CHAPTER 41

Maternal-Fetal Immunology

Gabrielle Rizzuto, MD, PhD • Adrian Erlebacher, MD, PhD

INTRODUCTION

Reproductive immunology is the study of phenomena that lie at the intersection of reproductive biology and immunology. It encompasses the immunology of male and (nonpregnant) female reproductive organs, which we do not discuss here, as well as the immunology of pregnancy, which is the topic of this chapter. Historically, the field has been dominated by interest in the paradox of "fetomaternal tolerance"—that is, how the fetus and placenta avoid being rejected by the maternal immune system—and this question will also be the focus of much of our discussion. Indeed, there is the sense that immunologists' failure to have "solved" this problem, despite its articulation almost 70 years ago, means that there is something fundamental to the nature of peripheral tolerance that we still do not have a handle on. Insight into fetomaternal tolerance, thus, in turn, is felt to have the potential of suggesting new ways to modulate the immune system in the clinic, with obvious application to autoimmune disease, transplantation, and cancer.

In addition to fetomaternal tolerance, we will discuss the influence of the maternal immune system over key developmental processes of pregnancy, including embryo implantation, placental development, and parturition (the act of giving birth). This influence, which has been increasingly appreciated over the last 30 years,[1] normally fosters pregnancy success but can also cause pregnancy complications with attendant detrimental effects on maternal and neonatal health. For example, intrauterine inflammation is now thought to be a significant component of the pathogenesis of preterm birth (PTB), whose adverse effects on neonatal health can extend into adulthood, while systemic maternal inflammation is thought to negatively affect fetal brain development and increase the risk of schizophrenia and autism spectrum disorders. We will also discuss infectious disease control during pregnancy, the pathogens that take advantage of the unique immunological environment of the maternal-fetal interface, and the specialized defense mechanisms that have evolved to counteract these pathogens and thus minimize vertical transmission to the fetus. In fact, reproductive immunology becomes a fascinating case study in evolutionary biology when considering the many adaptations that must be present to reconcile the competing demands of reproduction and host defense.

THE MATERNAL-FETAL INTERFACE

Anatomy, Development, and Microbiology

Maternal-fetal immunology is a challenging field since female reproductive systems are highly divergent across mammalian species. Fortunately, the basic topological arrangement between mother and conceptus (ie, all tissues derived from the fertilized egg, which includes the placenta) is always the same. The trophectoderm (ie, outer, epithelial) layer of the blastocyst gives rise to trophoblast cells, which comprise much of the placenta, including its outermost layer. Trophoblasts also comprise the outermost layer of the chorioamniotic membranes, which enclose the amniotic cavity where the fetus develops suspended in amniotic fluid.[1,2] Accordingly, trophoblasts constitute the entire "fetal" component of the maternal-fetal interface. Fortuitously, mouse and human placentas are also both "hemochorial," which means that the trophoblasts that mediate nutrient and gas exchange between mother and conceptus are directly bathed in maternal blood. However, there are key differences between mice and humans in placental substructure and trophoblast subtypes, as well as in the development of the decidua, which is the uterine tissue layer that encases the conceptus and thus forms the maternal component of the maternal-fetal interface. Given that the mouse is the primary model organism for work in maternal-fetal immunology, we will highlight these differences as we present some necessary background on reproductive biology.

The Decidua

The nonpregnant uterus of all mammals is a three-layered tube (Fig. 41.1A [left] and C). Its outer serosal layer surrounds the myometrium, which is the layer of thick smooth muscle that contracts during labor to expel the conceptus. The endometrium—the uterus's inner layer that abuts the uterine lumen and gives rise to the decidua—is essentially a dense fibroblastic stroma, lined by a simple cuboidal epithelium that contains glands and torturous "spiral" arteries. In mice, the endometrium becomes receptive to embryo implantation following copulation, an act that sets in motion a stereotypical endocrinological response that culminates in the ovary producing increasing amounts of progesterone overlaid with a small spike in estrogen production on gestation day (gd) 3.5 (see section *Implantation, Decidualization, and Early Pregnancy Failure*; N.B.: given that mice typically copulate at night, we will use a standard nomenclature that counts noon of the following day as gd0.5). Together, these hormones alter gene expression in endometrial stromal and epithelial cells to allow implantation to occur on gd4.5. In humans, the endometrium becomes receptive to embryo implantation on a monthly basis during the secretory phase of the menstrual cycle (Fig. 41.1C), a period similarly associated with increased progesterone production by the ovary.

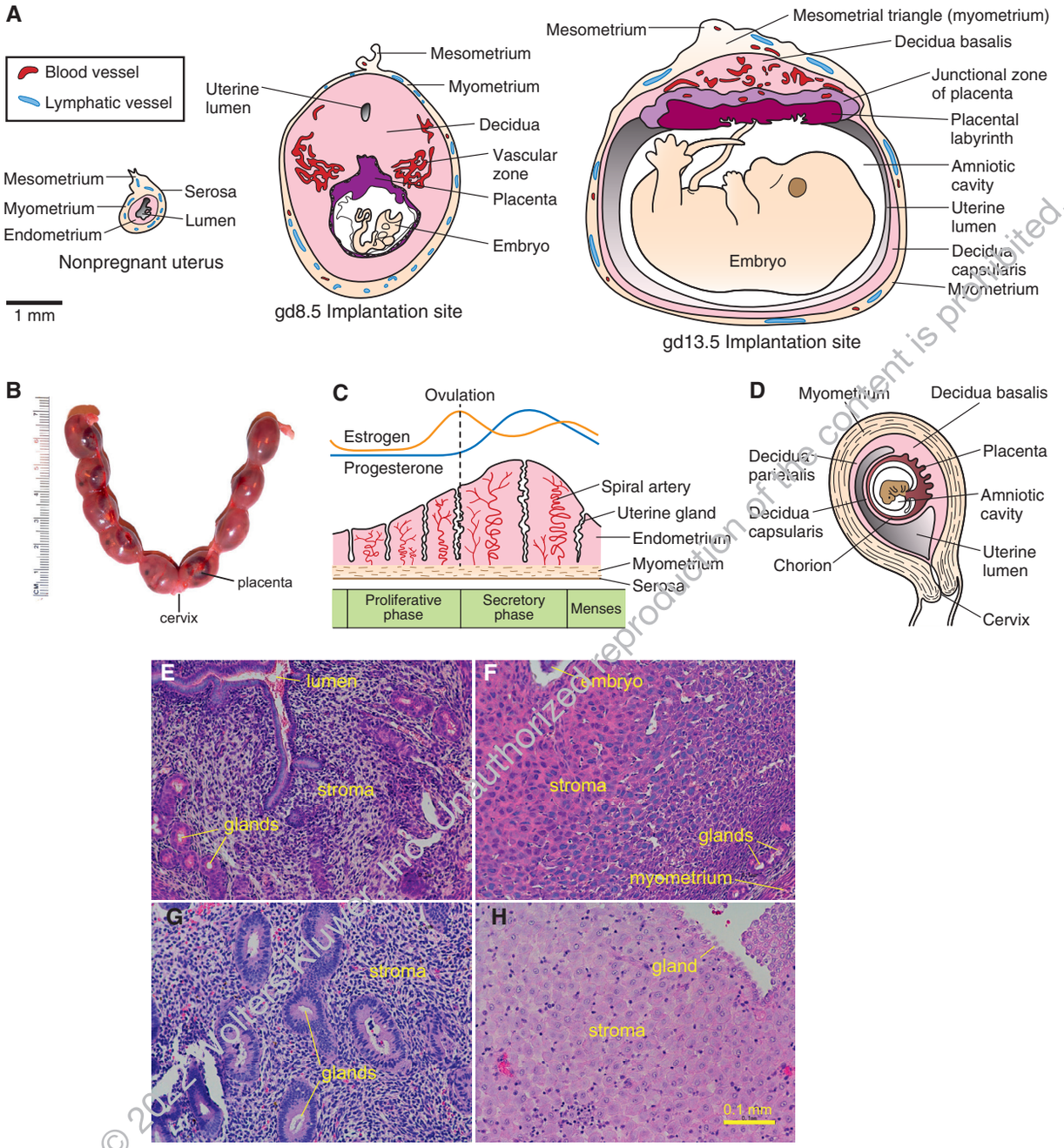

FIG. 41.1. Anatomic and histologic overview of the pregnant and nonpregnant uterus. A: Schematic of the pregnant and nonpregnant mouse uterus. The three images are shown to scale and all depict cross-sections that are perpendicular to the long axis of the uterine horn. The uterine serosa covers the myometrium in all three cases but is only indicated for the nonpregnant uterus. The middle and right images encompass all the tissues and tissue layers that constitute what we refer to as an "implantation site"—that is, the conceptus (embryo/fetus, placenta, and ancillary structures like the chorion and amnion), the decidua, and the overlying segment of myometrium. The mesometrium is the membrane that runs along the length of the uterus and harbors all the blood and lymphatic vessels that supply the uterus. Its position defines the mesometrial and antimesometrial poles of the implantation site. **B:** Whole-mount photograph of a pregnant mouse uterus on gd17.5. Note that the mouse uterus is bicornuate (ie, it possesses two horns). **C:** Schematic of the human endometrium as it appears over the course of the menstrual cycle. The associated fluctuations in serum levels of estrogen and progesterone, produced by the ovary, are also shown. **D:** Schematic of the pregnant human uterus in the first trimester. At ~17 weeks gestation (not shown), the chorioamniotic membranes (which arise from the fusion of the chorion and amnion) and associated decidua capsularis fuses with the decidua parietalis on the far side of the uterus. The chorioamniotic membranes then detach again prior to delivery, still attached to a layer of decidual tissue (now called the decidua parietalis). There is no equivalent layer of decidua parietalis in mice; rather, the entire antimesometrial pole of the decidua is comprised of decidua capsularis, and this tissue regresses around midgestation, leaving behind a layer of undecidualized endometrium covered with luminal epithelial cells that are not attached to the chorion (not depicted). **E-H:** H&E, stained sections of the undecidualized mouse **(E)** and human **(G)** endometrium and the decidualized mouse **(F)** and human **(H)** decidua. Panel E is a section of a segment of undecidualized uterus between implantation sites on gd6.5; Panel F is from one such implantation site. Panel G is from the human uterus during its proliferative phase; Panel H is from a first-trimester elective termination specimen.

The transformation of the endometrium into the decidua, that is, decidualization, entails the transdifferentiation of endometrial stromal cells (ESCs) into decidual stromal cells (DSCs) (for a review, see Ref. 3). The former cells are small and fibroblastic, whereas the latter are large and epithelioid (Fig. 41.1E-H). In mice, decidualization is triggered by implantation and unfolds in a highly stereotypical fashion around each embryo, both temporally and spatially. Thus, since mice are multiparous and all embryos implant at the same time, decidualization occurs synchronously at multiple locations along the length of each uterine horn, giving rise to a set of synchronously growing and developing "implantation sites"—a term we will use to refer to the conceptus, its associated decidua, and the segment of overlying myometrium (Fig. 41.1A [middle and right] and B). In contrast to mice, the human endometrium spontaneously decidualizes to a limited extent during the secretory phase of the menstrual cycle in anticipation of implantation; however, the full transformation of ESCs into DSCs is not apparent unless implantation occurs.

Importantly, the decidua shows regional specialization. The decidua basalis anchors the placenta to the uterus and thus serves as the physical substratum for placental development and the support structure for the uterine spiral arteries that supply the placenta with maternal blood[3] (Fig. 41.1A [middle and right] and D). By contrast, the decidua capsularis lies at the opposite pole of the embryo, which means that in humans, it surrounds the chorioamniotic membranes (see Fig. 41.1 legend for additional detail). Commonly referred to as the "fetal membranes" by researchers and pathologists, the chorioamniotic membranes and associated decidua are delivered along with the rest of the conceptus and provide much of the material for the published analyses of the human decidua in late gestation.

From an immunological perspective, the decidua is important because it is a prime location for infection and harbors all the maternal leukocytes that come into proximity with trophoblasts under normal circumstances. How its immunological milieu is established thus has major implications for mechanisms of fetomaternal tolerance (see section *Mechanisms of Fetomaternal Tolerance*), host defense (see section *Infectious Diseases and Pregnancy*), and the immunological control of placental development (see section *Developmental Influences of the Maternal Immune System Over Pregnancy*). At present, there are indications that trophoblasts themselves can modulate decidual leukocyte phenotypes, as will be discussed immediately below. However, a much more fundamental role has been ascribed to DSCs and the gene expression changes that occur as ESCs transform into DSCs given the pervasive effects of these changes over decidual immune cell phenotypes, trafficking, and population dynamics. For example, differentiating mouse and humans DSCs upregulate genes encoding the cytokine IL-15 and the chemokine CXCL14. These factors are thought to promote the massive accumulation of decidual natural killer (dNK) cells necessary for uterine spiral artery remodeling, the process that ensures sufficient placental perfusion with maternal blood (see section *Spiral Artery Remodeling, IUGR, and Preeclampsia*). Conversely, mouse DSCs transcriptionally silence *Cxcl9*, *Cxcl10*, *Cxcl12,* and *Cxcl16*, which encode chemokines that recruit type-1 polarized T cells (Th1 cells and cytotoxic T-lymphocytes [CTLs]) from the blood to peripheral tissues, as well as *Csf1*, which encodes the prototypical macrophage growth factor CSF-1.[4,5] Thus, and as discussed further in sections *Immune Cells of the Pregnant Uterus* and *Mechanisms of Effector Phase Tolerance to the Conceptus*, the mouse decidua cannot accumulate activated T cells, in contrast to the endometrium, nor can it homeostatically expand its resident macrophage population as it grows in the early gestation.[5,6]

In mice, the gene signature of experimentally induced "deciduomas" that lack embryos are nearly identical to true pregnancy decidua.[7] Moreover, cultured human ESCs upregulate IL-15 and CXCL14 when treated with progesterone.[8] These data suggest that DSCs establish their unique transcriptional state through an endocrine-regulated developmental program without much input from the conceptus. Specific regulatory circuits with relevance to immune cell control, however, have only recently started coming into view, and considerable challenges face attempts to identify pathways that are conserved across species. For example, *Cxcl9*, *10*, *12*, *16,* and *Csf1* silencing represents a small part of a much broader epigenetic program activated in mouse DSCs that affect ~800 protein-coding genes.[4] The program is mediated via polycomb repressive complex-2 (PRC2), which catalyzes generation of the repressive histone mark H3K27me3 on gene promoters. However, it is unknown what induces PRC2 activity during the early stages of decidualization or how PRC2 is targeted to these 800 specific loci. It is also unclear whether an analogous pathway applies to human DSCs, even though human T cells, like mouse T cells, appear unable to accumulate at the maternal-fetal interface (see sections *Immune Cells of the Pregnant Uterus* and *Mechanisms of Effector Phase Tolerance to the Conceptus*). The role of progesterone also remains incompletely defined—even though ESCs express its nuclear receptor, progesterone exposure *in vivo* is insufficient to induce the DSC phenotype in mice (since decidualization only occurs at implantation sites) nor do secretory phase ESCs in humans fully manifest the DSC phenotype, as mentioned above. Further complicating the picture is the likelihood that the DSC transcriptome evolves over course of gestation to meet the changing needs of pregnancy, including the onset of labor.[4] Thus, the regulation of decidual leukocytes is also thought to change over time.

