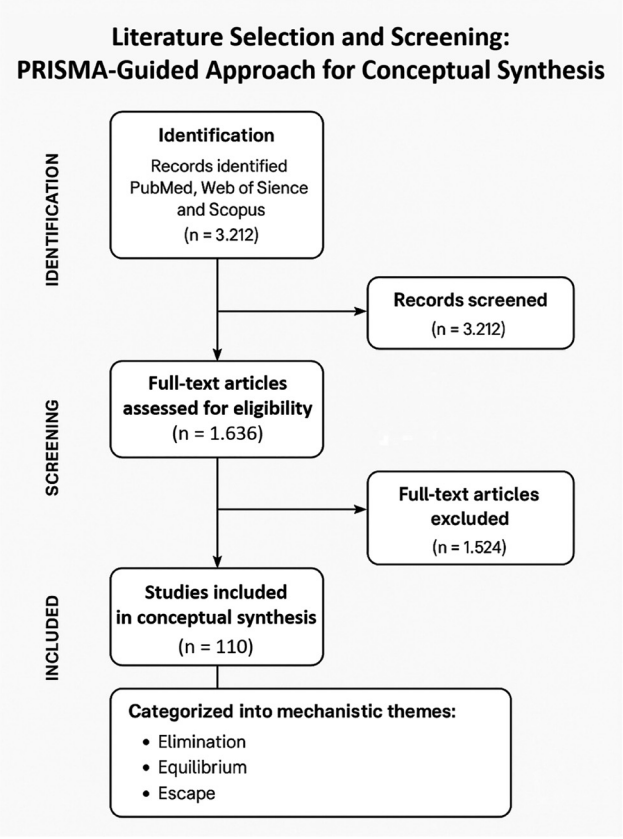

Figure 1: PRISMA-guided literature selection and screening for conceptual synthesis in fetal immune tolerance. This PRISMA-guided flowchart outlines our literature selection process for a conceptual review on fetal immune tolerance. From 3,212 identified records, 1,636 full-text articles were assessed, and 110 were included based on relevance to immune mechanisms in pregnancy. These studies were categorized into three immunoediting phases: Elimination, equilibrium, and escape, adapting an oncology framework to the maternal-fetal context.

Each study was thematically categorized according to one of three immunoediting phases – elimination, equilibrium, or escape – based on its findings and relevance to immune checkpoints, regulatory cell function, trophoblast signaling, or clinical outcomes (Table 6 summarizes these phases as applied to pregnancy). These themes were further refined into four major mechanistic domains: immune checkpoint regulation, regulatory T cell (Treg) dynamics, HLA-G and major histocompatibility complex (MHC) modulation, and placenta-derived exosomal signaling [57, 58, 63, 66–73].

To support interpretation and communication of complex immunological concepts, the review also included several visual models and data representations. These included:

- A conceptual diagram illustrating immunological crosstalk at the maternal-fetal interface (Figure 5).
- A schematic of placental exosome-mediated immune suppression (Figure 6).
- Diagrams depicting Treg pathways and fate decisions (Figures 7–8).
- A comparison between cancer and pregnancy immune escape mechanisms (Figure 9, Table 7).
- A pathway model linking immune dysregulation to obstetric complications (Figure 10, Table 8).

Additionally, Table 1 provides a curated summary of high-impact studies across the immunoediting spectrum, while Table 5 outlines the immune-relevant cargo of placenta-derived exosomes. Tables were also constructed to present key findings on immune checkpoints (Table 3), Treg subtypes (Table 4), and emerging therapeutic strategies (Table 9) [61, 74–80].

The synthesis of data across molecular, cellular, and systemic levels was designed to generate a coherent and

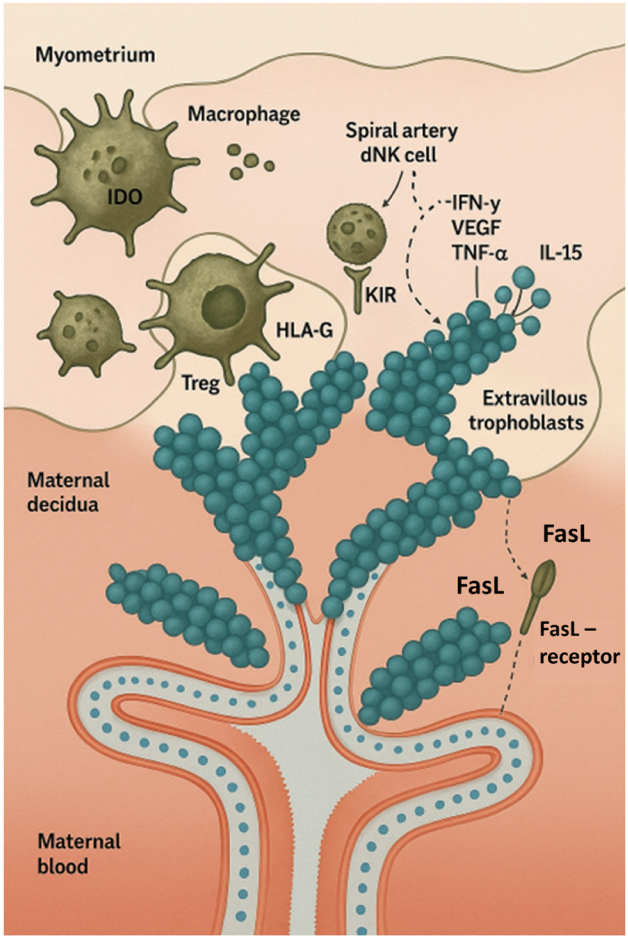

Figure 2: Maternal-fetal immune regulation at the decidual interface. This illustration shows the complex immune interactions at the maternal-fetal interface. Extravillous trophoblasts invade the maternal decidua and interact with immune cells such as decidual NK (dNK) cells, macrophages, and regulatory T cells (Tregs). Key mechanisms include: HLA-G/KIR signaling promoting immune tolerance by modulating dNK cells. Ido production by macrophages suppressing T effector cells. FasL expression inducing apoptosis in activated maternal T cells. Cytokines like IL-15, IFN-γ, TNF-α, and VEGF coordinating vascular remodeling and immune modulation.

translationally relevant model of pregnancy immunology. Emphasis was placed on identifying mechanisms that may serve as future biomarkers or therapeutic targets in obstetrics, drawing direct analogies to cancer immunotherapy where appropriate [81].

No experimental procedures involving human or animal subjects were performed as part of this review. Therefore, institutional ethics approval was not required. All analyzed studies were published in peer-reviewed journals and are assumed to have adhered to appropriate ethical standards at the time of their original publication. This comprehensive methodology ensured a rigorous, inclusive, and interdisciplinary synthesis of available evidence. By consolidating data from 110 high-quality sources, the review provides a robust immune-centric reinterpretation of pregnancy and its associated disorders through the immunoediting lens.

Results and findings

Literature selection and screening

A PRISMA-guided approach was applied to ensure methodological transparency and reproducibility. Database searches (PubMed, Web of Science, and Scopus) covering January 2000 to March 2025 yielded 3,212 records. After duplicate removal, 1,636 full-text articles were screened based on inclusion criteria focused on maternal-fetal immune tolerance, checkpoint biology, exosomal signaling, and complications such as preeclampsia, recurrent pregnancy loss (RPL), and preterm labor [19, 20, 27, 60, 77, 82, 83] (Figure 4).