The Placenta

The placenta is the organ of nutrient and gas exchange between fetal and maternal blood.[2] This takes place in its central region—the labyrinth in mice and the villous tree in humans—where a vast fetal capillary network sheathed by layers of specialized trophoblast subtypes receives deoxygenated fetal blood from umbilical cord arteries and sends oxygenated and nutrient-rich blood back to the fetus via the umbilical cord vein. The outermost cell layer of the human villous tree is a fused, syncytial layer comprised of syncytiotrophoblasts. These cells are bathed in maternal blood but are not a site of leukocyte-trophoblast interaction under normal circumstances. Indeed, routine microscopic examination of the human placenta rarely, if ever, reveals leukocytes adherent to syncytiotrophoblasts even though the latter cells' apical surface is under low

shear stress. Why this is the case has not been mechanistically explored in mice, but in humans, it likely relates to the inability of syncytiotrophoblasts to express many of the adhesion molecules typically used by endothelial cells to recruit blood-borne leukocytes, including E-selectin, VCAM-1, and ICAM-2 even when the cells are exposed to inflammatory cytokines.[9,10] Only ICAM-1 is inducible, and this is apparent *in vivo* only in focal pathological lesions of placental villi that show leukocyte infiltration (eg, see section *Are There Any Examples of Placental "Rejection"?*).[9-12] In addition, syncytiotrophoblasts express high levels of ACKR2, a decoy receptor for CC chemokines, which thus potentially mitigates firm adhesion for all responsive leukocytes.[13,14] By whatever mechanism, its upshot is that maternal immune cells only interact with trophoblasts within the decidua under normal circumstances, as alluded to above. These trophoblasts, which in humans are called extravillous trophoblasts (EVTs) because they originate from the villi that anchor the placenta to the decidua, populate the decidua interstitially as well as migrate into uterine spiral arteries to reroute maternal blood flow to the placenta. Importantly, syncytiotrophoblasts express the neonatal Fc receptor, FcRn, which demonstrates low pH-dependent binding to maternal IgG in endosomes and then releases the IgG at the syncytiotrophoblast's basolateral surface into the villous core.[15,16] Maternal IgG is then transferred across the villous capillary endothelium, likely via FcγRIIb2,[17] to reach the fetal circulation. This passive transfer of maternal antibodies occurs predominantly in the third trimester and provides the neonate with a certain level of preexisting immunity to the spectrum of pathogens that will be present in its new environment.

Like DSCs, trophoblasts within the decidua are also thought to regulate decidual immune cells. Most clearly, classical major histocompatibility complex (MHC) class I (MHC-I) molecules expressed by both mouse and human trophoblasts modulate the phenotypes of dNK cells and their influence over spiral artery remodeling (see sections *Immune Cells of the Pregnant Uterus* and *Spiral Artery Remodeling, IUGR, and Preeclampsia*). Other than this example, however, trophoblast-leukocyte interactions are poorly understood and starkly illustrate the mouse-human dichotomy in reproductive systems. For example, human EVTs and syncytiotrophoblasts express the T cell inhibitory molecule PD-L1, in contrast to mouse trophoblasts.[18-22] Although not a uniform finding,[20] human EVTs have also been reported to produce the macrophage growth factor CSF-1 and the anti-inflammatory cytokine IL-10[23] in contrast to mouse trophoblasts.[9,24] Perhaps, most famously, human EVTs express human leukocyte antigen (HLA)-G, a nonclassical MHC class I molecule that does not even exist in mice. Extensive work on HLA-G since its discovery in the 1980s[25] has revealed multiple transmembrane and secreted isoforms, a limited degree of polymorphism, and an unusual mode of transfer between cells known as trogocytosis, and its provision through its leader sequence of a high-affinity peptide for HLA-E, another nonclassical MHC class I molecule.[25,26] There is also agreement that HLA-G does not directly interact with the T-cell receptor (TCR) complex on CD8 T cells but rather engages two inhibitory receptors known as LILRB1 and LILRB2 expressed primarily by myeloid cells. LILRB1 is also expressed by subsets of NK cells, including dNK cells. However, there is considerable controversy over whether HLA-G performs an important function at the maternal-fetal interface, such as the attenuation of local immune responses. Given that it lacks a mouse homolog, all functional studies to date have been inferential in nature and indirect. For contrasting opinions, the reader is referred to references 25-28, with key points of contention being whether HLA-G is ever actually expressed by cells other than EVTs, whether it meaningfully engages KIR2DL4, a killer Ig-like receptor expressed by NK cells, and whether correlations between HLA-G alleles and clinical outcomes in the setting of various human diseases have true significance. Of note, some people are homozygous for null alleles for HLA-G, indicating that the molecule is not singularly required for pregnancy.

Does the Maternal-Fetal Interface Have a Microbiome?

For over a century, microbiology experiments supported the "sterile womb paradigm," which posits that the healthy placenta and pregnant uterus do not harbor commensal organisms. Indeed, the fact that germ-free mammals can be generated by cesarean delivery provides support for fetal sterility *in utero*.[29] Modern advances in sequencing technology have led investigators to revisit this paradigm, however, and some studies have instead concluded that healthy human and mouse placentas are colonized by a low abundance, metabolically rich microbiome,[30-33] and that the fetal gastrointestinal tract may even become colonized *in utero*[34,35] Although intriguing, these conclusions are currently controversial. Thus, with the exception of the ~5% of placentas colonized with Group B *Streptococcus (GBS)* organisms, which are common and well-appreciated causes of "ascending" placental infection (see section *Immune Defenses at the Maternal-Fetal Interface*), other work finds that the bacteria detected in healthy placental samples are instead environmental contaminants.[36-39] Of note, recent sequencing studies have identified a predominance of *Lactobacillus* bacteria in the nonpregnant human uterus,[40,41] and there is some evidence that altered colonization may be associated with reproductive failure. [42,43] The field thus awaits a consensus understanding of whether a microbiome is present in the nonpregnant and pregnant uterus, the placenta, and/or the fetus; and if so, how this impacts fertility, pregnancy, and fetal immune development.

Immune Cells of the Pregnant Uterus

Although it would inherently make sense that the maternal-fetal interface would be an immunological desert in order to avoid any possibility of causing immunological damage to the conceptus, research over the last 30 years has revealed this to be only partially true. Thus, while certain immune cell types in certain species (eg, Th1 cells and CTLs in mice) are actively excluded from the decidua, others are present in large numbers and contribute to some of the key developmental events of pregnancy. In this section, we provide an overview of how immune cell dynamics and phenotypes are controlled within the decidua and myometrium. Endometrial immune cell dynamics in response to copulation and semen exposure are discussed, along with the role of the maternal immune system in implantation in section *Implantation, Decidualization, and Early Pregnancy Failure*.

NK Cells

NK cells are the most prevalent immune cell type at the maternal-fetal interface and have characteristics that distinguish them from NK cells elsewhere in the body (for reviews, see Refs. 44-47). In humans, they were first visualized histologically as large granulated lymphocytes that appear in the late secretory endometrium and then become prominent in the first-trimester decidua, where they constitute ~70% of all leukocytes.[48,49] Subsequent flow cytometric studies revealed the cells to have a characteristic lin$^-$ CD56^{superbright} CD16$^-$ surface phenotype that contrasts with peripheral blood NK cells.[46] Thus, these CD56^{superbright} cells have historically been referred to as dNK cells. We will also refer to NK cells in mouse implantation sites as dNK cells, although we note that in this species, the cells also accumulate in portions of the myometrium (see below). Mouse dNK cells are CD45$^+$ CD3$^-$ CD19$^-$ NKp46$^+$ NK1.1$^+$ (strain-dependent) by flow cytometry, uniformly express the transcription factor T-bet (Tbx21), and are distinguished from rare uterine group 1 innate lymphoid cells (ILC1s) by their expression of the transcription factor Eomes.[50-54] They comprise ~50% of all decidual leukocytes as early as gd5.5,[55] and, like human dNK cells, become large and granular but only after implantation. This phenotypic shift is evident histologically, as the cells become positive for periodic acid Shiff (PAS) reagent and the lectin *Dolichos biflorus* agglutinin (DBA), a unique feature of dNK cells in mice. NK cells decline in frequency in both the mouse and human decidua after their peak in early-mid gestation, but in humans, they remain a sizable population even at term gestation.[56-62]

A key function for dNK cells is to provide developmental support to the conceptus via the elaboration of cytokines, chemokines, and growth factors. Most importantly, the cells control uterine spiral artery remodeling, a critical developmental process that ensures adequate perfusion of the placenta with maternal blood[44-46] and that will be discussed in section *Spiral Artery Remodeling, IUGR, and Preeclampsia*. In addition, recent work on human cytomegalovirus (HCMV) and *Listeria monocytogenes* has revealed that they contribute to host defense at the maternal-fetal interface. This function will be discussed in section *Immune Defenses at the Maternal-Fetal Interface*. As researchers dissect these functions, they are starting to incorporate recent data indicating that dNK cells fall into distinct subsets. In mice, dNK cells are comprised of CD49a$^+$ DX5$^-$ and CD49a$^-$ DX5$^+$ cells.[50-53] Parabiosis experiments have revealed the CD49a$^+$ cells to be noncirculating tissue-resident (tr)NK cells, consistent with the CD49a$^+$ DX5$^-$ phenotype being a general indicator of tissue residency, and the CD49a$^-$ DX5$^+$ cells to be derived from circulating, conventional (c)NK cells.[52,62] trNK cells are ~threefold more abundant than cNK cells in the nonpregnant uterus,[50-52,54] but their ratio changes in a highly dynamic fashion as both populations expand over the first half of gestation within the growing implantation site.[54] Thus, trNK cells become by far the dominant subset prior to ~gd8.5 as a result of a rapid burst of proliferation, after which point cNK cells become the dominant subset, presumably as a result of their recruitment from the blood since they do not proliferate in situ.[53,54,62] The two subsets also appear to have distinct functions, with cNK cells being the primary drivers of spiral artery remodeling, a process that commences with onset of their influx on gd8.5.[51] This function is consistent with their higher expression of interferon (IFNγ), a cytokine long known to be critical for spiral artery remodeling in mice.[53,54,63] The functions of trNK cells are less well understood but potentially involve restricting trophoblast invasion into the decidua and controlling fetal growth.[64,65]

In the first-trimester human decidua, almost all dNK cells are CD49a$^+$ tissue-resident cells, with single-cell (sc) RNA-seq and CyTOF analyses dividing them into two subsets, both of which are proliferating to some extent: CD49^{hi} EOMES^{hi} TBX21^{lo} dNK1 cells and CD49^{int} EOMES^{int} TBX21^{int} dNK2 cells.[20,53,66] A third population, called dNK3 cells in the scRNA-Seq study,[20] are likely intraepithelial ILC1s.[66] Intriguingly, dNK1 cells, which have a low capacity to produce cytokines and chemokines following nonspecific stimulation,[66] resemble a population of "pregnancy-trained" dNK cells that increase in prevalence with repeat pregnancies, which suggests that dNK cells can demonstrate features of immunological memory as described for NK cells elsewhere in the body.[66,67] Whether they contribute to any of the pregnancy complications that decline in incidence with increasing gravidity, such as preeclampsia,[68] is currently unknown.

Aside from their division into subsets, dNK cells are instructed to assume their final, unique phenotype by locally produced factors. In humans, these include TGF-β and IL-15, which together cause peripheral blood NK cells to display certain features of dNK cells, including their distinct patterns of surface marker and activating/inhibitory receptor expression.[53,66,69-72] While IL-15 in the decidua is produced by DSCs (see below), the source of TGF-β may be either DSCs or decidual macrophages.[70,73] Activating/inhibitory receptor expression patterns differ between dNK subsets and are influenced by an NK cell education process that takes place partly within the endometrium, prior to pregnancy, and partly within the decidua.[20,66,74-76] For example, dNK1 cells express high levels of the HLA-G receptor LILRB1, suggesting direct interactions with EVTs.[20,66] Once established, these patterns allow EVTs and other cell types to modulate dNK cell secretory phenotypes in ways that impact upon pregnancy success.[65,72,77] Importantly, dNK cells show substantially reduced cytotoxicity toward MHC-I–deficient cells, despite their granules containing perforin and granzymes, and an extremely limited ability to kill EVTs (which express a limited repertoire of MHC-I; see section *Introduction to Fetomaternal Tolerance – History and Overview*). These findings have implications for our understanding of mechanisms of NK cell tolerance toward the conceptus and are discussed further in section *NK Cell Tolerance Toward the Conceptus*.

The factors that drive dNK cell expansion and localization during pregnancy remain incompletely defined. In the human decidua, dNK cells are somewhat enriched at sites of trophoblast invasion and vascular remodeling but are otherwise relatively homogeneously distributed.[78] In contrast, the distribution of dNK cells in mouse implantation sites is highly polarized, as they accumulate in the decidua basalis (the portion of the decidua described in section *Anatomy, Development, and Microbiology; The Decidua* that anchors the placenta; Fig. 41.2A) and overlying

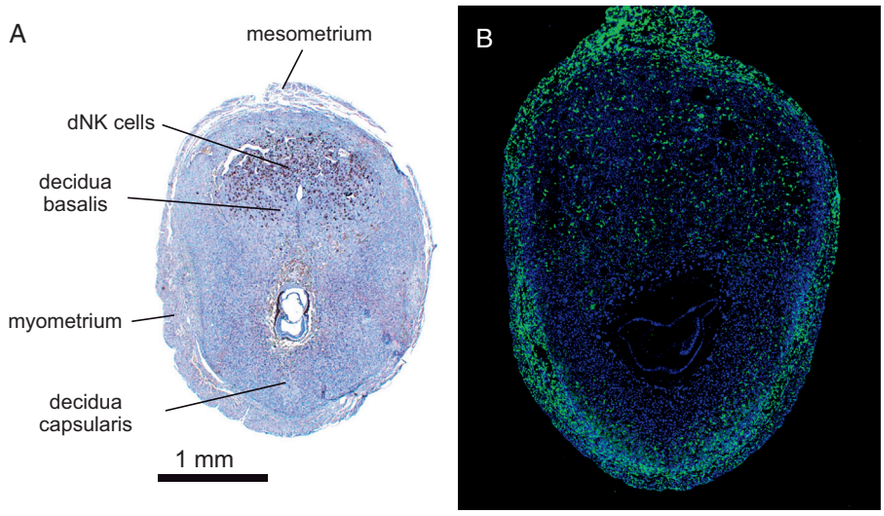

FIG. 41.2. Distribution of natural killer (NK) cells and macrophages in mouse implantation sites. A: A gd7.5 implantation site was stained with *Dolichos biflorus* agglutinin (DBA) lectin (*brown*) to reveal the accumulating population of decidual (d)NK cells in the decidua basalis. As gestation progresses, NK cells also accumulate in the mesometrial triangle above the decidua basalis. **B:** A gd8.5 implantation site was stained with antibodies to F4/80 (*green*) to reveal macrophages. Notice the clearing of macrophages from the decidua, in particular the decidua capsularis. The density of macrophages in the myometrium is similar to what is seen in the myometrium of the nonpregnant uterus.[6,79] DAPI (4′,6-diamidino-2-phenylindole) counterstain. (A, Image courtesy of Patricia Lima and B. Anne Croy, Queen's University).

segment of myometrium (variously called the mesometrial triangle, metrial gland, or mesometrial lymphoid aggregate of pregnancy), but are absent from the decidua capsularis.[46] This distribution makes physiological sense given that the decidua basalis contains the spiral arteries that supply the placenta with maternal blood and that will be remodeled by dNK cells.

One cytokine that likely drives dNK cell accumulation is IL-15. IL-15 required for the generation of dNK cells in mice[80,81] is highly expressed by both mouse and human DSCs and is detectable on the surface of mouse DSCs consistent with their concomitant expression of IL-15Rα.[4,20,82] IL-15 induction in the mouse decidua likely promotes the expansion of both trNK cells and cNK cells by prolonging their survival, but the extent to which it drives dNK cell proliferation is unclear since trNK but not cNK cells proliferate within the pregnant uterus.[62] cNK cell recruitment to the decidua is likely mediated by the chemokine CXCL14, which is highly expressed by DSCs of both mice and humans[4,20,83] and is likely further promoted in mice by the endothelial cell adhesion molecule VCAM-1, which is expressed by vessels in the decidua basalis.[84] Members of the TGF-β superfamily also locally control dNK cell numbers, directly or indirectly, as does adrenomedullin produced by the murine placenta.[85,86] Importantly, mice with artificial deciduomas lacking implanted embryos contain high numbers of dNK cells distributed with a pattern essentially the same as that seen with true implantation sites,[87] demonstrating that the pattern is established independently of embryonic/placental signals.