Immune elimination: early immune engagement

The elimination phase represents early recognition of fetal antigens by the maternal immune system. This response involves uterine natural killer (uNK) cells, macrophages, and dendritic cells, which generate pro-inflammatory signals facilitating implantation [2–5, 12, 30, 32] (Figure 5). Extravillous trophoblasts (EVTs) expressing HLA-C and HLA-G modulate these immune cells, promoting immune tolerance [3, 41, 42]. Insufficient HLA-G expression or excessive cytotoxic activity can disrupt implantation, causing early pregnancy loss [5, 34, 41, 42, 71] (Table 1). Similar to failed tumor immune elimination, unchecked immune activation at this stage can impair fetal survival [6, 29, 56, 59, 62, 65, 84–108]. A key transition point toward equilibrium is expansion of regulatory T cells (Tregs), as demonstrated by Aluvihare et al. and Zenclussen et al. [6, 9] (Table 2, Figure 6).

Immune equilibrium: sustained tolerance

During equilibrium, fetal antigens persist, yet immune responses are actively regulated. Central mediators include $CD4^{+}FoxP3^{+}$ Tregs, recruited by trophoblast-secreted factors such as transforming growth factor beta (TGF-β) and interleukin 10 (IL-10), as well as placenta-derived exosomes [6, 8, 9, 20, 25, 26, 59, 60, 76, 83–99] (Table 4). Exosomes enriched in PD-L1, Fas ligand (FasL), and HLA-G suppress maternal

Table 2: Immunoediting phases in pregnancy.[a]

Immunoediting phase	Key immune players	Mechanisms	Outcome in normal pregnancy	Pathological shift	References
Elimination	uNK cells, macrophages, dendritic cells, T cells	Initial detection of fetal antigens; inflammatory cytokine production; immune cell recruitment	Promotes implantation and vascular remodeling	Implantation failure, recurrent miscarriage due to overactivation or insufficient tolerance	[1, 5, 12, 22, 30, 92]
Equilibrium	Regulatory T cells ($CD4^+FoxP3^+$, $CD8^+$ Tregs), tolerogenic DCs, exosomes, PD-1/PD-L1	Immune suppression via IL-10, TGF-β, PD-L1; exosomal delivery of tolerogenic molecules	Fetal tolerance, sustained placental growth	Loss of tolerance, immune imbalance, preeclampsia risk	[6, 9, 10, 20, 54, 96, 97]
Escape	Activated Th1/Th17 cells, dysfunctional Tregs, cytotoxic T cells, inflammatory macrophages	Checkpoint failure, reduced Treg function, pro-inflammatory cytokines (IFN-γ, TNF-α)	None – this phase reflects pathology	Preeclampsia, preterm labor, fetal growth restriction	[13, 15, 18, 30, 35, 58, 72, 98]

[a]This table summarizes the three immunoediting phases – Elimination, Equilibrium, and Escape – as applied to pregnancy. Each phase is characterized by distinct immune players, mechanisms, and outcomes in normal gestation or pathological conditions. Reference numbers correspond to the sources cited in the manuscript.

Table 3: Immune checkpoints in pregnancy.[a]

Checkpoint molecule	Source	Function at maternal-fetal interface	Role in tolerance	Dysregulation in disease	References
PD-1/PD-L1	Trophoblasts, exosomes, decidual stromal cells	Suppresses maternal T cell activity; promotes M2 macrophage polarization	Maintains immune equilibrium and fetal protection	Reduced in preeclampsia and miscarriage	[13, 15, 18, 57, 72]
TIM-3	T cells, NK cells, trophoblasts	Promotes immune exhaustion and tolerance via interaction with galectin-9	Suppresses Th1/Th17 responses	Associated with recurrent miscarriage and inflammation	[27, 31, 98]
CTLA-4	Regulatory T cells	Inhibits APC co-stimulation via CD80/CD86	Promotes Treg-mediated suppression of effector responses	Reduced expression linked to pregnancy loss	[6, 9, 98]
OX40/OX40L	Activated T cells, decidual tissue	Modulates Treg stability and effector T cell survival	Balances immune activation and regulation	Altered expression in recurrent pregnancy loss	[58, 98]
FasL	Trophoblasts, exosomes	Induces apoptosis in activated maternal T cells	Immune silencing and protection of fetal cells	Not fully defined; under investigation	[10, 59, 79]
LILRB4	Myeloid cells, decidual macrophages	Inhibits dendritic cell maturation and T cell activation	Promotes immune suppression and anti-inflammatory macrophage phenotype	Emerging evidence in preeclampsia and immune dysregulation	[43]
B7-H4	Trophoblasts, endometrial epithelium	Suppresses T cell proliferation; promotes immune quiescence	Contributes to fetal immune privilege, similar to tumor escape	Proposed role in immune escape during inflammation	[23]
Galectin-9	Trophoblasts, immune cells	Ligand for TIM-3; promotes T cell exhaustion and tolerance	Enhances TIM-3 mediated immune suppression	Reduced expression may impair tolerance signaling	[27, 31]

[a]This table outlines major immune checkpoints involved in pregnancy tolerance, including their sources, roles, and associations with pregnancy complications.

cytotoxic T cell responses [10, 59, 65, 79, 86, 87] (Figure 7). Similar to tumor-derived exosomes, placental exosomes act as immune-modulatory packages that maintain tolerance [65, 78, 82, 88, 108–110] (Table 5). Breakdown of this phase – due to Treg insufficiency [97, 98], PD-L1 downregulation [13, 15, 18, 57, 72, 103–106], or altered exosome composition [65, 78, 85, 88, 89] – is associated with RPL and preeclampsia [14, 35, 41, 56, 91–93] (Table 8, Figure 8).

Table 4: Regulatory T cells in pregnancy.[a]

Treg subtype	Source/Recruitment signals	Mechanism of action	Impact on pregnancy	Evidence from Models/Studies
$CD4^+FoxP3^+$ Tregs	Thymus, peripheral expansion via TGF-β, IL-2	Suppress effector T cells; secrete IL-10, TGF-β; express CTLA-4 and PD-1	Essential for implantation, tolerance, and fetal survival	[6, 9, 20, 96, 198]
Memory Tregs	Expansion from previous pregnancies or antigen exposure	Rapid recall and enhanced suppressive response at the maternal-fetal interface	Promotes improved tolerance in subsequent pregnancies	[20, 97]
$CD8^+FoxP3^+$ Tregs	Peripheral induction by fetal antigens and TGF-β	Suppress dendritic cell and T cell activation; cytotoxic regulation	Contributes to early maternal tolerance	[54, 97]
Induced (iTregs)	Peripheral naive $CD4^+$ T cells under TGF-β/IL-2 influence	Promotes tolerance through suppressive cytokines and checkpoint expression	Maintains peripheral immune balance at the fetal interface	[20, 78, 98]
Tissue-resident Tregs (trTregs)	Localized expansion in decidua via local cytokines and antigens	Provide site-specific immune suppression; adapt to local signals	Ensure site-specific tolerance and placental development	[54, 97, 98]
$Helios^+/Helios^-$ Tregs	$Helios^+$: thymic (nTregs); $helios^-$: Peripherally induced (iTregs)	Both suppress effector T cells, but differ in origin and cytokine profiles	$Helios^-$ iTregs are particularly important for fetal-specific tolerance	[56, 66, 98]
T-bet^+ Tregs	Differentiation under IFN-γ and IL-12 signals in Th1 environment	Suppress Th1-type immune responses; maintain Th1/Treg balance	Prevent pro-inflammatory responses at maternal-fetal interface	[66, 97]
RORγt$^+$ Tregs	Peripheral polarization influenced by IL-6 and microbiota	Control Th17 responses and mucosal tolerance	Contribute to immune balance and protection from inflammation	[66, 67, 97]

[a]This table summarizes the major subtypes and functional variants of regulatory T cells (Tregs) involved in pregnancy, detailing their origins, mechanisms, and roles in establishing and maintaining maternal-fetal tolerance.