Innate Lymphoid Cells

In addition to NK cells, the pregnant uterus harbors other kinds of ILCs. As mentioned above, mouse implantation sites contain a few ILC1s,[50-52,54] and the first-trimester human decidua contains ILC1s that are likely to be intraepithelial.[66,88] The first-trimester human decidua also contains ILC3s, but these cells are very rare in the mouse decidua.[50,53,66,88] ILC2s are completely absent from both the first-trimester human and mouse decidua[50,88] but are present in the mouse myometrium during pregnancy where they constitutively produce their signature cytokine, IL-5.[50] This tissue distribution may explain the parallel uterine distribution of eosinophils, as ILC2s locally control tissue eosinophil numbers throughout the body through their expression of this key eosinophil survival factor[89] (see below). Otherwise, the function of uterine ILCs during pregnancy is unknown. Interestingly, recent work suggests that decidual ILC2s become quite abundant in the late gestation human decidua, suggesting that they are dynamically regulated.[90]

T Cells

After NK cells, T cells are the best studied cell type in the pregnant uterus, given the field's interest in mechanisms of fetomaternal tolerance. In the first-trimester human decidua, they comprise ~10% of all leukocytes,[59,60,91] a frequency that progressively increases to ~40% to 50% by term gestation.[60,91,92] The cells divide roughly evenly between $CD4^+$ and $CD8^+$ cells, with the two subsets constituting ~40% each of all $CD3^+$ cells at term gestation and the remaining ~20% being $CD4^-$ $CD8^-$ T cells in turn comprised of γδ T cells and poorly understood αβ T cells.[92,93] Importantly, the increase in T cell frequencies with advancing gestation likely reflects a relative loss of NK cells rather than change in true histological tissue densities, which remain relatively constant.[58,59] Indeed, the most dramatic shift in endometrial/decidual T cell tissue densities, assessed histologically, occurs with the onset of pregnancy, as T cells are ~50% less dense in the decidua as compared to the secretory endometrium.[94] An analogous pattern is seen in mice with respect to the ability of the endometrium but not the decidua to recruit, and thus accumulate, blood-borne effector T cells.[5] This phenomenon, which is relevant to mechanisms of fetomaternal tolerance, was discussed in sections *Anatomy, Development, and Microbiology* and will be discussed further in *Mechanisms of Effector Phase Tolerance to the Conceptus*. In mice, T cells comprise ~5% of all leukocytes in both the decidua and myometrium on gd9.5.[95] Like in humans, $CD4^-$ $CD8^-$ T cells with unknown function[96] comprise ~20% to 40% of all decidual $TCR\alpha\beta^+$ T cells.[97]

CD8 T cells in the human decidua are mainly $CD45RO^+$, indicative of prior antigen encounter, and have been historically considered to be effector memory cells given their

predominant CD45RA$^-$ CCR7$^-$ surface phenotype.[56,98-100] However, the cells also uniformly express high levels of CD69, which is now recognized as the signature marker of tissue-resident memory (Trm) cells in humans,[101] and many also express CD103, another Trm marker.[56,102-106] Thus, decidual CD8 T cells might largely be Trm cells, as noted explicitly in recent work,[107] and thus likely the same Trm cells that comprise half of all endometrial CD45RO$^+$ CD8 T cells at the time of implantation.[108] Decidual CD8 T cells moreover show an activated surface phenotype as well as a robust capacity to proliferate, kill target cells, and produce cytolytic molecules and cytokines (IFNγ, TNFα, IL-2, IL-10) upon mitogen stimulation.[99,100,103-105,109,110] Thus, they might also be "effector-like" Trm cells that are able, without chronic antigenic stimulation, to persist in peripheral tissues in a semiactivated state, poised to mount rapid recall responses.[111] The cells also express PD-1 and other exhaustion markers,[100,103,110] a phenotype that may be relevant to mechanisms of fetomaternal tolerance, but it is worth noting that nonexhausted Trm cells in other locations, including the nonpregnant endometrium, also express these markers.[101,108]

Like decidual CD8 T cells, decidual CD4 T cells in humans are primarily CD45RO$^+$ CD45RA$^-$ CCR7$^-$ CD69$^+$ and robust cytokine producers. Thus, they may also largely be Trm cells and/or effector memory cells.[56,98,100,105,112] Like elsewhere in the body, they divide into the various T-helper subsets, with 5% to 40%, 1% to 5%, 1% to 7%, and 5% to 10% being Th1, Th2, Th17, and FoxP3$^+$ CD25^{hi} T_{reg} cells, respectively, in both the first and third trimester.[91,100,112-115] Like their CD8 counterparts, many of the cells express PD-1,[100] while the T_{reg} cells are predominantly HELIOS$^+$ and thus thymically derived.[116] In the mouse decidua, CD4 T cell subset proportions remain poorly defined, and the extent to which mouse decidual T cells, in general, are Trm cells has not been addressed. T_{reg} cells comprise ~2% to 4% of the CD4 T cells; however, surveys performed to date need to be interpreted with caution since mouse decidual T cell preparations contain large numbers of naïve cells, indicating extensive blood contamination.[97]

The antigenic specificity of decidual T cells remains largely unknown. To the extent that the cells are Trm cells, we would expect their specificity to be determined by events prior to pregnancy onset. In particular, prior infections, not only of the uterus itself but also systemically given that circulating Trm precursors widely seed peripheral tissues, would be expected to define the decidual T cell repertoire. Accordingly, HCMV- and EBV-specific CD8 T cells can be detected at nontrivial frequencies of 1% to 3% in first and third trimester decidual specimens.[103,117] Given that pregnancy systemically generates memory T_{reg} cells and quasimemory CD8 cells specific for trophoblast antigens (see section *The Nonimmunogenic Nature of Trophoblast Antigens*), it is likely that prior pregnancies would generate decidual T cells with these specificities as well. Indeed, paternal HLA-C alloreactivity and clonal expansion of human decidual T cells have been documented to a limited extent.[20,93,100] Importantly, however, the apparent activated state of decidual T cells does not necessarily imply antigen reengagement since, as mentioned, effector-like Trm cells show the same phenotype at baseline. Moreover, IL-15, which as mentioned is highly expressed by human and mouse DSCs, strongly induces surface activation marker expression on human CD8 T cells in the absence of concurrent TCR stimulation.[118] In a similarly antigen-independent fashion, human decidual macrophages and EVTs each mildly increase T_{reg} cell frequencies in bulk CD4 T cell cultures,[23,116,119] although paternal alloantigen-specific T_{reg} cell expansion in the pregnant mouse uterus has also been documented in certain experimental systems.[120,121]

Given their potential to produce proinflammatory cytokines and, in principle, even kill trophoblasts, decidual Th1 cells, and Th17 cells, and CTLs are assumed to pose latent threats to pregnancy success. In contrast, decidual T_{reg} cells are thought to promote successful pregnancy via effects on implantation, decidual vascular remodeling, fetomaternal tolerance, and the maintenance of uterine quiescence prior to labor onset. These functions will be described in sections *Mechanisms of Effector Phase Tolerance to the Conceptus*, *Implantation, Decidualization, and Early Pregnancy Failure*, *Spiral Artery Remodeling, IUGR, and Preeclampsia*, and *Parturition and PTL*. Importantly, Rag-deficient mice show no reproductive defects, demonstrating that B and T cells are not required for pregnancy success in this species and that the proposed functions for decidual T_{reg} cells all involve the suppression of inflammation generated by other adaptive immune cell types and not the direct regulation of developmental processes.

B Cells

B cells comprise only ~2% of decidual leukocytes, a percentage that remains constant over gestation.[60] The population is largely comprised of naïve and transitional B cells, suggesting that they might be mainly intravascular.[122]

Macrophages and Monocytes

Macrophages constitute ~20% of all leukocytes in the first-trimester human decidua are identified by their CD14$^+$ surface phenotype and uniformly express CD68, consistent with tissue residence.[123] Although subsets are coming into view,[124,125] the cells in aggregate express high levels of CD163, CD206, CD209 (DC-SIGN), and IL-10, indicating a specialized M2-like phenotype with the potential to suppress inflammation and promote tissue repair.[123,126-128] Indeed, macrophages appear to be a major source of IL-10 in the first-trimester decidua and secrete this cytokine spontaneously.[129]

Macrophages in mouse implantation sites divide evenly into two subsets, F4/80$^+$ MHCII^{hi} and F4/80$^+$ MHCII^{lo}, with the MHCII^{lo} subset roughly corresponding to M2 cells.[6] As with dNK cells, their population dynamics in early gestation demonstrate how the developmental changes undertaken by the pregnant uterus determine resident immune cell behavior. Accordingly, uterine macrophage densities are controlled in a tissue layer-specific fashion by local levels of CSF-1, which, as mentioned, is the prototypical macrophage growth and survival factor and whose encoding gene *Csf1* is transcriptionally silenced in DSCs (see section *Anatomy, Development, and Microbiology*). Thus, while *Csf1* expression increases in the myometrium as it rapidly grows, it remains low in the decidua, and this means that only the myometrium maintains relatively constant macrophage tissue densities[6] (through a combination of in situ proliferation and Ly6C^{hi} monocyte precursor recruitment from the blood). In contrast, macrophage tissue densities, which are high in the undecidualized

endometrium, drop off in the decidua[4,6,79,130-132] (Fig. 41.2B). Remarkably, Ly6C^{hi} monocytes are abundant in the early mouse decidua, but the cells remain intravascular in association with the endothelial cells of the vascular zone.[6,133] CSF-1 also prevents myometrial macrophages from converting into MHCII^{hi} cells, thus fostering the M2-like phenotype.[6]

It is unlikely that analogous pathways control human uterine macrophage dynamics since macrophages robustly proliferate in the first-trimester human decidua, and their histological tissue density in this tissue layer is similar to or even modestly higher than that of endometrial macrophages in the nonpregnant uterus.[48,126,127,134] Moreover, CSF-1 exposure *in vitro*, particularly in combination with IL-10, causes human blood monocytes to assume the M2-like phenotype of first-trimester decidual macrophages, a phenotype that contrasts with their more M1-like phenotype in the endometrium.[122,124,126,127,134] Together, these data suggest that first-trimester decidual macrophages are under the influence of CSF-1. Interestingly, *CSF1*, while expressed by human DSCs at relatively low levels, like murine DSCs, is highly expressed by human decidual pericytes.[20] This observation might explain not only why macrophages modestly accumulate around spiral arteries in humans[78] but also since pericytes are largely absent from the mouse decidua,[135] why decidual macrophages do not expand in mice. Additionally, CSF-1 is produced by first trimester human EVTs but not by mouse trophoblasts.[23,24] Decidual macrophage tissue densities modestly decline after the first trimester,[58] suggesting that CSF-1 production wanes with advancing gestation.

While macrophages likely clear the endometrial debris generated by menstruation,[136] their role in normal pregnancy remains unclear. Human decidual macrophages might contribute to spiral artery remodeling (see section *Spiral Artery Remodeling, IUGR, and Preeclampsia*),[78,126,137] and their production of IL-10 might help ensure that the uterus remains in a noninflamed, quiescent state until term gestation (see sections *Implantation, Decidualization, and Early Pregnancy Failure* and *Parturition and PTL*). This latter function might involve perpetuation of the M2-like phenotype and the induction of decidual T_{reg} cells.[23,116] Human decidual macrophages also form conjugates with dNK cells in situ and inhibit dNK cell-mediated killing of EVTs *in vitro*, in this case via a TGF-β–dependent mechanism.[73,127] Macrophages, perhaps with a more M1-phenotype, may also promote normal human parturition since they accumulate within decidua and myometrium upon labor onset (see section *Parturition and PTL*).[138-141] Similar, but mild, accumulations of monocytes and macrophages are also apparent in the late gestation rodent uterus.[138,142]

However, pending a close examination of possible roles in spiral artery remodeling, uterine macrophages, and monocytes in mice appear to play little role in normal pregnancy and parturition. Thus, CSF-1–deficient *op/op* mice, which bear very few uterine macrophages, do not have reported reproductive phenotypes aside from reduced ovulation rates.[130,143,144] Similarly, *Ccr2*$^{-/-}$ mice, which are unable to recruit Ly6C^{hi} monocytes from the blood to the uterus, have no reported reproductive defects and display normal parturition timing, as do mice depleted of circulating monocytes.[6,145,146] Rather, the existence of mechanisms to actively prevent macrophage accumulation within the mouse decidua, and to induce the unique M2-like phenotype of decidual macrophages in humans, highlights the potential negative impact of these cells. Such a net-negative likely reflects their ability to produce inflammatory mediators and is consistent with the cells, in humans, being more M1-like in spontaneous preterm labor (PTL) and in cases of spontaneous abortion.[128,141]

Macrophages also comprise almost all the immune cells that reside within the body of the placenta, that is, within the villous tree in humans (where they are called Hofbauer cells) and the placental labyrinth in mice.[147-149] These populations are fetal in origin. While mouse placental macrophages have barely been studied, Hofbauer cells assume an M2-like phenotype like their decidual counterparts, presumably in order to attenuate placental inflammation under normal conditions. Recent work in the rhesus macaque has also identified multiple subsets.[148] As will be described in sections *Are There Any Examples of Placental "Rejection"?* and *Immune Defenses at the Maternal-Fetal Interface*, the cells have roles in placental inflammation and infection,[147] but their functions during normal gestation are unknown.

Dendritic Cells

Like elsewhere in the body, conventional CD11c^{+} dendritic cells (DCs) (ie, both cDC1s and cDC2s) populate the mouse endometrium and are able to migrate to the draining LN, where they presumably initiate T cell responses to uterine pathogens.[79] But like their macrophage counterparts, their tissue density in the growing decidua drops off dramatically in early gestation due to their failure to undergo homeostatic expansion, leaving very few DCs near the conceptus.[6,79] Remarkably, the mouse decidua also lacks lymphatic vessels, which means that the few decidual DCs that do exist are unable to migrate to the uterine-draining LN.[79] Together, these observations mean that there is minimal DC surveillance of the maternal-fetal interface, a feature of mouse pregnancy that has implications for mechanisms of fetomaternal tolerance and infectious disease control and that will be discussed further in sections *How Maternal T Cells Come to Engage Trophoblast Antigens* and *Immune Defenses at the Maternal-Fetal Interface*. Plasmacytoid DCs are largely absent from the mouse decidua.[97]

Identified as CD83^{+} cells, human DCs are exceedingly rare in the decidua, but in contrast to mice, they are also quite rare in the endometrium.[127,134,150-152] Moreover, DC and macrophage population dynamics in the human uterus appear unlinked since DC tissue densities, if anything, are lower in the first-trimester decidua compared to the late secretory endometrium, whereas macrophage tissue densities are similar or higher, as mentioned above.[48,127,128,134] Provocatively, the first-trimester decidual DCs form conjugates with T cells in situ and have potent stimulatory capacity when cultured with allogeneic T cells *ex vivo*, which together suggest that they might activate decidual T cells.[150] However, the data on whether the human decidua contains lymphatic vessels and thus could support decidual DC trafficking to the uterine LN is contradictory.[150,153-155] Interestingly, the fetal membranes have recently been shown to contain lymphatic vessels at term gestation, but the route of drainage is not yet

established, nor did the single-cell RNA-Seq study that identified these vessels uncover the presence of membrane-resident DCs.[57]

Potential developmental functions for decidual DCs have remained unclear.[152] There have been suggestions that they are required for implantation and decidualization and to tolerize maternal T cells toward fetoplacental antigens, but the lack of overt reproductive deficits in DC-deficient *Flt3l*$^{-/-}$ mice, even in strain disparate (allogeneic) matings, has called these ideas into question.[6,152,156-159] Similarly, indications that decidual DCs might induce decidual T_{reg} cells, or bidirectionally interact with dNK cells to promote decidual angiogenesis, currently lack direct *in vivo* experimental support.[157,160-163] Instead, their low density and tissue entrapment, together with their ability to mature in response to inflammatory stimuli[79] and activate T cells,[150] highlights their potential detrimental effects on pregnancy outcome.