Immune escape: failure of tolerance and disease onset

The escape phase parallels immune evasion in malignancies [17, 56, 88, 89–94, 109, 110]. In pregnancy, failure of tolerance results in obstetric disorders such as preeclampsia, preterm birth, or fetal growth restriction (FGR). This phase is characterized by decreased PD-L1 expression, reduced Treg activity, and heightened Th1/Th17 cell responses [15, 30, 62, 72, 95–103]. Activated macrophages and dendritic cells regain antigen-presenting capacity, driving maternal cytotoxic T lymphocyte infiltration and systemic inflammation [18, 35, 63, 93, 102–106]. Exosomes lose tolerogenic signals and may carry damage-associated molecular patterns (DAMPs) [85, 89]. These processes closely resemble malignant immune escape pathways [88, 108, 110] (Figure 9, Table 9). Preclinical interventions – including PD-L1 or TIM-3 restoration and Treg cell transfer – have shown efficacy in rescuing pregnancies in animal models [21, 27, 31, 71, 111, 112] (Table 6).

PD-1/PD-L1 axis in gestation

The PD-1/PD-L1 pathway is a central regulator of maternal-fetal tolerance. PD-L1 expression on trophoblasts, exosomes, and decidual stromal cells suppresses maternal $CD8^+$ T cell cytotoxicity [13, 15, 18, 57, 70, 74, 81, 103–106]. PD-L1 blockade in mice induces fetal resorption, highlighting its physiological importance [21, 44]. In humans, PD-L1 downregulation is observed in preeclampsia and miscarriage [15, 58, 72, 104–106]. Beyond T cell suppression, PD-L1 drives M2 macrophage polarization, supporting placental vascular remodeling and nutrient exchange [18, 29, 33, 107] (Table 3). PD-L1 expression is modulated by hypoxia-inducible factors (HIFs) and nuclear receptor signaling [75, 107], mechanisms also exploited by tumors for immune evasion [19, 62, 106–108].

Regulatory T cells: immune calibration mechanism

Tregs are indispensable for maintaining maternal-fetal tolerance. Their early gestational expansion is triggered by fetal alloantigens and supported by cytokines such as IL-10, TGF-β, and inhibitory receptors like cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [6, 20, 96–102]. Treg dysfunction is linked to preeclampsia, RPL, and intrauterine growth restriction (IUGR) [14, 35, 98–102]. Their activity is sensitive to inflammatory signals and metabolic stress pathways [64, 66–68, 102, 103]. Notably, $CD8^+FoxP3^+$ Tregs have emerged as an additional regulatory subset, though understudied [54, 89,

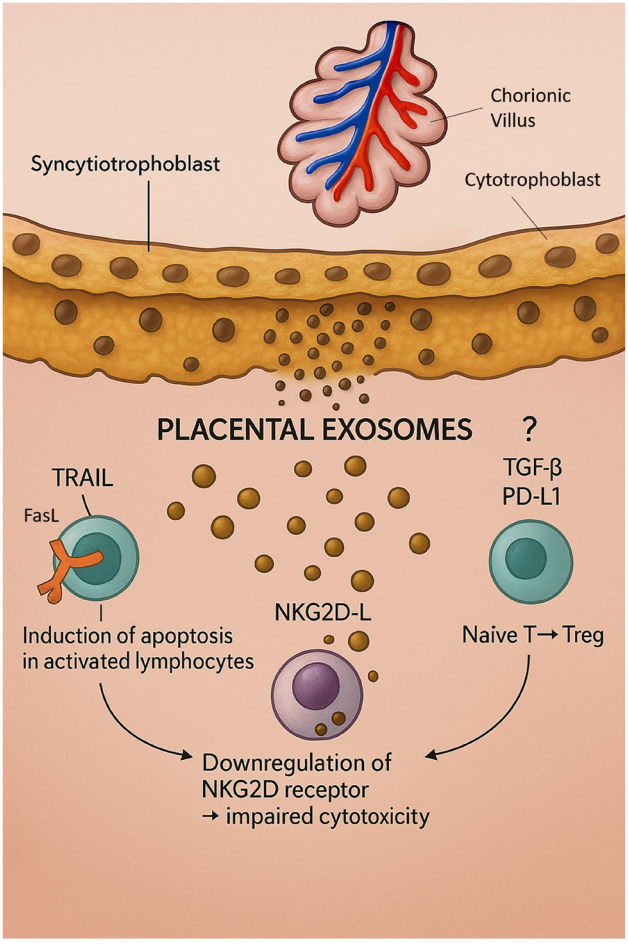

Figure 3: Immunomodulatory roles of placental exosomes at the maternal-fetal interface. This illustration highlights how placental exosomes, released from syncytiotrophoblasts, shape maternal immune tolerance during pregnancy. These exosomes carry key immunoregulatory molecules: TRAIL and FasL induce apoptosis in activated lymphocytes. NKG2D-L downregulates the NKG2D receptor on NK cells, impairing cytotoxicity. TGF-β and PD-L1 promote the conversion of naive T cells into regulatory T cells (Tregs). Together, these exosomal signals suppress maternal immune activation, ensuring fetal survival in a semi-allogeneic environment. Figure adapted from Mincheva-Nilsson L and Baranov V [10].

110]. Animal studies demonstrate that Treg-based therapy can restore tolerance and prevent fetal loss [21, 96, 98, 111, 112] (Table 6, Figure 10).

Discussion

Rethinking pregnancy as a dynamic immunological process

For much of modern medical history, pregnancy was regarded as a passive immunological state characterized by maternal immune suppression to prevent fetal rejection. However, a growing body of human and animal studies now challenges this static model. Contemporary evidence reveals that pregnancy is, in fact, immunologically dynamic and governed by tightly regulated mechanisms of immune surveillance and tolerance. These insights are supported by a spectrum of studies across immunology, reproductive biology, and oncology, illustrating that gestation is an actively modulated state of immune equilibrium rather than immune dormancy [2, 3, 6, 12, 24, 56, 90] (Figure 4).

This review introduces the cancer-derived immunoediting model – comprising the sequential phases of elimination, equilibrium, and escape – as a unifying theoretical framework to interpret maternal-fetal immune interactions [1, 7, 17, 109] (Figure 5, Table 7). Applying this triphasic paradigm to gestation clarifies the immunological transitions that underpin implantation, tolerance, and obstetric pathology. The elimination phase maps onto early pro-inflammatory immune responses at implantation; the equilibrium phase reflects sustained immune regulation via Tregs, PD-L1 expression, and exosomal signaling; and the escape phase corresponds to breakdowns in tolerance that lead to clinical syndromes such as preeclampsia, recurrent pregnancy loss, and fetal growth restriction [5, 14, 30, 41, 92, 93, 98] (Tables 2 and 9).