Neutrophils and Other Myeloid Cells

In humans, neutrophils comprise a negligible fraction of first-trimester decidual leukocytes and accumulate in the decidua only in cases of infection (see sections *Immune Defenses at the Maternal-Fetal Interface* and *Infection-Mediated Pregnancy Complications*). They are similarly scarce in the myometrium for most of gestation but then become abundant in this tissue layer upon labor onset, similar to macrophages.[139,140,164] In mice, they comprise ~20% and ~1% of all leukocytes in the decidua and myometrium on gd9.5, respectively, and accumulate in the decidua at the leading edge of invasive trophoblasts and in the decidual vascular zone, where they remain intravascular.[95,133] Antibody-mediated neutrophil depletion during this period impairs placental development and causes intrauterine growth restriction (IUGR), suggesting that neutrophils regulate placentation;[165] however, these results have not been confirmed using genetically engineered mice with low-neutrophil numbers. At the end of mouse gestation, neutrophils represent ~1% to 2% of all uterine leukocytes, and their tissue densities mildly increase in both the decidua and myometrium as a consequence of labor onset.[138,142,146,166]

Strikingly, eosinophils are virtually absent from the mouse decidua but are present in the endometrium and myometrium.[95,167] As this distribution parallels that of ILC2s, which control tissue eosinophil numbers (see above), the mouse decidua, thus, assumes a decidedly nontype 2 immune flavor. Eosinophils cyclically infiltrate the nonpregnant mouse uterus via estrogen-induced CCL11 expression, but CCL11-deficient mice show no obvious reproductive defects.[167] The numbers and location of mast cells, which have recently been implicated in implantation and spiral artery remodeling in mice, are unclear.[168] Mast cells are detectable in the human endometrium throughout the menstrual cycle, while eosinophils appear only with the onset of menses.[169] Both cell types remain poorly characterized in the human decidua. Their potential role in parturition is discussed in section *Parturition and PTL*.

SYSTEMIC CHANGES TO THE MATERNAL IMMUNE SYSTEM DURING PREGNANCY

In addition to the work described above on uterine immune cells, many studies have used human peripheral blood specimens to characterize the systemic changes to the immune system that occur with pregnancy. These studies have been motivated by desires to gain insights into mechanisms of feto-maternal tolerance and the potentially altered responses of pregnant women to infection and vaccination,[170,171] and, more recently, by the goal of developing blood tests that might be able to predict PTL and other pregnancy complications.[172,173]

Perhaps, the most straightforward interpretation of this work is just how little the maternal immune system is systemically altered during pregnancy. At the cellular level, every alteration so far detected has been at most twofold, and many are far subtler. Moreover, certain parameters have shown remarkable variability between studies—for example, the question of whether blood T cell numbers decline during pregnancy, as suggested by some studies, remains unsettled.[174-177] One consistent finding has been a mild increase (<twofold) in blood neutrophil numbers,[173,174,177,178] which is presumably due to increased granulopoiesis given that serum G-CSF levels are also elevated during pregnancy.[179,180] Plasmacytoid DCs also increase (~twofold) in number.[174,181,182] Observations on the numbers of monocytes and NK cells have been very inconsistent, although there might be some subset-dependent alterations in functionality.[174-177,181-189] There are also slight reductions in Th1 and Th17 cell frequencies in the blood of women in their second and third trimesters, as measured by surface markers as well as IFNγ and TNFα production, but very little evidence of a Th2-skewing, in contradiction to the historical suggestion that pregnancy is a Th2-like phenomenon.[174,182,184,188,190,191] As will be discussed in more detail below (see section *Limits to the Treg Cell Paradigm*), studies on T_{reg} cell frequencies in pregnant women have also yielded inconsistent results,[192] in contrast to the relatively uniform observation that T_{reg} cells systemically expand in mice by midgestation (<twofold), particularly following strain disparate (ie, allogeneic) as opposed to strain identical (ie, syngeneic) mating.[156,193-197]

Although not a universal finding, several studies have documented small reductions in B cell numbers in the maternal blood during the third trimester of human pregnancy, particularly affecting transitional B cells.[174-178,188,198,199] This observation is consistent with work in mice showing that pregnancy levels of estrogen impair B cell development by inhibiting IL-7 production by bone marrow stromal cells.[200-202] Total splenic B cells in mice also decrease in absolute number starting at midgestation, in association with decreased splenic expression of the B cell survival factor BAFF/Blys.[203] In contrast, splenic marginal zone B cells increase in number, as do total B cells in the uterine LN and peritoneal cavity.[203] These increase parallel augmented production of "natural antibodies" of the IgA, IgM, and IgG3 subclasses in both mice and humans[199,204] and together suggest that B cell responses during pregnancy become somewhat more innate-like. Pregnancy also alters the properties of newly produced antibodies. First, there is an increased proportion of IgG with galactosylated and sialylated Fc regions, which are more efficiently transported across the placenta into the fetal bloodstream,[205] and which also happen to exert an anti-inflammatory effector function.[206,207] Second, the proportion of IgG antibodies bearing mannose-rich oligosaccharides attached to the Fd fragment of one Fab chain, which renders them univalent and less effective at mediating

antigen precipitation, complement fixation, and clearance, rises from ~10% in nonpregnant humans to 30% to 40% during pregnancy.[208] The frequency of such "asymmetric antibodies" is reduced with recurrent spontaneous abortion (RSA).[209,210]

Together with the aforementioned alterations in T cell responses, these observations suggest that adaptive immunity is impaired or suppressed to some extent during pregnancy, at least quantitatively. This possibility is consistent with analyses of human immune responses to Hepatitis C virus (HCV) and influenza virus, as discussed further in section *Systemic Immunity to Infection and Vaccines During Pregnancy*, with studies in mice showing systemic reductions in the magnitude of adaptive immune responses to live attenuated Zika virus (ZIKV) vaccination,[211] and with observations that antibody titers generated against certain but not all influenza virus vaccine strains are upward of twofold diminished in women vaccinated in the third trimester (even though these titers are still effective at preventing infection).[212] Moreover, women with MS and RA show symptomatic improvement during pregnancy, a phenomenon linked to increased IgG galactosylation/sialylation as well to increased T_{reg} cell functionality (see section *Pregnancy and Maternal Autoimmune Disease*). As the most simple example of a pregnancy-associated systemic immune deficit, the expansion of endogenous ovalbumin (OVA)-specific CD8 T cells following the intravenous injection of soluble chicken egg OVA plus adjuvants is fivefold lower in pregnant versus nonpregnant mice (although still robust in absolute terms).[213] Not all adaptive immune responses are impaired, however. For example, immune monitoring studies have failed to detect differences following primary HCMV infection or following *Listeria monocytogenes*, *Fusobacterium nucleatum*, or lymphocytic choriomeningitis virus (LCMV) infection in mice; similarly, systemic infections other than that by HCV and influenza virus do not show worsened clinical severity during pregnancy. These responses are discussed further in section *Immune Defenses at the Maternal-Fetal Interface*. In addition, baseline frequencies of IFNγ- and granzyme B-producing T cells specific for tetanus toxoid and antigens derived from a variety of pathogens, including HCMV, influenza virus, measles virus, herpes simplex virus-1 (HSV-1), and Epstein-Barr virus, are largely unaltered during human pregnancy.[182] Perhaps, most strikingly, pregnant women can mount robust immune responses to paternal alloantigens expressed by fetal blood cells, with the most important example being Rh(D) antigen, the inciting antigen of Rh disease (see section *Humoral Fetomaternal Tolerance*). Together, these observations suggest that pregnancy generates a select set of systemic "holes" in the adaptive immune system, but the exact nature of these holes, their causes, and why they are relevant to only certain pathogens is unclear.

Proximal and ultimate causes for these alterations also remain incompletely defined, although the dominant steroid hormones of pregnancy, progesterone, and estrogen, play key roles.[214] Serum levels of both hormones are elevated during pregnancy, which in the case of progesterone allows it to activate the broadly expressed nuclear glucocorticoid receptor. This cross-reactivity contributes to the pregnancy-associated expansion of T_{reg} cells in mice mentioned above.[215] To the extent that progesterone acts through its own nuclear receptor (PR) to modulate immune cell behavior, such effects are presumably induced indirectly given that immune cells barely express PR.[216,217] For example, pregnancy-induced thymic involution, a universal phenomenon across species that might contribute toward the reductions in blood T cell numbers sometimes seen in late gestation, requires PR expression by thymic stromal cells.[218] Various immune cell types also express membrane progesterone receptors, but their functions have remained poorly characterized. In contrast to progesterone, nuclear estrogen receptors (ERα and ERβ) are broadly expressed across immune cell types, and estrogen is known to have many direct and indirect immunological effects.[219] Of known relevance to pregnancy, these include the inhibition of B cell lymphopoiesis mentioned above and the fostering of CD4 T cell conversion to T_{reg} cells.[220] Immune modulatory function has also been ascribed to chorionic gonadotropin, a primate-specific protein produced by trophoblasts,[214] as well as to nonhormonal material released by the placenta into maternal blood, including pregnancy-specific glycoproteins and exosomes.[221,222] Systems biology approaches might help shed light on the relative importance of these various factors in altering immune cell behavior; for example, recent work has revealed increased STAT5 signaling in blood T cells during human pregnancy.[173]

MECHANISMS OF FETOMATERNAL TOLERANCE

Introduction to Fetomaternal Tolerance—History and Overview

The conceptus is not genetically identical to the mother yet fails to elicit a traditional allograft rejection response. Pregnancy, therefore, is a striking exception to the self/nonself paradigm of immune tolerance, an exception that was obvious to the original leaders in the field. Accordingly, in 1953, Peter Medawar hypothesized three mechanisms that could ensure survival of the fetoplacental allograft: (1) "antigenic immaturity" of the conceptus, meaning that it does not express rejection-inducing antigens; (2) anatomic separation of the conceptus from the mother; and (3) generalized immunosuppression of the mother.[223]

Research performed over the decades since Medawar proposal has mostly disqualified his three ideas. First, the conceptus is not antigenically "immature" since trophoblasts alone express many protein species that could in theory mediate immune rejection. As will be discussed further below, these include classical MHC class I molecules (albeit to limited deg ree),[149,224-226] nonclassical class Ib molecules with limited polymorphism (ie, HLA-E and –G in humans[226]), trophoblast-specific proteins not otherwise expressed in normal adult tissues such as placenta specific glycoproteins[222] and cancer testes antigens,[227] and lastly ubiquitously expressed minor histocompatibility antigens including H-Y antigen encoded on the Y-chromosome.[228,229]

Second, and as we described in section *Anatomy, Development, and Microbiology*, the conceptus is not walled off from the maternal immune system. Rather, trophoblasts come into contact with

decidual immune cells, while endovascular trophoblasts and trophoblasts in the villous tree and labyrinth are bathed in maternal blood. In fact, this latter trophoblast-blood interface, with its massive surface area, is the site where the human placenta releases trophoblast-derived multinucleated "syncytial knots," microvesicles, exosomes, soluble protein, lipids, and nucleic acids directly into the maternal bloodstream, with quantity estimates reaching several grams each day in late gestation.[221,230,231] Analogous processes are likely to occur in mice with trophoblast-derived material also known to reach the uterine-draining LNs in this species by cell-free transport through the uterine lymphatics.[79] Lastly, occult placental hemorrhage, a frequent occurrence in humans, exposes the mother to fetal blood cells.[232] Thus, there is ample opportunity for the maternal immune system to become aware of fetal and placental cells. However, only fetal blood cell exposure induces productive immune responses, as we discuss below.

The third and final idea of Medawar proposal—that is, systemic immunosuppression—must also largely be discounted. Clearly, pregnant women bear little resemblance to nonpregnant transplant recipients who, as a consequence of pharmacologically induced immunosuppression, suffer from opportunistic infections and show worse clinical courses with common infections. Rather, systemic antipathogen defenses and vaccine responses remain strong during gestation, as we will describe in section *Systemic Immunity to Infection and Vaccines During Pregnancy*, while exposure to fetal blood cells leads to productive immunity, as mentioned immediately above. This is not to say that systemic immune alterations are not apparent during pregnancy—we have discussed these already in section *Systemic Changes to the Maternal Immune System During Pregnancy*—but they are not large enough in magnitude to explain fetomaternal tolerance and the ones that affect the adaptive immune system are seemingly quite selective.

In retrospect, a 1979 paper by Thomas Wegmann and colleagues provided prescient insight into the nature of the maternal T cell response to the fetoplacental allograft. Their work showed that maternal T cells in mice are not spontaneously primed to paternal alloantigens during gestation but *are* primed to these antigens when the mice are injected with paternal splenocytes.[233] Such intragestational priming could be induced without any adverse effects on pregnancy outcome. Together, these findings suggest a candidate fetomaternal tolerance paradigm that explains many of the observations thus far in the field. We state this paradigm in the form of three tenets, which, given the unique positioning of trophoblasts as the cells that directly contact maternal blood and tissue, focus on trophoblast antigens rather than paternal alloantigens more generally. Indeed, as will emerge from our discussion below, "paternal alloantigens" becomes less of a useful concept since it glosses over the cellular sources of these antigens, which current data suggest is critical.

Three tenets of fetomaternal tolerance are as follows:

1. Pregnancy does not trigger the generation of T cell effectors specific for trophoblast antigens.
2. Pregnancy does not elicit T cell tolerance to trophoblast antigens.
3. Pregnancy proceeds unharmed even in the presence of trophoblast antigen-specific effector T cells.

It is perhaps not so surprising that Wegmann findings were not universally appreciated at the time of their publication. Other analyses of the responses to antigens expressed by the conceptus in some cases suggested effector T cell priming and in other cases tolerance induction,[234,235] while it was already well-established that productive humoral responses could be mounted to fetal blood group antigens and paternal HLA molecules (see section *Humoral Fetomaternal Tolerance* below). Furthermore, muddying the water was the inferential nature of all immune tolerance studies performed in this era. The field thus awaited direct visualization of antigen-specific T cell responses to defined trophoblast antigens. Initially, this came about in the 1990s with descriptions of systemic T cell phenotypes in pregnant TCR-transgenic female mice bearing concepti that expressed the cognate antigen (paternal strain [ie, allogeneic] H-2K or male H-Y). These experiments unfortunately also yielded a variety of conflicting findings, including no obvious differences,[224,225] clonal deletion, and transient anergy,[236,237] or mild increases in T cell numbers.[238] Their inherent relevance was also called into question with the realization that peripheral tolerance studies on intact TCR-transgenic mice could yield aberrant responses given the exceedingly high T cell precursor frequencies involved.[239]

The more contemporary era in the study of fetomaternal tolerance started in the mid-2000s with the applications of TCR-transgenic T cell adoptive transfers and MHC-peptide tetramer technologies, which together have allowed researchers to directly visualize the antigen-driven responses of maternal T cells when the cells are present at more physiologically relevant, if not endogenous, precursor frequencies. Thus armed, researchers have been able to dissect the precise anatomic and cellular pathways that mediate T cells awareness to trophoblast antigens and to directly explore how T cells with defined specificities respond to trophoblast antigens under controlled experimental conditions. Remarkably, the conclusions of this work are similar to those of Wegmann et al, namely that trophoblast antigens induce neither T cell immunity nor tolerance—an outcome that leads us to refer to them as being "nonimmunogenic"—and that mechanisms also exist to protect the fetus from rejection even if trophoblast antigen-specific maternal T cells do become activated. The sections below (*How Maternal T Cells Come to Engage Trophoblast Antigens* to *Mechanisms of Effector Phase Tolerance to the Conceptus*; see also Fig. 41.3) will discuss the key data that support these conclusions, as well as potential underlying mechanisms. We emphasize that unanswered questions and inconsistencies persist. Critically, a different picture emerges when we consider nontrophoblast antigens, such as those expressed by fetal blood cells, since these antigens can clearly drive class-switched B cell responses during pregnancy, and thus also, by inference, helper T cell responses. These responses are addressed in their own section (see section *Humoral Fetomaternal Tolerance*). We then discuss various examples of fetal loss and placental damage in mice and humans and whether or not they represent true rejection (see section *Are There Any Examples of Placental "Rejection"?*). Lastly, we discuss NK cell tolerance to the fetus (see section *NK Cell Tolerance Toward the Conceptus*).

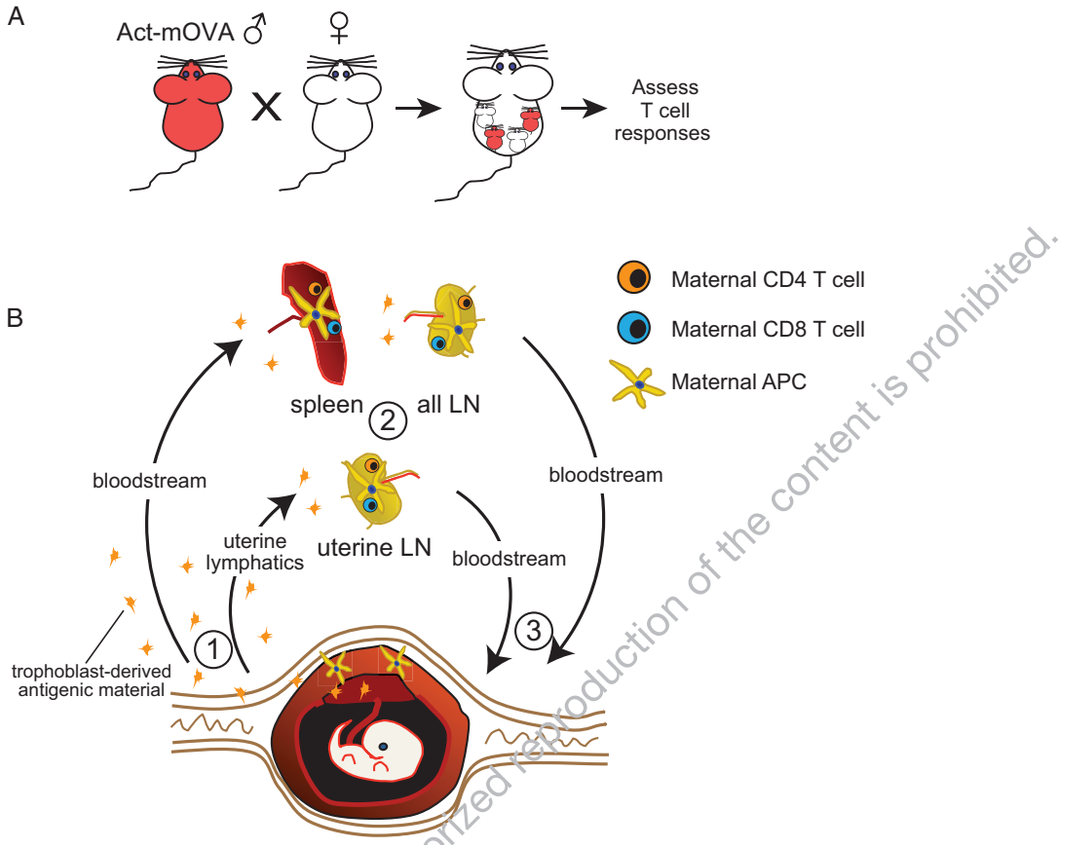

FIG. 41.3. Responses of T cells to trophoblast antigens based upon evidence from the mOVA mouse model. A: The membrane-bound form of ovalbumin (mOVA) model. Use of a transgenically expressed mOVA as a surrogate fetal/placental antigen has allowed researchers to identify the antigen presentation pathways that govern maternal T cell recognition of trophoblast antigens. In this model, nontransgenic females are mated to males that are hemizygous for the Act-mOVA transgene,[240] which directs mOVA expression, under control of the ubiquitously active β-actin promoter, throughout the conceptus. Endovascular trophoblasts, which are bathed in maternal blood, show particularly high mOVA expression.[241] OVA-specific T cell responses can be monitored via the use of OVA-specific peptide-MHC (major histocompatibility complex) tetramers or via the adoptive transfer of OVA-specific T-cell receptor (TCR) transgenic T cells. Since, on average, only 50% of the concepti within a litter express mOVA, antigen-specific fetal loss can be assessed as significant deviations from this Mendelian proportion. **B:** Responses of T cells to mOVA: key points of regulation. (1) Due to the low tissue density of dendritic cells (DCs) and absence of lymphatic vessels within the decidua, maternal T cells become aware of mOVA exclusively as a result of its release from trophoblasts and cell-free transport within the uterine lymphatic vessels and the maternal bloodstream, followed by its uptake and presentation by spleen- and LN-resident antigen-presenting cells (APCs). The conceptus starts releasing mOVA at midgestation (~gd10.5), coincident with the onset of placental perfusion, but mOVA is robustly expressed prior to this time. (2) Presentation of mOVA is "nonimmunogenic" in that it induces an abortive proliferative response and fails to elicit effector T cell priming even when the mice are injected with adjuvants to induce costimulation. The causes of this response are currently incompletely understood but in part involves the action of T_{reg} cells. (3) Even if OVA-specific T cells are activated via experimental means, both mOVA-expressing and nontransgenic concepti remain completely viable up through midgestation because the decidua excludes the cells from the maternal-fetal interface. In late gestation, experimentally activated OVA-specific T cells induce antigen nonspecific fetal demise, likely, through their elaboration of circulating inflammatory mediators that nonspecifically impair placental function. See text for further details.

How Maternal T Cells Come to Engage Trophoblast Antigens

Due to their 10-fold greater prevalence in otherwise naïve hosts, the T cells that recognize intact, nonself MHC molecules collectively pose a much greater threat to organ transplants than the T cells that recognize minor histocompatibility antigens, that is, antigens ingested by host antigen-presenting cells (APCs) and presented by self-MHC molecules. These two pathways have thus been given different names, the direct and indirect allorecognition pathways.[242] A third allorecognition pathway, called the semidirect pathway, involves the transfer of intact donor MHC/peptide complexes to host APCs in a process termed "cross-dressing." This pathway might be of even greater operational relevance than the direct pathway but activates the same large set of T cells.[242]

Accordingly, any discussion of why trophoblasts do not activate maternal T cells needs to start with a consideration of the nature of trophoblast antigens and the relevant pathways of their recognition. As mentioned above, trophoblasts express tissue-specific antigens, ubiquitously expressed minor histocompatibility antigens, and MHC class Ib molecules with limited polymorphism (which in the case of HLA-G are also

trophoblast-specific). All of these could provide peptides to activate maternal T cells via the indirect pathway. On the other hand, trophoblasts express a very limited repertoire of classical MHC molecules: they do not express MHC-II whatsoever and show restricted, trophoblast subtype-specific expression of classical MHC-I. In humans, only HLA-C is expressed, and only by EVTs,[226,243,244] while in mice the only trophoblasts that express high MHC-I levels are glycogen cells, a subtype that appears in late gestation and invades interstitially into the decidua, like EVTs.[149,224,225] Endovascular trophoblasts that line remodeled decidual spiral arteries in mice express low levels of H-2K/D,[241] while the trophoblasts of the human villous tree and mouse labyrinth are completely negative for classical MHC molecules.[149,224,225,241] These observations predict less of an opportunity for trophoblasts to trigger T cell activation via the direct and semidirect pathways or for them to serve as targets for directly alloreactive CTLs. Moreover, they predict less T cell activation via the indirect pathway as well, given that MHC molecules themselves provide allopeptides that drive indirect allorecognition.[242] However, it does not entirely remove the threat posed by these pathways: for example, HLA-C mismatch alone compromises graft acceptance in the bone marrow transplant setting.[245]

The extent of direct/semidirect versus indirect allorecognition of trophoblasts has been resolved in mice using a surrogate trophoblast antigen system in which wild-type females are mated to males hemizygous for a transgene that directs ubiquitous expression of a transmembrane form of chicken ovalbumin (mOVA)[241] (Fig. 41.3A). In transgenic concepti, mOVA is highly expressed by trophoblasts of the developing placenta as early as ~gd7.5, and then by the endovascular trophoblasts that are bathed in maternal blood. Beginning at midgestation, when the placenta starts being perfused with maternal blood, adoptively transferred OVA-specific TCR-transgenic CD4 and CD8 T cells start proliferating in the spleen and all lymph nodes, indicating systemic immune recognition of mOVA$^+$ concepti.[241,246-248] Using this system in conjunction with congenic maternal strains unable to present mOVA-derived peptides to the transgenic T cells, it could be demonstrated that T cells engage mOVA exclusively via the indirect allorecognition pathway, that is, following the antigen's uptake by maternal APCs and its presentation in the context of maternal MHC.[241] The lack of a proliferative response in adoptively transferred TCR-transgenic CD4 and CD8 T cells directly alloreactive against paternal MHC molecules confirmed these results,[241,249] and also refuted data from the 1990s using intact TCR-transgenic mice that suggested direct recognition of paternal MHC molecules.[237] Together, these observations also demonstrated the absence of professional APCs of fetal origin that could somehow reach the secondary lymphoid organs of the mother. Rather, since large amounts of mOVA can be detected in maternal blood in both cell-free and exosome-associated forms starting at midgestation,[213,250] immune recognition of the mouse conceptus appears mediated by the hematogenous release and systemic circulation of trophoblast-derived antigenic material, which then gets taken up by spleen and LN-resident APCs (Fig. 41.3B).

While the lack of direct allorecognition of trophoblasts thus greatly reduces the numerical threat to pregnancy posed by maternal T cells and could therefore be considered a "mechanism" of fetomaternal tolerance, T cell activation via the indirect pathway alone can still elicit graft rejection in the transplant setting.[242] In fact, expression of mOVA as a sole minor histocompatibility is sufficient to trigger skin graft rejection in mice.[240] In this kind of MHC-matched context, rejection is thought to be initiated by tissue-resident DCs of host origin that interact with the transplant and then migrate to its draining LN loaded with minor histocompatibility antigens. Remarkably, in the case of the fetoplacental allograft, an analogous process does not take place in mice since, as discussed in section *Immune Cells of the Pregnant Uterus*, DCs are scant within the decidua, and those that reside there are unable to migrate to the uterine-draining LNs due to the decidua's lack of lymphatic vessels.[79] Rather, trophoblast antigens are presented by uterine LN-resident APCs only after their transport in cell-free form via the myometrial lymphatics and bloodstream (Fig. 41.3B). As also discussed in section *Immune Cells of the Pregnant Uterus*, the human decidua contains exceedingly few DCs and might also lack lymphatic vessels.

The Nonimmunogenic Nature of Trophoblast Antigens

Thus far, we have described how the placenta differs from a surgical organ transplant in two critical ways: first, there is an absence of direct and semidirect allorecognition, and second, immunogenic DCs do not survey the maternal-fetal interface. However, we have not yet described the behavior of maternal T cells that do encounter trophoblast antigens within secondary lymphoid organs. Again using the mOVA model antigen system, it was found that OVA-specific CD8 T cells proliferate and alter their activation marker profile but fail to numerically accumulate to a substantial degree (indicating concurrent deletion) and fail to acquire effector functions (IFNγ production and cytotoxicity).[213,241,246,247,250] This nonimmunogenic outcome is perhaps unsurprising given that T cell priming to foreign antigens typically requires the presence of danger signals. However, systemic administration of strong adjuvants such as the TLR3 agonist poly(I:C), even together with agonistic anti-CD40 antibodies to simulate CD4 T cell help, still fails to elicit robust CD8 T cell priming to trophoblast mOVA.[213,241,250] Perhaps, even more remarkably, pregnant females bearing mOVA concepti nonetheless manifest robust CD8 T cell immunity when intravenously injected with soluble OVA (from chicken eggs) plus adjuvants.[213] These results thus mirror those obtained by Wegmann in the 1970s: during pregnancy, CD8 T cells are not primed to trophoblast antigens, but they can be primed to these same antigens when their source is not a trophoblast.

The above findings also demonstrate that exposure to trophoblast antigens does not induce antigen-specific tolerance, a failure that is perhaps even more evident from analyses of the long-term fate of CD8 T cells that encountered trophoblast mOVA. After undergoing the abortive proliferative response mentioned above, these cells are not completely deleted but persist for up to 6 months postpartum and show

a surface phenotype indicating prior antigen exposure.[247,250,251] Moreover, mice bearing these cells demonstrate accelerated rejection of mOVA-expressing skin grafts and an increased ability to clear OVA-expressing tumor cells, although the T cells themselves show some defects in cytokine production and cytotoxicity, as well as quantitative impairments in their ability to expand following antigen reengagement.[213,247,250,251] Similar findings have emerged from studies on maternal T cell responses to male H-Y antigen. These studies are less conclusive, given the near impossibility of generating pregnant mice with all-female litters as antigen-specificity negative controls, nor have adoptive transfer studies using H-Y–specific TCR-transgenic T cell been performed. Nonetheless, tetramer staining experiments have revealed expanded (albeit minute) numbers of H-Y–specific CD8 T cells during mouse pregnancy, suggesting antigen exposure and persistence of the cells into the postpartum period, at which point they demonstrate a memory phenotype and the capacity to produce IFNγ and kill male cells *ex vivo*.[252,253] On the other hand, parous mice are partially impaired in their ability to reject male skin grafts.[252] Together with the results from the mOVA system, these data provide evidence that at least some trophoblast antigens do not induce long-term tolerance but rather a quasimemory phenotype. Although much less thoroughly studied, CD4 T cells also display the same kind of response to trophoblast antigens as CD8 T cells—abortive expansion and lack of differentiation into effector cells, with some conversion to T_{reg} cells as described further below.[197,241,254,255]

Due to technical limitations and ethical considerations, there has been much less analysis of how maternal T cells respond to paternal antigens during human pregnancy. In one study, the use of peptide-HLA dextramers revealed expansion of a minute population of functional, H-Y–specific CD8 T cells in the blood of pregnant women bearing male fetuses.[256] In other studies, nonpregnant multiparous women were found to sometimes bear expanded numbers of functional CD8 T cells specific to minor histocompatibility antigens, including H-Y, and to have developed CTL reactivity to cells expressing paternal class I HLA.[252,257-259] However, it needs to be emphasized that priming to these antigens could have resulted from exposure to fetal blood cells given that prenatal placental hemorrhage is a significant feature of human but not mouse pregnancy[232,253,260] and likely the reason antibodies to RBC alloantigens and paternal HLA molecules sometimes develop before delivery (see section *Humoral Fetomaternal Tolerance* below). Antibodies to paternal HLA, in fact, arise in the same women who develop paternal HLA-specific CTLs.[258,259] Tetramer studies that evaluate maternal T cell responses to oncofetal antigens, which are frequently expressed by trophoblasts,[227] might thus provide better insight into true trophoblast antigen-induced responses. Provocatively, exposure to oncofetal antigens during human pregnancy does not significantly raise or lower the risk of subsequent nonhormonally driven cancers,[261] consistent with the aforementioned mouse studies demonstrating the lack of strong outcomes. Of note, direct contact between maternal T cells and fetal leukocytes, which is expected following placental hemorrhage, predicts that a large fraction of the paternal HLA-specific CTLs will be directly alloreactive to paternal HLA, in contrast to the T cells that respond to trophoblast antigens, which occurs solely via the indirect pathway.

T_{reg} Cells and the Attenuation of T Cell Priming to Trophoblast Antigens

Given their general importance in peripheral tolerance, many studies have focused on the potential role of T_{reg} cells in attenuating effector T cell priming to trophoblast antigens. Indeed, the notion that pregnancy could generate dominantly suppressive lymphocytes was originally raised in the 1970s[262] but then fell out of fashion along with the field of "suppressor T cells." In 2004, however, the idea was reignited with the observation of midgestation fetal loss following strain-disparate (ie, allogeneic) mating but not strain-identical (ie, syngeneic) mating when T cell-deficient females were reconstituted with CD25-depleted T cells within 4 days prior to copulation.[193] Similar results soon followed[196,263] along with observations that T_{reg} cell transfer could attenuate fetal loss in a model of early gestation spontaneous abortion.[264,265] T_{reg} cell frequencies were also found to increase in the uterine LN of mice soon after mating, as well as systemically at midgestation, an effect more consistently observed following allogeneic (as opposed to syngeneic) mating.[120,156,193-195,197,266-269]

Importantly, interpretation of these studies in light of subsequent ones using the Foxp3-DTR system, which allows for timed $FOXP3^+$ T_{reg} cell depletion via diphtheria toxin injection, suggested that T_{reg} cells might contribute to pregnancy success in part via paternal antigen-independent effects on implantation and decidualization (see section *Implantation, Decidualization, and Early Pregnancy Failure*). Thus, to better address the role of T_{regs} cells in fetomaternal tolerance, researchers have also interfered with their function after midgestation, that is, when maternal T cells become aware of trophoblast antigens. Strikingly, partial T_{reg} cell depletion at midgestation using the Foxp3-DTR system was found to induce a high rate of fetal loss following allogeneic but not syngeneic mating, an effect that could be prevented by either CD8 T cell depletion or blockade of the CXCR3 chemokine receptor that partially mediates CTL homing to peripheral tissues.[255,270] A similar but much more subtle pattern of late gestation fetal loss was evident in female mice bearing a deletion of the "conserved noncoding sequence 1" (CNS1) enhancer element of the *Foxp3* locus, but this observation was provocative in its own right since the CNS1 element is required to induce *Foxp3* expression in naïve CD4 T cells and thus convert them to "induced" i T_{reg} cells in the periphery.[121] Together, these results suggested that trophoblast antigens induce antigen-specific peripheral iT_{reg} conversion and expansion, which then prevents the generation of effector Th1 cells and CTLs. Indeed, using MHC-II tetramers and a variation of the mOVA mating system in which a peptide, termed 2W1S, has been incorporated into the mOVA construct, it was shown that 2W1S-mOVA antigen release from the placenta induces the expansion of 2W1S-specific iT_{reg} cells as well as the appearance of anergic 2W1S-specific CD4 T cells on a path to iT_{reg} conversion.[255,271] The 2W1S-specific

iT_{reg} cells, moreover, persist postpartum as memory cells and help attenuate immunological threats to second pregnancies.[255] These observations provided a clear antigen-specific example of the aforementioned finding that T_{reg} cells mildly expand at midgestation in allogeneically mated mice. The idea of placental antigen-driven T_{reg} conversion/expansion is also appealing because placental mammals are the only animals bearing the CNS1 element and appear to be experiencing purifying selection in the functional domains of FOXP3 protein.[121,272] Thus, the evolution of iT_{reg} cells appears linked to the evolution of placentation, and thus, the need to prevent fetal rejection.