Importantly, this model recasts immune dysfunction not as a secondary phenomenon but as a possible initiating factor in obstetric complications [5, 15, 30, 35, 71, 98] (Figure 9). It elevates the immune system from a background player to a primary determinant of gestational outcome, a role it also holds in cancer biology through tumor surveillance and immune escape [1, 88, 89].

Pregnancy vs. malignancy: limits of the analogy

While the immunoediting framework derived from oncology provides a valuable heuristic for understanding maternal-fetal immune tolerance, pregnancy and malignancy are fundamentally distinct biological processes [11, 88, 110]. A fetus is a semi-allogeneic but physiologically intended entity, the product of evolutionary pressure to support species survival [2, 3, 24], whereas a tumor is an abnormal, pathological proliferation of cells designed to escape immune surveillance [88, 89, 62].

The immune suppression observed in pregnancy is highly localized and temporally regulated, aimed at protecting both maternal and fetal well-being without compromising systemic host defense [90, 92, 101]. In contrast,

Table 5: Placenta-derived exosomes – immune cargo and Function.[a]

Cargo Component	Immune Target	Function	Clinical Correlation	References
PD-L1	T cells, NK cells	Suppresses T cell activation and cytotoxicity; promotes immune tolerance	Reduced in preeclampsia and miscarriage	[10, 13, 72, 85]
HLA-G	NK cells, T cells	Induces immune tolerance by interacting with inhibitory receptors	Low levels linked with RSA and immune activation	[3, 10, 59]
miRNAs (e.g., miR-146a, miR-210)	Monocytes, T cells, DCs	Modulate cytokine release, inflammation, and T cell responses	Dysregulated miRNAs in preeclampsia and fetal growth restriction	[10, 78, 85]
FasL	Activated T cells	Induces apoptosis in effector T cells	Implicated in immune privilege; variable expression in disorders	[10, 59, 79]
Galectin-9	TIM-3^{+} T cells, NK cells	Promotes T cell exhaustion and Th1 suppression	Impaired signaling linked with pregnancy loss	[27, 31, 78]
TGF-β	T cells, DCs, NK cells	Promotes Treg differentiation and suppresses effector responses	Key factor in establishing immune tolerance; reduced in preeclampsia	[10, 78, 98]
IL-10	T cells, macrophages	Suppresses pro-inflammatory cytokine production and antigen presentation	Reduced IL-10 signaling implicated in miscarriage and PE	[10, 98]
Other miRNAs (e.g., miR-155, miR-223)	T cells, APCs	Regulate immune cell differentiation, activation, and cytokine profiles	Altered miRNA profiles linked to inflammation and fetal growth restriction	[78, 85]

[a]This table outlines key immunoregulatory components of placenta-derived exosomes, detailing their immune targets, functional roles in maternal-fetal tolerance, and clinical relevance to pregnancy disorders.

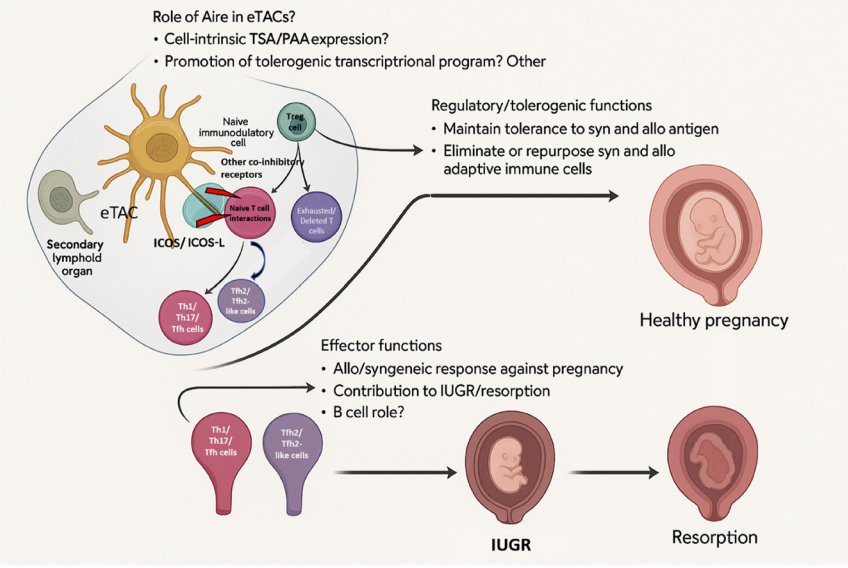

Figure 4: Aire-driven T cell fate and immune regulation in pregnancy outcomes. This diagram shows how eTACs (extrathymic aire-expressing cells) guide naive T cells toward either tolerance or effector pathways, influencing pregnancy success. Treg and exhausted T cells promote fetal tolerance and support healthy pregnancy. Th1/Th17/Tfh2 cells drive inflammation, contributing to IUGR or fetal resorption. Figure adapted from Gillis-Buck E et al. [111].

tumors exploit immune escape pathways – such as PD-1/PD-L1 upregulation and regulatory T cell recruitment – for unchecked growth and dissemination, often at the expense of host survival [17, 88, 108, 109].

Moreover, the maternal-fetal interface involves a dual-patient dynamic, where therapeutic decisions must consider both maternal and fetal outcomes – a complexity not present in cancer immunotherapy [20, 96, 108]. Pregnancy also displays unique evolutionary adaptations, such as non-classical HLA-G expression and placental exosome-mediated immune regulation [10, 25, 59, 76, 79], that have no direct equivalent in cancer biology [73, 78, 88].

Thus, the analogy should be viewed as conceptual and hypothesis-generating, not as an assertion of equivalence. It serves to highlight overlapping mechanisms (e.g., PD-1/PD-L1, Treg induction, exosome-mediated signaling) while recognizing that pregnancy represents a symbiotic rather than a pathogenic state [11, 84, 87].

Table 6: Therapeutic and diagnostic implications based on immunoediting.[a]

Immune target	Proposed intervention	Status	Potential obstetric application	References
PD-1/PD-L1 pathway	Checkpoint agonists or exosomal PD-L1 supplementation	Preclinical	Prevention or treatment of miscarriage, immune-based diagnostics	[13, 15, 72, 78]
Regulatory T cells (Tregs)	Treg adoptive transfer or Treg-boosting agents (e.g., low-dose IL-2)	Preclinical/ Experimental	Immunotherapy for recurrent pregnancy loss or preeclampsia	[6, 20, 78, 98]
TIM-3/Galectin-9 axis	Galectin-9 supplementation or TIM-3 agonism	Preclinical	Restoring tolerance in immune-mediated miscarriage	[27, 31, 98]
Exosomal miRNAs	Therapeutic delivery of regulatory miRNAs (e.g., miR-146a)	Exploratory	Diagnostic and therapeutic monitoring for preeclampsia, FGR	[10, 78, 85]
TGF-β/IL-10 signaling	Cytokine therapy or engineered exosomes	Experimental	Rebalancing inflammatory responses in complicated pregnancies	[10, 98]
CTLA-4 pathway	CTLA-4 agonists or enhancement of Treg-mediated suppression	Preclinical	Boosting tolerance in pregnancy loss or inflammatory complications	[6, 9, 96, 98]
OX40/OX40L signaling	OX40 modulation to enhance Treg stability or suppress effector T cells	Experimental	Immune rebalance in recurrent miscarriage	[58, 98]
Checkpoint combination therapy (PD-1 + TIM-3)	Dual checkpoint agonists or engineered exosomes	Exploratory	Restoring complex tolerance in severe immune-mediated pregnancy disorders	[31, 58, 98]
$CD8^+FoxP3^+$ Tregs	Expansion or adoptive transfer of cytotoxic Tregs	Preclinical	Enhancing early maternal-fetal tolerance	[9, 54]

[a]This table highlights key immune targets and emerging therapeutic or diagnostic strategies in pregnancy, based on the immunoediting framework. Each entry includes intervention type, development status, and potential clinical applications.