Limits to the T_{reg} Cell Paradigm

Despite its many attractions, several findings have prevented universal acceptance of the idea that T_{reg} cells are central to fetomaternal tolerance. One set of findings concerns the extent to which T_{regs} actually alter the response of maternal T cells specific for trophoblast antigens. Thus, while Foxp3-DTR–mediated T_{reg} cell depletion induces OVA-specific T cell expansion and effector functions in allogeneically mated mice bearing mOVA concepti, the effect is associated with massive fetal demise and so could be due to the release of large amounts of mOVA from the fetus proper or from nontrophoblastic placental cells.[197] Indeed, when T_{reg} cells are depleted at midgestation using anti-CD25 antibodies, OVA-specific CD8 T cells do not expand even in mice given adjuvants, nor does this treatment induce fetal demise.[196,213] Other findings do not align with standard views on how T_{reg} cells maintain peripheral tolerance. These include the existence of the nontolerant, quasimemory response described above for OVA-specific CD8 T cells persisting into the postpartum period,[247,250] the lack of tolerance induction to H-Y antigen during murine pregnancy,[252,253,273] and the observation that the injection of exogenous OVA plus adjuvants induces OVA-specific effector CD8 T cells in pregnant mice bearing mOVA concepti.[213] In addition, 2W1S-specific T_{regs} do not inhibit the expansion of 2W1S-specific CD4 T effectors or their upregulation of T-bet, but instead, only limit their production of IFNγ.[255] Lastly, the role of T_{reg} cells in human pregnancy is controversial—while some studies have uncovered correlations between pregnancy complications and reduced T_{reg} cell function (see sections *Are There Any Examples of Placental "Rejection"?*; *Implantation, Decidualization, and Early Pregnancy Failure* and *Spiral Artery Remodeling, IUGR, and Preeclampsia*), it is unclear whether blood T_{reg} cell frequencies increase during normal human gestation (reviewed in Ref. 192).

Thus, we would argue that both the specific functions and ultimate importance of T_{reg} cells in fetomaternal tolerance remain unclear. Indeed, various possibilities have been put forth to explain why Foxp3-DTR–mediated depletion induces fetal loss only in allogeneically mated mice that do not invoke suppression of T cells specific for trophoblast antigens and direct T cell assault on the conceptus.[274] Unfortunately, alternative suggestions to account for the unique T cell response to trophoblast antigens have remained controversial and/or have lacked mechanistic detail.[18,213,248,275] One idea is that trophoblasts render their set of expressed proteins less immunogenic via posttranslational carbohydrate modifications. This possibility has a controversial history[276-278] but is consistent with older work on the immunogenicity of ectopically transplanted trophoblasts, the unique biology of protein glycosylation by trophoblasts, and recent observations on how protein glycosylation alters antigen immunogenicity.[274,279-282] It is also consistent with the aforementioned inability of trophoblast mOVA to prevent CD8 T cell priming to exogenously injected OVA.[213]

Even if their role in determining trophoblast antigen-specific responses turns out to be limited, T_{reg} cells might nonetheless contribute to the other curtailments of adaptive immunity evident during pregnancy and discussed in section *Systemic Changes to the Maternal Immune System During Pregnancy*. Expanded T_{reg} cell function has also been implicated in the increased susceptibility of pregnant mice to *Listeria monocytogenes* and *Salmonella Typhimurium* infection;[197,283] however, the experimental demonstration of this idea is confounded by the fact that the immune-privileged state of the pregnant uterus (see below) allows these same organisms to establish intrauterine infectious reservoirs. Thus, the improvement in bacterial clearance seen following T_{reg} cell depletion might be due to loss of these reservoirs, given that T_{reg} cell depletion also causes fetal demise and resorption of implantation sites. More clearly, expanded T_{reg} cell function during mouse pregnancy prevents the onset of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (MS) (see section *Pregnancy and Maternal Autoimmune Disease*).[215] There has also been recent interest in the possible role of IL-10- or IL-35–producing regulatory B cell and B-1a B cell subsets in dampening inflammation during gestation.[284-289] Importantly, the extent to which fetomaternal tolerance relies upon antigen-nonspecific immune suppression, whether induced by T_{reg} cells, regulatory B cells, or any other mechanism, remains unknown.

Mechanisms of Effector Phase Tolerance to the Conceptus

In addition to the obstacles to effector T cell priming outlined above, it is clear that uterus-specific mechanisms also prevent activated T cells from harming the conceptus—that is, the third tenet of fetomaternal tolerance listed at the beginning of this section. The contemporary evidence for existence of such mechanisms is the inability of Th1 cells and CTLs with established trophoblast specificity to induce antigen-specific fetal loss in mice even after they are systemically activated during pregnancy through experimental means.[5,241,273] A similar kind of failure is evident when solid tumors persist despite the successful induction of systemic Th1/CTL responses toward tumor antigens. Importantly, many of the mechanisms of this added layer of protection are expected to apply not only to T cells with specificity toward trophoblast antigens but also to T cells with other specificities. For example, activated T cells generated during pregnancy in response to a nonuterine viral or bacterial infection might negatively impact upon reproductive outcome, if not cause frank fetal

demise, if the cells could accumulate at the maternal-fetal interface and produce proinflammatory cytokines there. This is a significant concern given the ability of activated T cells to widely disseminate throughout the body. But, as will be discussed in section *Systemic Immunity to Infection and Vaccines During Pregnancy*, gestational infection by pathogens that do not directly infect the maternal-fetal interface can stimulate robust systemic immune responses without causing pregnancy complications.

One major reason effector Th1 cells and CTLs cannot attack the fetus in mice is that these cells cannot access the decidua from the bloodstream.[5] In contrast, the myometrium and segments of undecidualized endometrium between each implantation site are competent for T cell recruitment (Fig. 41.4). Mechanistically, the decidua excludes Th1 cells and CTLs because DSCs are unable to express the key chemokines that otherwise would recruit these T cell subsets to peripheral tissues. As alluded to in section *Anatomy, Development, and Microbiology*, these include CXCL9, CXCL10, CXCL12, and CXCL16, whose encoding genes are rendered transcriptionally silent in DSCs through the actions of the repressive histone mark H3K27me3.[4] In addition, DSCs are unable to express CCL5, the last of the currently appreciated set of Th1/CTL-attracting chemokines, but this apparently occurs in an H3K27me3-independent fashion.[4,5] It is unknown whether T cell exclusion from the decidua is a feature of human pregnancy, although the aforementioned reduction in T cell tissue densities in the first-trimester decidua compared to the secretory endometrium is suggestive, as is the failure of T cells to accumulate around foci of decidual HCMV infection (see Section *Immune Defenses at the Maternal-Fetal Interface*). There are also indications of H3K27me3-mediated *CXCL10* silencing in human ESCs exposed to chorionic gonadotropin.[290] It is currently unknown whether mechanisms exist to exclude Th17 cells from the decidua, as well as the point in late gestation when (and if) loss of the H3K27me3 mark across the DSC genome might again allow for T cell recruitment.[4]

Even if Th1 cells and CTLs are unable to access the human decidua from the blood, this tissue still hosts many Th1, CD8, Th17, and T_{reg} cells, all with broad functional capabilities (see section *Immune Cells of the Pregnant Uterus*). A large fraction of these cells are likely tissue-resident memory (Trm) cells that had seeded the endometrium prior to pregnancy and that lack specificity for trophoblast antigens. However, given that multiparous women systemically bear memory CD8 T cells (and presumably CD4 T cells) with specificities to paternal HLA and minor histocompatibility antigens such as H-Y (see above), the decidual memory T cell population of multiparous women likely contains cells with these specificities as well. Indeed, fetal alloreactivity and clonal expansion of human decidual T cells have been documented to a limited extent.[20,93,100] Thus, the fact that decidual T cells fail to attack the conceptus under normal circumstances implies yet additional mechanisms of fetomaternal tolerance that operate within the decidua itself, including potentially at the level of direct T cell-trophoblast interactions. The existence of such mechanisms also explains the lack of significant fetal loss in mice in reports in which Trm cells with known trophoblast specificity are expected to populate the uterus.[5,224,273,291-293]

Accordingly, and as guided by human decidual leukocyte phenotypes, many mechanisms of intradecidual fetomaternal tolerance have been proposed over the last few decades. Unfortunately, the experiments that have attempted to functionally evaluate them in mice are difficult to interpret because they were not designed to take into account our more recent appreciation of the limited extent of T cell priming to trophoblast antigens and the inability of effector T cells to access the decidua. For example, the fertility of PD-1- and PD-L1–deficient mice, even when mated in allogeneic fashion,[248] ostensibly rules out the idea that decidual T cells are inactivated by PD-L1 expressed at the maternal-fetal interface.[294] However, this interpretation is complicated by the absence of trophoblast antigen-specific T cell activation in PD-1- and PD-L1–deficient mice,[248] nor would PD-1/PD-L1 deficiency be expected to overcome the inability of blood-borne T cells to access the decidua. Similar concerns apply to the literature that ostensibly rules out IL-10–mediated suppression of decidual T cells.[295] It has also been hard to understand how examples of fetal loss resulting from attempts to

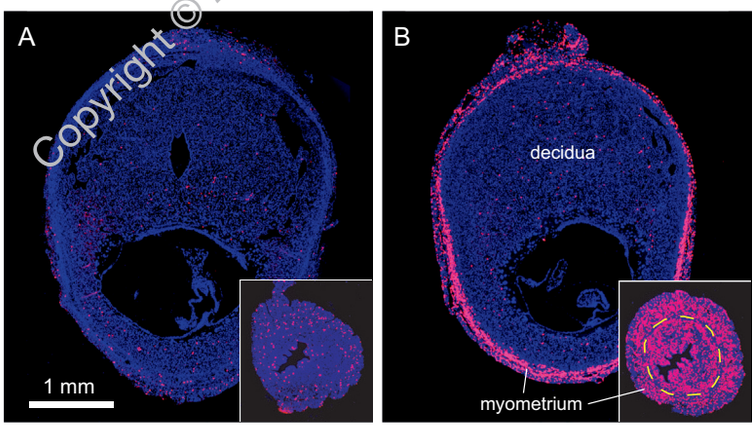

FIG. 41.4. Exclusion of activated Th1 cells and cytotoxic T-lymphocytes (CTLs) from the mouse decidua. Mice were given ovalbumin (OVA)-specific T-cell receptor (TCR) transgenic CD8 T cells and immunized with OVA plus adjuvants 2 to 3 weeks prior to mating. On gd5.5, the mice were either given no additional treatment **(A)** or were rechallenged via intravenous injection with OVA and adjuvants to reactivate the OVA-specific T cells **(B)**. The mice were sacrificed on gd8.5 and implantation sites, and segments of undecidualized uterus between implantation sites (insets) were stained with antibodies to CD3 to visualize all T cells (*red*, with DAPI [4′,6-diamidino-2-phenylindole] counterstain). For the rechallenged mouse, T cells are recruited to the myometrium of implantation sites and to both the myometrium and endometrium (within *yellow dashed line*) of undecidualized uterine segments. In contrast, T cells are excluded from the decidua. (From Nancy P, Tagliani E, Tay CS, et al. Chemokine gene silencing in decidual stromal cells limits T cell access to the maternal-fetal interface. *Science*. 2012;336:1317-1321.)

disrupt proposed mechanisms of intradecidual fetomaternal tolerance[159,296] could represent true T cell-mediated rejection without claiming that the experimental manipulation in question also somehow induced T cell priming to trophoblast antigens and allowed for T cell influx into the decidua.

T_{reg} cells have also been proposed to act within the decidua to help maintain fetomaternal tolerance.[297] This idea grew out of the work described above on the detrimental effects of depleting T_{reg} cells during mouse pregnancy and was bolstered by the finding of decreased decidual T_{reg} cells frequencies in patients with spontaneous abortion.[298-302] However, the specific contribution of decidual T_{reg} cells to pregnancy success remains unclear since we currently lack the experimental means to selectively interfere with their function. Thus, fetal loss following T_{reg} ablation, even if trophoblast antigen-driven, could reflect systemic rather than intrauterine processes. This possibility is discussed further below in sections *Are There Any Examples of Placental "Rejection"?* and *Implantation, Decidualization, and Early Pregnancy Failure*. These sections also discuss the possibility that decidual T_{regs} foster pregnancy success not by promoting fetomaternal tolerance per se but rather by maintaining general immune homeostasis at the maternal-fetal interface.

Mechanisms of intradecidual fetomaternal tolerance thus emerge as another open area in reproductive immunology. It even remains unclear whether mouse and human trophoblasts are intrinsically susceptible to being killed by CTLs in an antigen-specific fashion. We anticipate that experiments in mice that start with the seeding of the endometrium with Trm cells bearing defined specificities will provide a rigorous way to probe key questions. Indeed, this approach, although not framed as such, was taken by investigators who tested whether fetomaternal tolerance depended upon the restricted placental expression pattern of MHC-I or trophoblast expression of FasL, a T cell apoptosis-factor implicated in immune privilege at other anatomic sites. In these experiments, virgin mice were immunized with paternal strain allogeneic splenocytes to generate a pool of paternal alloantigen-specific memory T cells, most likely including uterine Trm cells. Following mating, however, there was no evidence of fetal loss even when the placenta was transgenically directed to express high levels of a paternal MHC-I molecule, when the conceptus was rendered FasL-deficient, or when the mother was rendered Fas deficient.[224,292] These observations make a strong case that neither low MHC-I expression by the placenta nor placental FasL expression are key intradecidual mechanisms of fetomaternal tolerance. Considering that tumor cell expression of PD-L1 attenuates the activity of tumor-infiltrating lymphocytes and the high expression of PD-L1 on human syncytiotrophoblasts and EVTs,[20-22] the role of this molecule, in particular, seems ripe for reassessment. Roles for other immune checkpoint molecules are also of significant interest.[303] Intriguingly, there are now three case reports of pregnant women with cancer who received checkpoint blockade reagents in their first trimester, including anti-PD-L1 antibodies, and all three gestations were successful with no evidence of placental inflammation.[304]

Humoral Fetomaternal Tolerance

Currently, there is the presumption that trophoblast antigens are nonimmunogenic for maternal B cells, like they are for T cells, since there is no known example of a mouse or woman who has mounted an antibody response against an antigen exclusively expressed by trophoblasts. Moreover, the inability of trophoblast antigens to prime CD4 T cells predicts that any trophoblast-directed humoral response would generate only lower affinity antibodies that have not undergone affinity maturation. However, our appreciation of the maternal B cells response to trophoblast antigens is far more rudimentary than our appreciation of the T cell response, as experiments to directly address this aspect of pregnancy immunology have not been reported. Thus, our discussion here instead emphasizes the dichotomy we encountered above for T cells, namely that strong responses can be generated to paternal alloantigens—HLA and ubiquitously expressed minor antigens in humans; OVA in the mOVA mouse model—so long as sources of these antigens are not trophoblasts. In fact, an even more striking example of this dichotomy comes from the B cell side of the story, as maternal B cells are robustly activated during pregnancy to alloantigens expressed by fetal blood cells. In the most severe example of this situation, sensitization to alloantigens expressed by fetal red blood cells (RBCs) causes the clinical condition of hemolytic disease of the fetus and newborn (HDFN). Prenatal sensitization to the entire set of paternal HLA molecules, including all those not expressed by trophoblasts, also occurs. We will discuss both entities below. Importantly, the antibodies in both cases are class-switched,[305,306] implying the induction of T cell help. Thus, the existence of RBC and HLA alloimmunization provides yet additional evidence that T cells (in this case, CD4 T cells) can be primed to paternal alloantigens during pregnancy, so long as their source is not a trophoblast.

B Cell Responses to Nontrophoblast Paternal Alloantigens

Although many different RBC alloantigens can cause HDFN, most cases involve antibodies against the integral RBC membrane protein Rhesus (Rh)D.[306,307] We will thus discuss "Rh disease" as representative of the larger disease entity. Rh disease occurs when anti-Rh(D) antibodies present in $Rh(D)^-$ pregnant women cross the placenta, bind to the RBCs of a $Rh(D)^+$ fetus, and induce their lysis (Fig. 41.5). Outcomes range from mild neonatal jaundice to heart failure, generalized edema, and fetal or neonatal death. Since most sensitization events occur during delivery of a $Rh(D)^+$ baby, Rh disease is typically a problem for subsequent pregnancies. However, sensitization can also occur from unrecognized or therapeutic abortions or, with greatest relevance to the present discussion, from prenatal placental hemorrhages that are often occult but nonetheless allow antigenically relevant quantities of fetal RBCs to access the maternal bloodstream. Rh(D) alloimmunization and full-blown Rh disease can thus occur during an otherwise normal first pregnancy. Prior to the advent of therapy, fetal and neonatal death due to Rh disease occurred in ~0.1% of all pregnancies and Rh incompatibility had a ~16% chance of inducing alloimmunization.[306,308] Happily, disease incidence was dramatically reduced following the advent of prophylactic therapy using anti-Rh(D) IgG, which successfully blocks alloimmunization when given to $Rh(D)^-$ women carrying a $Rh(D)^+$ fetus,[307] but the global

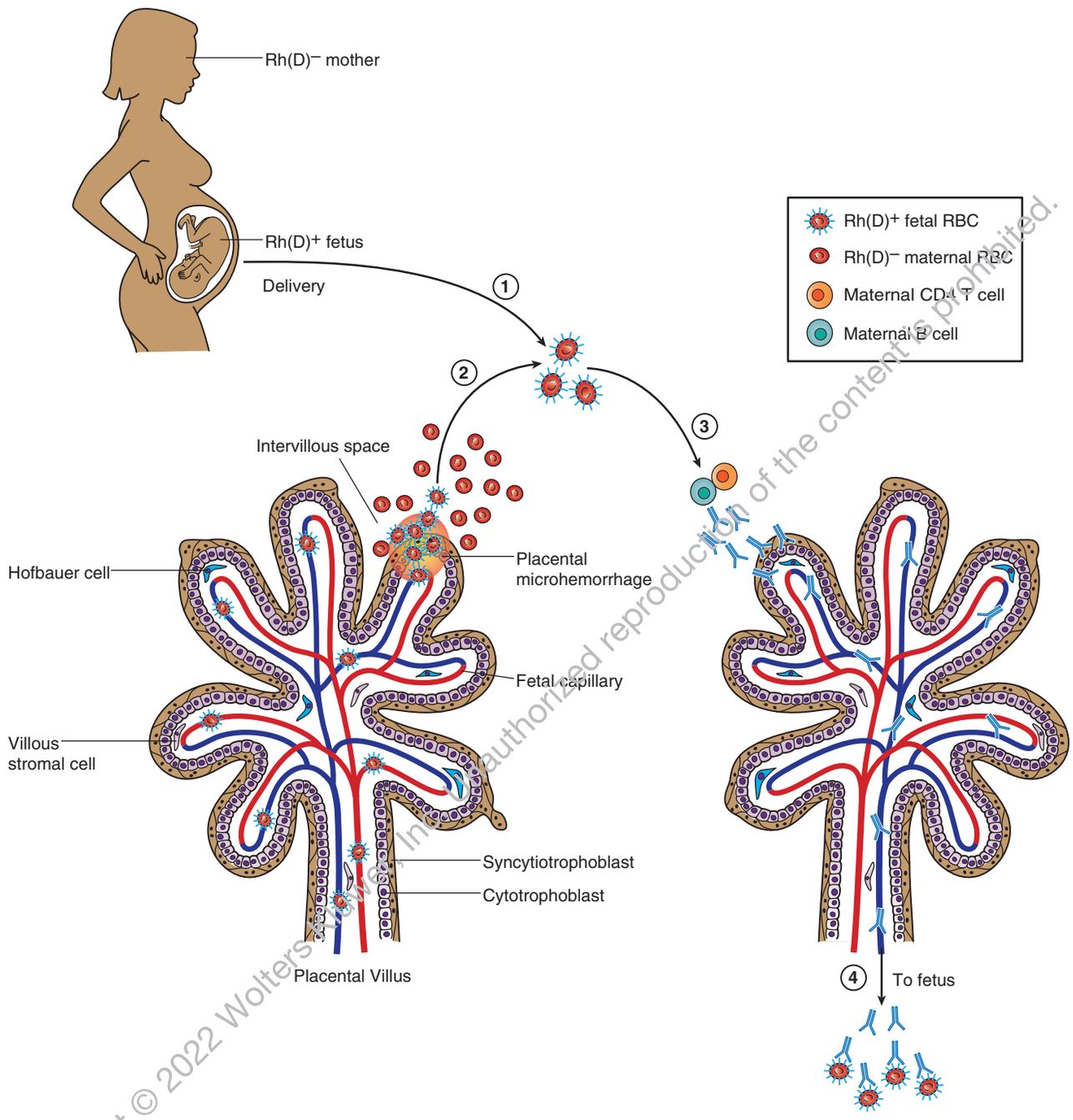

FIG. 41.5. Pathogenesis of Rhesus (Rh) disease. Rh disease occurs in Rh(D)⁻ women bearing Rh(D)⁺ fetuses. Sensitization typically occurs during delivery, when the mother is exposed to fetal blood (1); however, it can also occur as the result of a placental microhemorrhage during an otherwise normal pregnancy (2). In both cases, Rh(D) expressed by fetal red blood cells (RBCs) primes maternal B cells and CD4 T cells, leading to a class-switched antibody response (3). These Rh(D)-specific antibodies are transported across the placenta (when priming occurs during delivery, it is a second pregnancy that is affected), where they reach the fetal circulation and lyse fetal RBCs (4).

burden of Rh disease remains quite high given that this therapy is not employed in many low resource settings. Although rare, alloimmunization can also occur to fetal platelet antigens, causing neonatal alloimmune thrombocytopenia, or to neutrophil antigens, causing fetal neutropenia.[309]

How the administration of anti-Rh(D) IgG prevents immunization to Rh(D) is not entirely clear. Antigen masking that blocks maternal B cell receptor (BCR) recognition of Rh(D) is unlikely a major mechanism since effective suppression occurs with anti-Rh(D) IgG doses far below the point of antigen saturation.[310] Other mechanisms have therefore been proposed, including antibody-mediated clearance of fetal RBCs before an anti-Rh(D) response can be generated, antibody-mediated Rh(D)-antigen-loss ("antigen modulation"), and

anergy/tolerance induction via engagement of the inhibitory FcγRIIb receptor expressed by B cells.[311-314]

The generation of antipaternal HLA antibodies provides the second obvious example of how maternal B cell responses appear intact when directed toward nontrophoblast antigens. These antibodies have been known for decades to be present in parous women[315] and are clinically significant since they can mediate postpartum transfusion reactions and preclude a woman from receiving an organ transplant from her male partner.[316] They are also extremely common—a recent high-sensitivity study performed on samples obtained within several months of delivery revealed incidences of 48% after a first pregnancy and 74% after a third or more.[305] Critically, they are directed not only toward HLA-C, the sole classical HLA expressed by human trophoblasts but also toward HLA-A, HLA-B, and HLA-DR.[305,317] Thus, as with RBC alloantigens, they are likely generated as a result fetal blood exposure. Such exposure could occur during delivery or as a result of prenatal placental microhemorrhage, given that anti-HLA antibodies can be detected as early as 28 weeks into a first pregnancy.[318]

Maternal B Cell Responses During Pregnancy

At present, analyses of antigen-driven B cell responses toward any cellular component of the mouse conceptus have been rudimentary. Mice lack Rh(D) and related antigens, but a transgenic model of HDFN has been developed in which the human RBC protein KEL is expressed by fetal RBCs. This leads to the progressive generation of pathogenic antibodies by maternal B cells over multiple pregnancies and can cause the intrauterine death of KEL^+ concepti.[260] Unlike with humans, however, sensitization occurs only during delivery and not prenatally since delivery is necessary in mice for fetal RBCs to access the maternal bloodstream.[260] Parous mice, like humans, also bear antipaternal alloantibodies, but their specificity and the circumstances of their generation remain poorly defined. They arise only in some strain-mating combinations and only after multiple pregnancies, similar to the anti-KEL response, but unlike the anti-KEL response they do not appear to cause disease.[319] Lastly, evidence that maternal B cells are even aware of trophoblast antigens during pregnancy comes solely from experiments that employed female mice bearing BCR transgenes specific for H-2K molecules, an approach that is inherently difficult to interpret due to the high precursor frequencies involved. These experiments revealed a 60% to 70% deletion of the transgenic B cells at midgestation in the spleen, blood, and bone marrow following mating with males expressing the cognate MHC molecule but not following syngeneic or third party mating.[320] A lower level of deletion was observed when allo-H-2K expression was restricted via a transgene to trophoblast giant cells and occurred only with developing B cells in the bone marrow and not with mature B cells in the periphery.[321]

Are Anti-trophoblast Antibodies Pathogenic?

Aside from HDFN and the rare alloimmunization conditions mentioned above, the presence of paternal alloantibodies in maternal blood does not typically cause pregnancy complications or even significant placental pathology. This is true not only for the multitude of women bearing anti-HLA antibodies but also for mice hyperimmunized prior to pregnancy with paternal cells so that cytotoxic antipaternal H-2 antibodies are expected to exist.[279] At present, there is no obvious explanation for these divergent outcomes. One possibility is that anti-Rh(D) antibodies have an inherently greater potential to cause disease given the high density of Rh(D) molecules on the RBC plasma membrane. Accordingly, antibodies to other paternal alloantigens (eg, paternal HLA) might also bind fetal and placental cells but cause only clinically insignificant damage. In support of this idea, anti-HLA antibodies may contribute to the pathogenesis of villitis of unknown etiology (VUE), a placental lesion described further below that is typically an incidental histological finding. Similarly, the role of anti-HLA antibodies in RSA appears minor.[322-324] Another possibility, suggested by mouse studies in the 1970s, is that the placenta functions as an immunoabsorbent that prevents antibodies with certain specificities, such as for H-2 molecules, from reaching the fetal circulation and thus causing widespread pathology.[325] Human syncytiotrophoblasts are also thought to be somewhat resistant to complement-mediated lysis since they express high levels of the complement inhibitors CD46, CD55, and CD59.[326,327] In mouse embryos, inactivation of the complement inhibitor Crry causes C3-dependent fetal demise in early gestation associated with complement deposition on trophoblasts.[328] Death occurs without prior immunization, thus revealing a role for Crry in inhibiting antibody-independent complement activation, but it is unknown whether Crry also minimizes damage caused by the antibody-triggered classical pathway. Similar C3-dependent death is evident in embryos lacking the sialic acid activating enzyme CMP-sialic acid synthase, suggesting that protein sialylation by trophoblasts also protects them from complement-mediated lysis.[329]

Importantly, trophoblasts are not completely impervious to the potentially pathogenic effects of antibody binding. This susceptibility is evident from the case of the antiphospholipid antibody syndrome, an autoimmune condition frequently associated with systemic lupus erythematosus (SLE) in which autoantibodies develop against phospholipid-binding proteins expressed on the surfaces of endothelial cells.[330,331] Whether preexisting or arising during pregnancy, these maternal antibodies bind the same proteins on syncytiotrophoblast membranes, where they activate both the complement and coagulation cascades and cause a variety of pregnancy complications, including preeclampsia, IUGR, and miscarriage.[330,331] These complications are thought in part to be due to placental thrombosis given the moderate therapeutic efficacy of antithrombotic agents, but animal models have also implicated roles for complement activation and inflammation.[330,332] Perhaps not surprisingly, given the ability of maternal alloantibodies to cross the placenta and cause HDFN, the transplacental transport of maternal autoantibodies can also be pathogenic. This is best exemplified by women with autoimmune diseases such as SLE or Sjogren syndrome who bear autoantibodies toward the ribonuclear proteins Ro/SSA. These antibodies cross the placenta to cause congenital heart block and other manifestations of neonatal lupus.[333]

Are There Any Examples of Placental "Rejection"?

Given that multiple, redundant mechanisms appear to enforce fetomaternal tolerance, the question arises of whether rejection of the fetus and/or placenta could ever occur, either spontaneously or when only one mechanism at a time is experimentally targeted. Clearly, HDFN is an example of alloimmune-mediated fetal loss, but its pathogenesis involves bypassing the placenta entirely—both as antigen source and target end-organ. Here, in this last section of fetomaternal tolerance, we discuss whether there exists any example of the maternal immune system causing fetal loss because it reacted to the placenta as if it were a classical allograft.

We begin by emphasizing that many immunological manipulations cause fetal loss in mice. Many of these do not show an alloantigen-specific component and instead just illustrate the potentially deleterious effects of nonspecific inflammation on pregnancy outcome. Most classically, the administration of low-dose *lipopolysaccharide* (LPS) to pregnant mice at midgestation rapidly causes isolated fetal resorptions, most likely secondary to focal, nonspecific uteroplacental inflammation and hemorrhage.[334,335] A second example is the complete fetal loss seen in early pregnancy following systemic activation of maternal B cells and DCs via the CD40 signaling pathway. In this case, pregnancy failure is due to the induction of systemic inflammation, and in particular, TNFα production that, in turn, inhibits progesterone production by the ovary.[335] A third example is the fetal loss induced by injection of antiphospholipid antibodies, which as mentioned above induces complement deposition on trophoblasts.[332]

Accordingly, examples of fetal loss that either require an adaptive immune response or that show paternal alloantigen-specificity—typically scored as fetal loss in allogeneic but not syngeneic mating combinations—are more suggestive of true fetal rejection. These examples include systemic T_{reg} cell depletion (see section *Treg Cells and the Attenuation of T Cell Priming to Trophoblast Antigens*), administration of anti-PD-L1- antibodies,[18] administration of the indoleamine 2,3-dioxygenase substrate 5-methyl-tryptophan,[296] and depletion of myeloid-derived suppressor cells.[336] Another example comes from work on the abortion-prone CBA/J(female) × DBA/2(male) mouse mating combination, a model of spontaneous early pregnancy failure that occurs in a pattern suggestive of T cell involvement.[337] However, in some of these cases, fetal loss was no longer evident when genetic approaches were employed,[248,338] and in all of these cases, the extent of maternal T cell accumulation at the maternal-fetal interface was very subtle (if at all evident) and in no way comparable to the level of infiltration seen during acute organ transplant rejection or tumor rejection.[121,270] Thus, even if T cell activation toward trophoblast antigens truly occurred, fetal loss in these examples was ultimately driven by circulating mediators rather than by direct T cell attack on the conceptus. Indeed, a clear example of this kind of situation is the partial, late-gestation fetal loss observed when large numbers of preactivated OVA-specific CD8 T cells are transferred at gd3.5 into mOVA-mated females, as both $mOVA^+$ and $mOVA^-$ concepti are equally affected.[339] A similar set of considerations applies to the view that spontaneous abortion in humans, either isolated or recurrent, represents fetal or placental rejection. Although associated with various alterations in maternal T cells, including decreased T_{reg} cell and increased Th17 cell frequencies within both the blood and uterus, it is not associated with overt T cell infiltration into the uterus.[297,298,301,340-345] Similarly, and as mentioned above, antipaternal HLA antibodies are not a major cause of spontaneous abortion in humans.[322-324]

Villitis of Unknown Etiology

VUE is a histologically identified lesion of the third-trimester placenta characterized by maternal CD8, and to a lesser extent, CD4 T cell infiltration into the chorionic villi in the absence of underlying infection.[346-348] Infiltration usually occurs multifocally, with the affected areas showing features of inflammation including expression of the T cell-attracting chemokines CXCL9, CXCL10, CXCL11, and CCL5, aggregation of activated Hofbauer cells, and upregulation of ICAM-1 by syncytiotrophoblasts.[11,12,349-352] Recent TCR-sequencing data[353] have moreover revealed not only that the infiltrating T cells are clonally expanded but that the specificities of the clones vary between individuals, as would be expected for a response toward a polymorphic target like HLA. In contrast, the expanded clones seen in cases of placental HCMV infection are shared between individuals and are largely absent from cases of VUE. VUE also has a high risk of recurrence with subsequent pregnancies, consistent with immunological memory and a noninfectious etiology, and is strongly associated with the presence of anti-HLA antibodies in maternal serum and the deposition of complement C4d and membrane attack complex components on and around the syncytiotrophoblasts of the inflamed villi.[352,354-356] Together, these observations make a compelling case that VUE represents a true form of placental rejection (Fig. 41.6). Although exact pathogenic mechanisms have not been defined, a possible scenario is that maternal CD4 and CD8 T cells become primed to paternal HLA molecules following maternal exposure to fetal blood cells, all via the canonical allorecognition pathways available to standard blood and organ transplants. Some of the CD4 T cells provide help for a humoral response to paternal HLA, while both CD4 and CD8 T cells, after reaching the villi via the bloodstream and breaching its trophoblastic layers, manifest effector function after being stimulated again by any of the fetal cell types that constitute the villi. Alloantibody binding and complement activation may both trigger villous inflammation and thus initial T cell adhesion to the syncytiotrophoblast layer, as well as fuel ongoing inflammation. Chronic chorioamnionitis and chronic deciduitis, two additional but much more subtle examples of lymphocyte accumulation at the maternal-fetal interface, may also reflect adaptive immune responses toward the conceptus.[346] These lesions are much less well studied but frequently coexist with VUE. Of note, even though villous trophoblasts show signs of apoptosis in the affected areas of VUE,[352] it is unclear whether they are being directly killed by the invading T cells or by complement. It is also possible that trophoblasts die secondarily to damage to the nontrophoblastic cell components of the villi.