Translational opportunities from oncology to obstetrics

The convergence of immune mechanisms in pregnancy and cancer suggests novel opportunities for therapeutic crossover. Immune checkpoint inhibitors, Treg-based interventions, and exosome-targeted therapies – currently revolutionizing oncology – may hold translational promise for obstetrics [19, 44, 46, 78, 108, 111, 112] (Table 6). In particular, the PD-1/PD-L1 axis has emerged as a cornerstone of maternal-fetal tolerance. Its expression on trophoblasts and exosomes helps suppress cytotoxic T cell activity and maintain fetal viability [13, 15, 18, 57, 59, 72] (Table 3, Figure 6). Reduced PD-L1 levels in the placenta and maternal circulation are consistently associated with preeclampsia and pregnancy loss, supporting its role as both a mechanistic factor and a potential biomarker [15, 58, 72, 78, 85] (Figure 10).

Treg-based therapies, such as adoptive transfer or pharmacological expansion of regulatory T cells, have been shown in preclinical models to restore immune tolerance and prevent fetal resorption [20, 21, 96, 98] (Table 4). The emerging recognition of $CD8^+FoxP3^+$ Tregs and memory Treg subsets further broadens the therapeutic landscape [54, 97, 99]. Additionally, placenta-derived exosomes, enriched with tolerogenic proteins such as HLA-G, FasL, and PD-L1, offer a promising delivery system for localized immunomodulation [10, 25, 59, 76–97] (Table 5). This exosome-based approach mirrors current efforts in oncology to use nanotherapeutics for immune reprogramming [83, 89, 108, 111, 112].

However, the objective in pregnancy is not immune activation but precisely timed immune modulation. Interventions must preserve systemic maternal immunity while selectively enhancing tolerance at the maternal-fetal interface [2, 24, 90]. Such nuanced interventions require new models of immune timing and immune profiling, tailored specifically to the pregnant state.

Clinical implications for obstetric practice

Framing pregnancy through the lens of immunoediting also opens pathways for clinical application. Immune-based diagnostics, widely used in oncology, could be adapted for obstetrics to improve early detection and risk stratification. PD-L1 levels in maternal blood and placental tissue have already demonstrated predictive value for preeclampsia and recurrent pregnancy loss [13, 15, 57, 58, 72]. Likewise, shifts in the Th17/Treg balance mirror immune dysregulation patterns observed in autoimmunity and graft rejection, and may be leveraged to identify pregnancies at risk for immune-mediated complications [30, 98, 100].

Exosomes in maternal circulation – detectable in the first trimester – carry immunological cargo such as PD-L1, HLA-G, cytokines, and microRNAs that reflect the status of

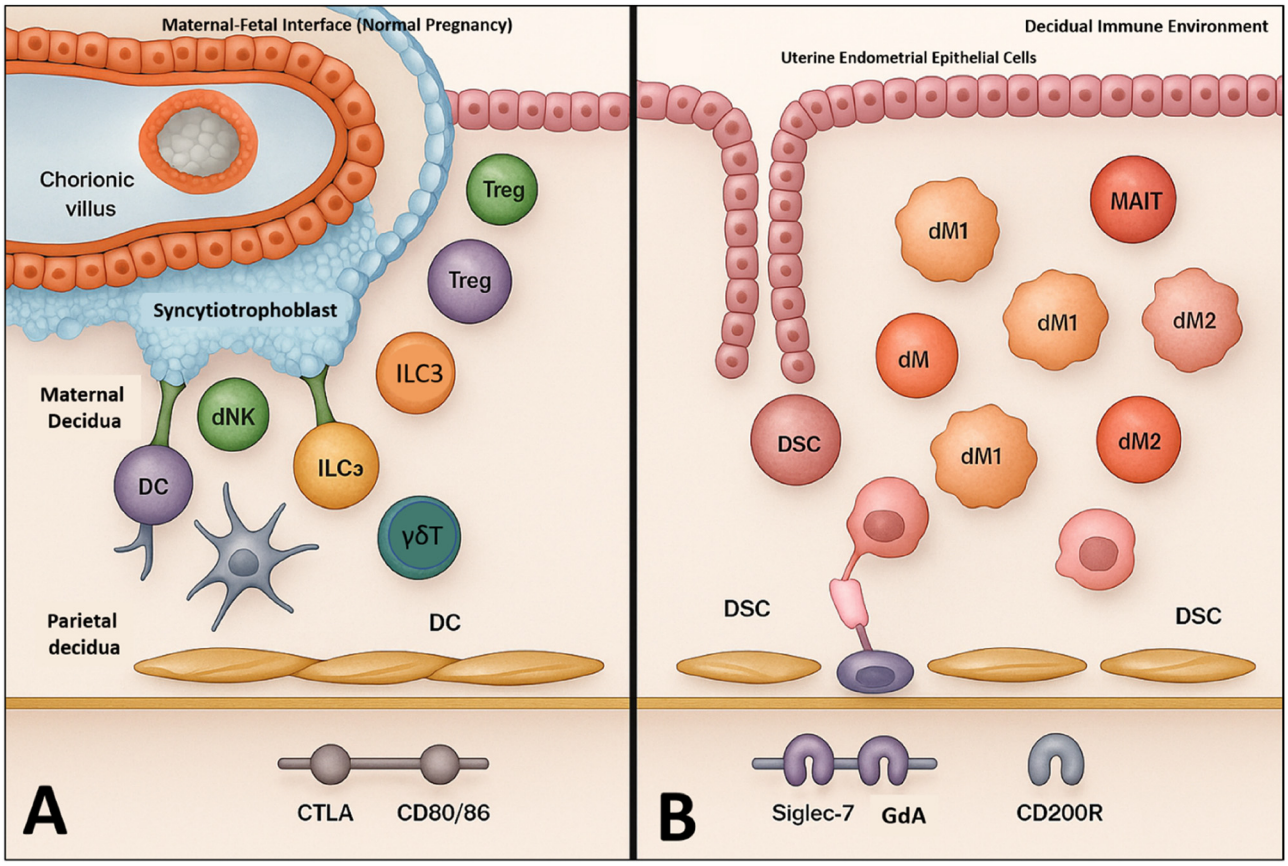

Figure 5: Immune cell crosstalk and checkpoint regulation at the maternal–fetal interface. This illustration compares the immune microenvironment in normal pregnancy across two anatomical contexts: Panel A (Left): At the maternal–fetal interface, decidual immune cells such as Tregs, dendritic cells (DCs), group 3 ILCs (ILC3s), γδ T cells, and decidual NK cells (dNKs) interact closely with trophoblasts (cytotrophoblast and syncytiotrophoblast) of the chorionic villi. Immune tolerance is promoted by immune checkpoint molecules, including CTLA–CD80/86 signaling, which limits T cell activation. Panel B (Right): Within the decidual stroma and uterine epithelium, immune populations such as MAIT cells, decidual macrophages (dM1, dM2), and dNK cells are modulated by stromal interactions and checkpoint regulators like Siglec-7, GdA, and CD200R, which help suppress inflammatory responses and support maternal tolerance.

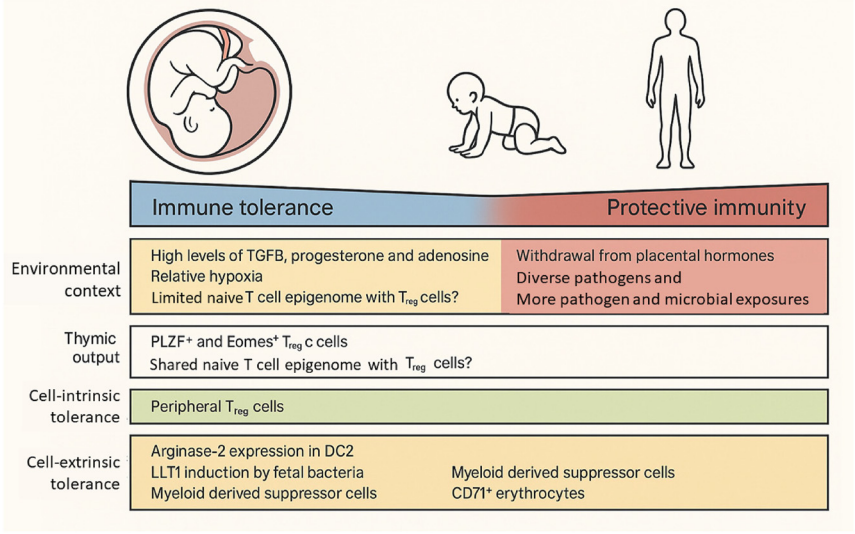

Figure 6: PLZF and Eomes: Orchestrators of early-life T cell programming. PLZF and Eomes are key transcription factors that shape early T cell development. PLZF drives the formation of innate-like T cells such as iNKT cells, promoting quick, regulatory responses important in fetal life. Eomes supports the development of cytotoxic and memory-like T cells, priming the immune system for future challenges. Together, they help balance immune tolerance and defense in early life. Figure adapted from Rackaityte E and Halkias J [112].

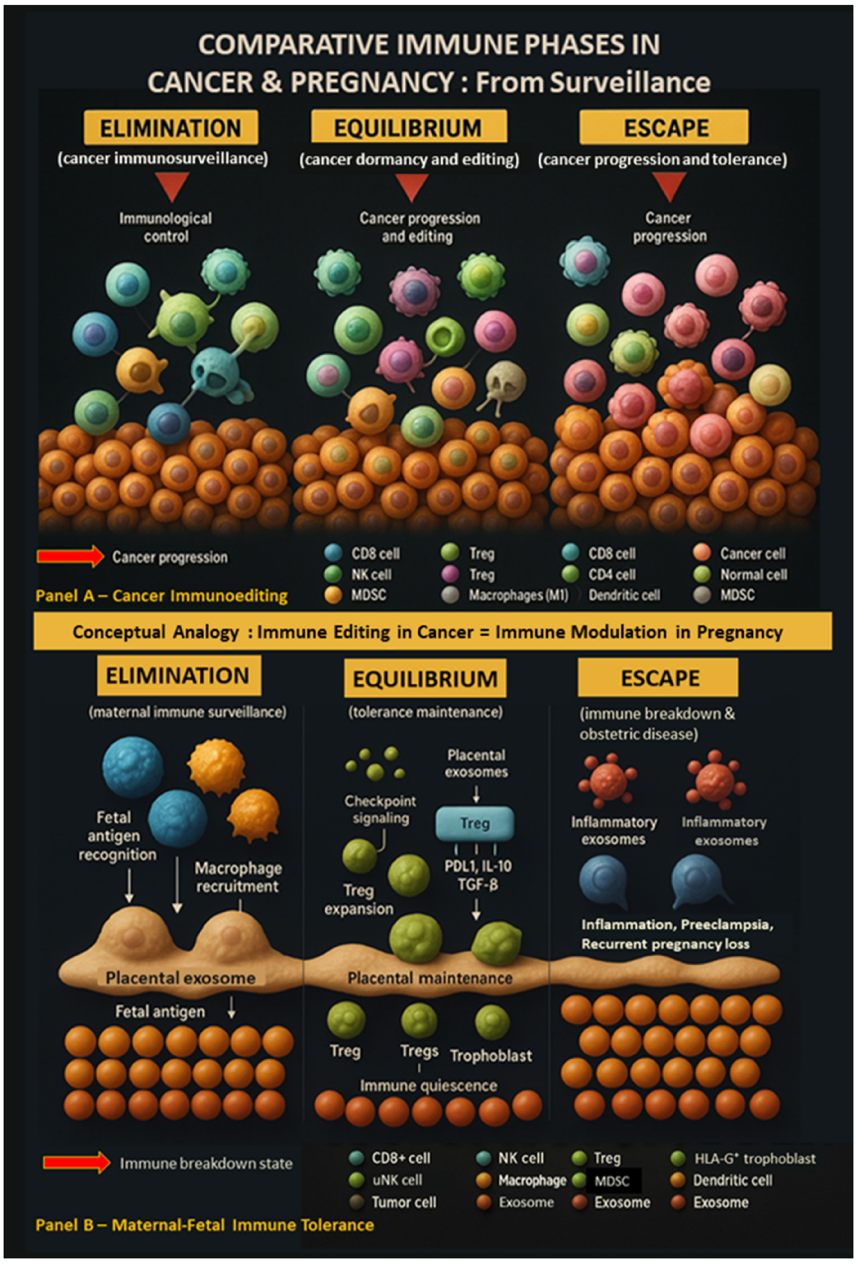

Figure 7: Comparative immune phases in cancer and pregnancy: A conceptual analogy of immunoediting and immune tolerance. This figure illustrates how cancer immunoediting and maternal-fetal immune tolerance follow similar immune phases: Elimination, equilibrium, and escape. In cancer (Panel A), immune cells first eliminate tumor cells. Surviving cells may persist in equilibrium under immune pressure, supported by regulatory elements like Tregs and MDSCs. In escape, tumors evade immune control and progress. In pregnancy (Panel B), maternal immune cells initially recognize fetal antigens. Tolerance is then maintained by Tregs, HLA-G$^+$ trophoblasts, and immunosuppressive signals. When tolerance fails, immune activation leads to complications such as preeclampsia or pregnancy loss. This analogy highlights shared immune dynamics in cancer progression and pregnancy maintenance.

immune regulation at the maternal-fetal interface [10, 25, 76, 85, 59] (Figure 10). Profiling this exosomal content could provide a minimally invasive method for longitudinal immune surveillance during pregnancy [78–80] (Table 5). Integration of such immune diagnostics into prenatal care would allow clinicians to identify immune deviations before they translate into clinical disease.

Ethical and policy considerations

The adaptation of immunotherapeutic approaches to pregnancy raises complex ethical and regulatory questions. Unlike cancer treatment, which targets pathology within a single host, obstetric immunomodulation must account for the well-being of both mother and fetus. Immune interventions must be precisely calibrated to avoid unintended consequences. While enhancing tolerance may prevent fetal loss, overmodulation could impair maternal defense mechanisms or reduce vaccine efficacy [8, 14, 64, 66]. Conversely, insufficient control may trigger fetal rejection or contribute to placental insufficiency [35, 72, 92] (Table 9).

Regulatory frameworks and clinical trial designs must therefore incorporate dual-host considerations, with long-term maternal and fetal safety as a central concern [20, 98, 110]. Furthermore, equitable access to emerging diagnostic

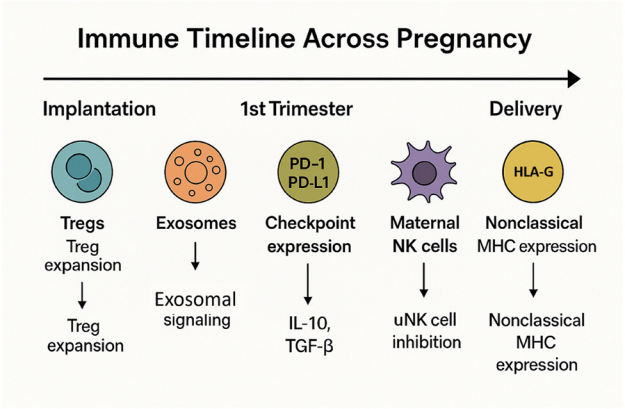

Figure 8: Temporal dynamics of immune regulation across pregnancy. This timeline illustrates the evolving landscape of immune regulation from implantation to delivery. Early pregnancy is marked by the rise of regulatory T cells (Tregs) and immunosuppressive exosomes. During the first and second trimesters, checkpoint molecules such as PD-1/PD-L1 and immunoregulatory cytokines (IL-10, TGF-β) maintain maternal-fetal tolerance. Toward term, uterine NK cells (uNK) and HLA-G interactions support placental stability and fetal protection, completing the immunological orchestration of gestation.

technologies, such as immune checkpoint assays and exosome profiling platforms, must be ensured. Many of the populations most affected by immune-mediated pregnancy complications – such as those experiencing eclampsia in low-resource settings – face systemic barriers to care [14, 35, 92]. Expanding access will require international policy support, investment in affordable technologies, and inclusive research practices [79, 85].

Call to action – rethinking obstetric immunology

Pregnancy must be recognized as a programmable immune state rather than an immune-suppressed condition. Clinicians and researchers should adopt immune profiling, develop immune-based diagnostic tools, and explore targeted immunotherapies to prevent and manage pregnancy complications.

Key takeaways

- Novel Perspective: Pregnancy framed as an immune-edited process rather than passive immune suppression.
- Interdisciplinary Integration: Uses oncology principles (PD-1/PD-L1, Tregs, exosomes) to interpret obstetric immunology.

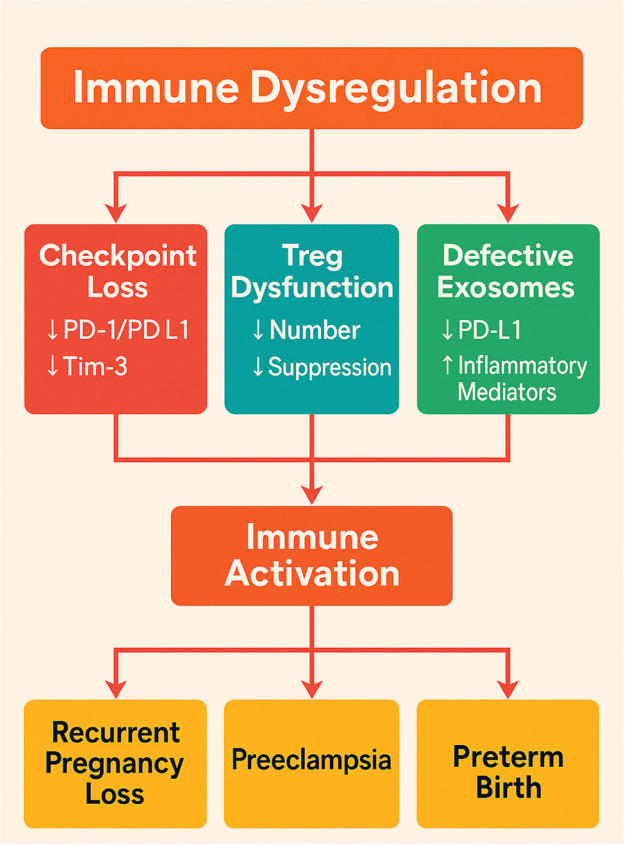

Figure 9: Pathway from immune dysregulation to pregnancy complications. This flowchart depicts how disruptions in immune regulation – such as checkpoint molecule loss (e.g., PD-1/PD-L1, Tim-3), regulatory T cell (Treg) dysfunction, and defective exosomal signaling – lead to immune activation. This dysregulated immune state contributes to key obstetric complications including recurrent pregnancy loss, preeclampsia, and preterm birth. The diagram highlights critical mechanistic links with potential for diagnostic and therapeutic intervention.

- Translational Potential: Diagnostics (immune profiling), therapies (Treg-based, checkpoint-targeted), and biomarkers (exosomes).
- Limitations: Conceptual nature, limited direct validation, experimental nature of proposed interventions.
- Ethics & Policy: Dual-host considerations and equitable access are essential for clinical translation.

Implementation checklist for future research

- Perform longitudinal immune profiling (checkpoint expression, Treg subsets) across pregnancy.
- Expand *in vivo* studies on placental exosome signaling and immune regulation.

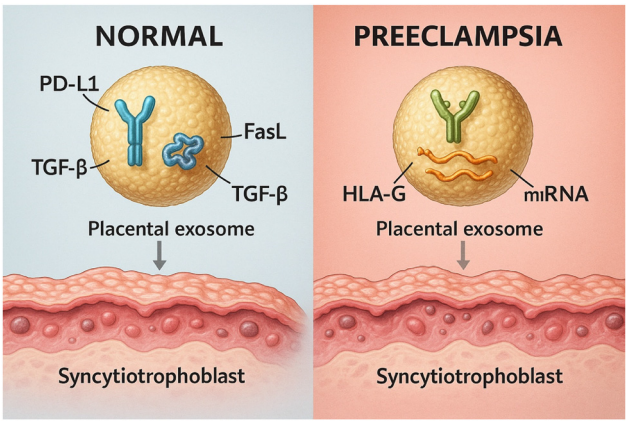

Figure 10: Placental exosome cargo in normal pregnancy vs. Preeclampsia. This comparative illustration highlights the molecular contents of placental exosomes under physiological and pathological conditions. In normal pregnancy, exosomes released by syncytiotrophoblasts carry immunoregulatory factors such as PD-L1, FasL, and TGF-β, which support maternal immune tolerance. In contrast, exosomes from preeclamptic placentas show altered cargo, including elevated HLA-G and pro-inflammatory microRNAs (e.g., miR-210, miR-155), contributing to immune dysregulation and endothelial dysfunction. These molecular shifts underscore the diagnostic and therapeutic potential of exosomal profiling in obstetric care.

Table 7: Comparative immunoediting – pregnancy vs. cancer.[a]

Category	Pregnancy	Cancer	References
Immunoediting trigger	Fetal alloantigens from the semi-allogeneic fetus	Tumor-specific neoantigens and altered self-proteins	[1, 7, 11, 17, 89, 98]
Tolerance mechanisms	Regulatory T cells, exosomes, immune checkpoints (PD-1, CTLA-4), HLA-G	Tregs, MDSCs, checkpoints (PD-1, CTLA-4), IDO, Galectin-9	[11, 17, 89, 98]
Checkpoint roles	Facilitates maternal-fetal tolerance via immune silencing	Enables immune escape and tumor persistence	[13, 15, 17, 27, 98]
Treg function	Suppress maternal immune response to fetal antigens	Suppress anti-tumor immunity and promote tumor survival	[6, 9, 20, 96, 98]
Outcome if dysregulated	Recurrent miscarriage, preeclampsia, FGR	Tumor progression, metastasis	[5, 13, 15, 72, 98]

[a]This table compares the immunoediting processes in pregnancy and cancer, highlighting shared immune mechanisms such as tolerance induction, checkpoint roles, and regulatory T cell function, while emphasizing their distinct biological outcomes.

- Design clinical trials for immune-targeted therapies with strict ethical oversight.
- Develop non-invasive biomarker panels (PD-L1, HLA-G, exosomal miRNAs).
- Build ethical and policy frameworks ensuring equitable access and patient-centered consent.

Strengths, limitations, and future directions

This review presents a novel and integrative perspective by systematically applying the cancer-derived immunoediting model to pregnancy. By framing maternal-fetal immune interactions through the phases of elimination, equilibrium, and escape, the model organizes a wide range of molecular and clinical observations into a coherent immunological structure. This includes key processes such as immune checkpoint signaling, regulatory T cell (Treg) dynamics, and placental exosome activity, all of which are linked to clinical outcomes like preeclampsia, recurrent pregnancy loss (RPL), and preterm labor. Rather than portraying pregnancy as a static state of tolerance, this model recasts it as a dynamic, time-sensitive immune process shaped by surveillance and regulation.

A major strength of this framework lies in its interdisciplinary reach. Drawing from 110 studies across both human and animal research, it integrates mechanistic findings on PD-1/PD-L1 pathways, Treg biology, non-classical MHC molecules (HLA-G), and exosomal signaling at the maternal-fetal interface. These components are synthesized into a temporally structured immune model that parallels immune escape in oncology, offering both theoretical clarity and potential clinical applications.

From a translational standpoint, the model highlights new opportunities for diagnostics and intervention. Immune profiling using markers like PD-L1 or Treg signatures, already in use in cancer medicine, could be adapted for early detection and risk stratification in pregnancy. Preclinical studies suggest that Treg-based therapies – such as adoptive cell transfer or pharmacologic expansion – may help restore tolerance and prevent fetal rejection in high-risk pregnancies. Similarly, the immunoregulatory capacity of placental exosomes could be harnessed through engineering approaches that deliver tolerogenic agents. These translational extensions demonstrate the broader utility of viewing pregnancy as an immune-edited process rather than an immunological anomaly.

However, this model also has important limitations. Its application to pregnancy is primarily conceptual and interpretive. While analogies with tumor immune escape provide a useful framework, direct empirical validation in human gestation remains limited. Fundamental biological differences between fetal symbiosis and tumorigenesis – including

Table 8: Immune cell profiles across pregnancy Trimesters.[a]

Trimester	Dominant immune cells	Functional role	Cytokine environment	References
1st trimester	uNK cells, macrophages, iTregs, Th1 cells	Facilitate implantation, spiral artery remodeling, and immune tolerance initiation	Pro-inflammatory (TNF-α, IFN-γ, IL-1β)	[3, 5, 9, 12, 22, 30, 92]
2nd trimester	Tregs ($CD4^+$, memory), tolerogenic DCs, M2 macrophages	Sustain immune tolerance and promote placental development	Anti-inflammatory (IL-10, TGF-β)	[6, 20, 54, 78, 96, 98]
3rd trimester	Th1/Th17 cells (mild rise), $CD8^+$ T cells, inflammatory macrophages	Prepare for labor; reactivation of immune surveillance	Mildly pro-inflammatory (IL-6, IL-8, TNF-α)	[5, 13, 15, 35, 72, 92]

[a]This table summarizes immune cell dynamics across pregnancy trimesters, highlighting dominant cell types, their functions, and cytokine profiles relevant to each phase.

Table 9: Immunological pathways in obstetric complications.[a]

Disorder	Dysregulated pathways	Immune players involved	Biomarker potential	References
Preeclampsia (PE)	Checkpoint failure (PD-L1), reduced Tregs, pro-inflammatory cytokines	Tregs, NK cells, macrophages, exosomes	PD-L1, miR-210, IL-10, TGF-β	[13, 15, 72, 78, 85, 98]
Recurrent spontaneous abortion (RSA)	Loss of Tregs, reduced checkpoint signaling (TIM-3, PD-1), increased Th1/Th17	Tregs, Th1 cells, Th17 cells, DCs	Galectin-9, PD-1, IL-17, IFN-γ	[5, 27, 31, 58, 97, 98]
Fetal growth restriction (FGR)	Exosomal miRNA imbalance, vascular dysfunction, inflammation	Trophoblasts, monocytes, macrophages	miR-155, miR-210, VEGF, IL-6	[10, 35, 78, 85, 92]

[a]This table summarizes key immune dysregulations and associated biomarkers in major obstetric complications, linking them to specific immune pathways and cell types.

their evolutionary goals and host contexts – warrant careful distinction. Furthermore, many of the proposed interventions, such as checkpoint-targeted therapies and exosome engineering, are still experimental and untested in human pregnancy. Their safety, optimal timing, and long-term effects on both mother and fetus must be thoroughly evaluated in large, well-characterized cohorts.

To move from theory to practice, future research should focus on longitudinal immune profiling across all trimesters of pregnancy. This includes mapping changes in checkpoint expression, cytokine networks, and Treg subsets to distinguish healthy immune trajectories from those associated with pathology. More *in vivo* studies are needed to elucidate the role of exosomes under both normal and inflammatory conditions. Immunomodulatory therapies should be tested in rigorously designed clinical trials with ethical oversight that addresses the dual-patient nature of pregnancy and considers both immediate and long-term fetal outcomes.

The development of non-invasive immune biomarkers, such as circulating PD-L1, HLA-G, or exosomal microRNAs, could allow for early detection of immune imbalance and enable more personalized management strategies. Equally important are policy and ethical frameworks that can support these innovations. Informed consent processes must reflect the complexity of immune interventions in pregnancy, while regulatory guidance should prioritize maternal-fetal safety. Global access must also be addressed, particularly in settings where immune-mediated complications are most prevalent and resources are scarce.

Conclusions

This review redefines pregnancy not as a passive state of immune suppression but as a dynamic, immune-edited process governed by phases of elimination, equilibrium, and escape – concepts originally derived from oncology. By synthesizing evidence from 110 studies, we demonstrate that immune checkpoints (PD-1/PD-L1), regulatory T cells (Tregs), HLA-G/MHC signaling, and placenta-derived exosomes orchestrate maternal-fetal immune tolerance. When these mechanisms fail, immune escape pathways emerge, manifesting as obstetric complications including preeclampsia, recurrent pregnancy loss, and preterm birth.

The proposed immunoediting framework provides both conceptual clarity and translational opportunity. It suggests that pregnancy complications may often stem from primary immune dysregulation, rather than secondary consequences of placental dysfunction alone. This opens new frontiers for immune-based diagnostics, non-invasive biomarkers, and targeted immunomodulation informed by advances in oncology.

However, moving from theory to clinical application will require longitudinal immune profiling, *in vivo* validation, and carefully regulated clinical trials designed for the unique dual-patient context of pregnancy. Ethical considerations – including patient consent, fetal safety, and equitable access – must be central to these efforts. Ultimately, adopting an immune-centric perspective has the potential to transform obstetric care from reactive disease management to precision-based early intervention, improving outcomes for both mother and child.

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