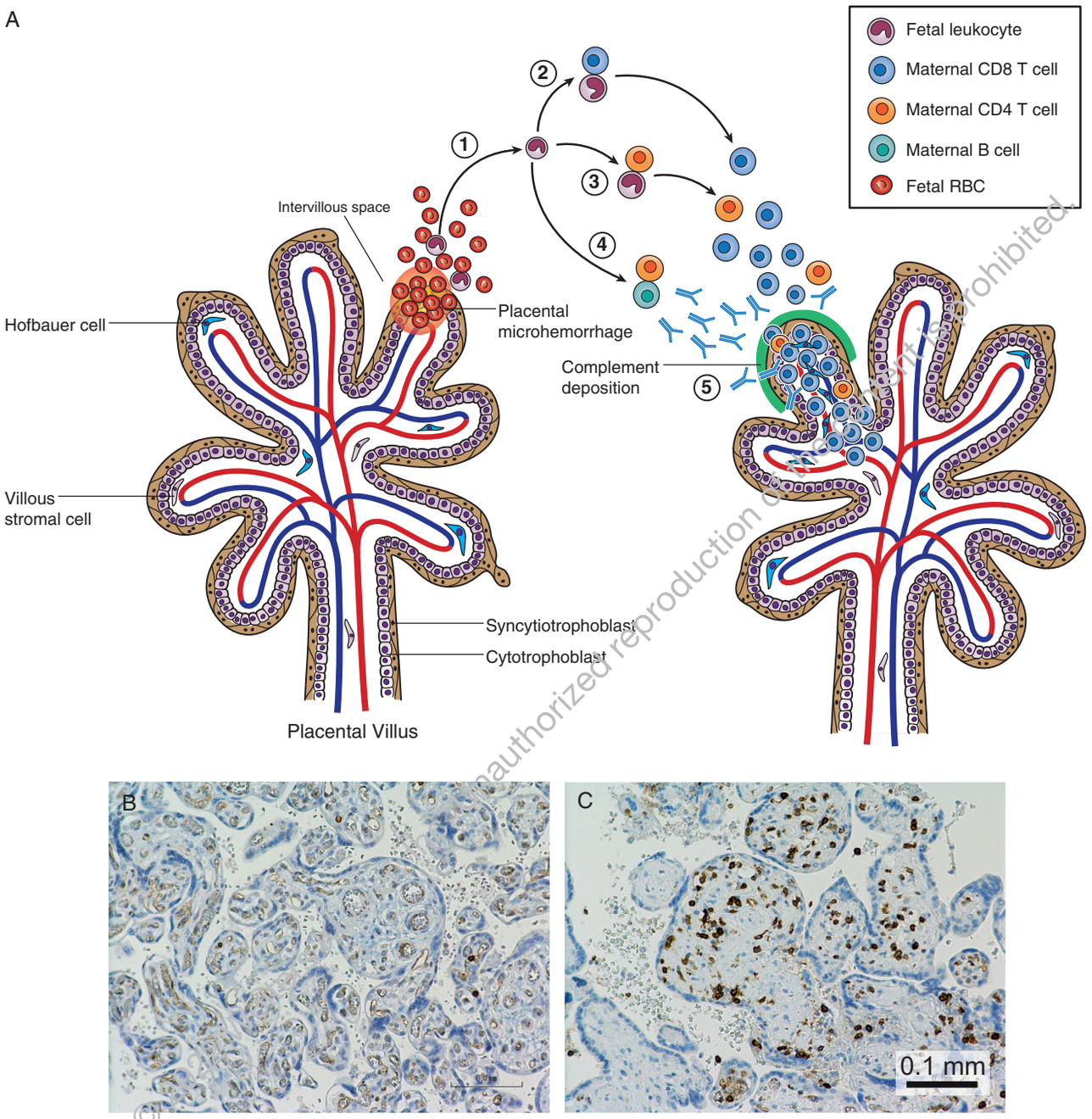

FIG. 41.6. Villitis of unknown etiology (VUE). VUE, a multifocal inflammatory lesion of the placental villi, likely represents a true example of placental "rejection." **A:** Proposed pathogenesis. We speculate that the series of events that cause VUE starts with placental microhemorrhage (or a prior delivery, like with Rh disease) that exposes the mother to fetal white blood cells (1). Priming of maternal T and B cells then proceeds according to the tenets of classical transplantation immunology. Thus, CD8 (2) and CD4 T (3) cells are primarily activated via the direct and semidirect (not depicted) allorecognition pathways, that is, by their T-cell receptor (TCRs), respectively, binding to paternal class I and class II human leukocyte antigen (HLA) molecules expressed by the fetal cells, while B cells are activated to these same molecules with help from CD4 T cells specific for paternal HLA-derived peptides (4). The antipaternal HLA antibodies so produced cross the syncytiotrophoblast layer of the placental villus, whereupon they bind to its nontrophoblastic cellular constituents, namely Hofbauer cells, stromal cells, and endothelial cells. This induces focal complement deposition, inflammation (including chemokine expression), and damage to the syncytium, which in turn fosters recruitment of the activated T cells and thus further damage (5). Minor histocompatibility antigens expressed by the fetal blood cells are also expected to activate additional T and B cells, which will also contribute to inflammation and damage (not depicted). **B and C:** Anti-CD3 immunostaining (*brown*) demonstrating T cell infiltration into villi affected by VUE **(C)** and the absence of T cells from normal villi **(B)**. The slight staining of fetal capillaries is nonspecific.

Remarkably, VUE is very common as it is present in 2% to 34% of all third-trimester placentas, depending on the study.[346,348] Although severe cases that diffusely affect the placenta have been associated with stillbirth,[357] VUE is typically an incidental, mild finding in an otherwise normal pregnancy and is only weakly associated with adverse pregnancy outcomes such as IUGR and PTL.[346,348] Thus, the ability of the T cells to cause clinically significant damage is limited. The reason for this remains unclear but may be linked to the focal nature of the lesion, suggesting a limited ability of CD8 T cells to breach the syncytiotrophoblast layer. Nonetheless, the link between VUE and PTB has suggested that PTB might be the consequences of an adaptive immune response toward the fetus and placenta in certain cases.[346] This possibility, in turn, is consistent with the ability of certain immune cell-derived cytokines to indirectly promote myometrial contractility (see section *Parturition and PTL*), but the idea lacks direct support at present. PTB has also been associated with the activation of fetal T cells with specificity toward maternal alloantigens and their production of IFNγ and TNFα, but precise pathways of T cell activation and labor induction remain undefined.[358]

NK Cell Tolerance Toward the Conceptus

One of the defining features of NK cells is that they kill cells that express low levels of self MHC-I molecules. While best understood as a barrier to bone marrow transplantation, there is an increasing appreciation that this activity also impacts upon the health of solid organ transplants.[359] Thus, given that EVTs only express HLA-C, an additional immunological paradox of pregnancy is that these cells are not killed by dNK cells despite the 2 cell types' close proximity within the decidua.

One piece of the puzzle likely relates to the intrinsically low cytotoxic potential of resting dNK cells and the restricted fashion that cytotoxicity can be induced in them. Unlike peripheral blood NK cells, freshly isolated dNK cells in humans are unable to kill MHC-I–deficient NK cell targets, a defect attributed to an inability of the cells to polarize their cytotoxic granules to the immune synapse.[360-362] Similar lytic defects have been observed for mouse dNK cells.[363] However, freshly isolated human dNK cells polarize their cytotoxic granules, degranulate, and kill cultured DSCs infected with HCMV, an effect that is initiated through ligation of the activating receptors NKG2D and CD94/NKG2C/E.[362,364,365] Increased cytotoxicity can also be induced via ligation of the NKp46 natural cytotoxicity receptor.[72] Thus, the engagement of activating receptors, and not just decreased inhibitory receptor signaling, appears critical for the ability of dNK cells to manifest cytotoxic responses. What induces the dNK cell's state of altered responsiveness *in vivo* is not entirely clear but has been linked to exposure to TGF-β produced by either DSCs or decidual macrophages.[69-71,73]

Superimposed upon this baseline reduction in dNK cytotoxicity, EVTs are intrinsically resistant to dNK cell-mediated lysis even when the cells are HCMV-infected.[362,364,365] This in part may be due to the ability of HLA-G expressed by EVTs to inhibit dNK cells via engagement of the inhibitory receptor LILRB1, as well as to the ability of HLA-E, presenting a HLA-G leader sequence-derived peptide, to inhibit dNK cells via engagement of CD94/NKG2A, another inhibitory receptor.[26] IL-15, which is produced by DSCs, also influences dNK cell cytotoxicity,[362,365,366] but its effects are complex and interpretations of *in vitro* experiments are complicated by the fact that this cytokine is not only a key NK cell survival factor but may act in combinatorial fashion with TGF-β to modulate dNK-cell phenotypes.[69] It is also unclear whether different dNK cells subsets have different capacities to kill virus-infected cells. Of note, dNK cells are not expected to be able to kill EVTs via antibody-directed cytotoxicity (ADCC), even in women with antipaternal HLA-C antibodies, since they do not express the Fc receptor CD16.

INFECTIOUS DISEASES AND PREGNANCY

Earlier, in this chapter, we described how pregnancy is not a generalized state of immunosuppression as once thought. This makes logical sense in light of the evolutionary imperative to protect the mother and fetus from infection. Nevertheless, certain pathogens cause novel pathologies during pregnancy due to their ability to infect the maternal-fetal interface where the uterus, placenta, and fetus provide new, fertile ground for colonization. In addition, a select few other pathogens show altered disease courses during pregnancy even though their organ tropism is the same in pregnant and nonpregnant hosts. We discuss this latter, select set first in section *Systemic Immunity to Infection and Vaccines During Pregnancy* due to the clinical importance of systemic immunity in pregnant women (see also section *Systemic Changes to the Maternal Immune System During Pregnancy*). In section *Immune Defenses at the Maternal-Fetal Interface*, we discuss the pathogens that infect the maternal-fetal interface. In one respect, the ability of these pathogens to do so reflects the diminished nature of cellular immunity within the decidua that is necessary to maintain fetomaternal tolerance. However, it is clear that many of the relevant pathogens employ virulence mechanisms that allow them to exploit this unique immunological environment. We will also discuss the distinctive tissue-specific countermeasures that have evolved to protect the placenta from infection and prevent vertical transmission to the fetus, in particular those mechanisms active within trophoblasts[367-369] (Fig. 41.7).

The systemic and local infections that do occur during pregnancy affect maternal, fetal, and neonatal health in many ways. Congenital infection, which occurs when pathogens gain access to the fetus, has the strongest negative impact on fetal outcome. However, placental infection, and even maternal or fetal inflammation, can impair placental function and thus indirectly affects fetal development. Infection is also the most commonly identified cause of preterm birth (PTB) and can lead to fetal loss. In section *Infection-Mediated Pregnancy Complications*, we review these infection-induced complications and describe treatment strategies. Lastly, in section *The Role of Infection in Infertility and Ectopic Pregnancy*, we discuss pathogens that prevent implantation or lead to ectopic pregnancy (ie, implantation outside of the uterus).

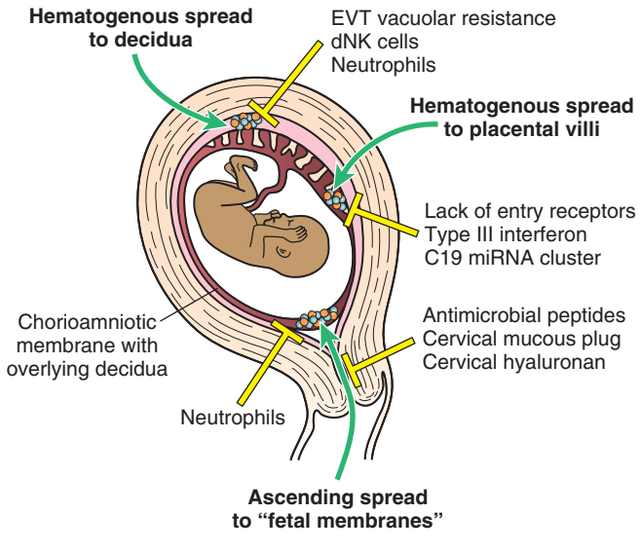

FIG. 41.7 Host defense mechanisms and routes of uterine infection during pregnancy. The three main routes of infection are depicted. For simplicity, infecting organisms are illustrated in a uniform way, but we note that different pathogens take advantage of different routes of spread (see text for details). The host defense lists are only partial and mainly serve to highlight that different locations within the pregnant uterus employ different mechanisms. Of note, infection of the decidua can be a launching point for spread to the placenta. Also, of note, this diagram is representative of the late second trimester up until term gestation, and thus shows the chorioamniotic membrane with overlying decidua capsularis fused with the decidua parietalis (see also Fig. 41.1D).

Systemic Immunity to Infection and Vaccines During Pregnancy

The influence of pregnancy on immunity to pathogens that do not infect the maternal-fetal interface has a controversial history,[370] but the consensus opinion at present is that the effect is subtle except in select cases of chronic HCV and influenza virus, which we discuss in detail here. Chronic HCV infection in nonpregnant, healthy individuals is characterized by stable viremia and CD8 T cell responses that exert selective pressure on the virus, leading to the evolution of viral quasispecies expressing escape mutations in class I HLA epitopes.[371] By contrast, women in the latter half of pregnancy do not show stable viremia but rather a small-to-moderate elevation in viral load and the appearance of quasispecies that lack escape mutations.[372,373] These changes are hypothesized to arise because of a loss of selective pressure, in turn due to the suppression of virus-specific CD8 T cells. Remarkably, ~30% of women experience dramatic reductions in viral load in the postpartum period, with complete viral clearance occurring in a small number of patients. This phenotypic reversal is associated with the emergence of polyfunctional HCV-specific CD4 effector T cells[374] and shows genetic linkage with polymorphisms in *IFNL3*, *IL-28B*, and certain *HLA-DPB1* alleles, supporting an immune mechanism.[375,376] Provocatively, the third trimester and postpartum waning and waxing of maternal T cell responses to HCV parallel a similar waning and waxing of rheumatoid arthritis (RA) and MS disease severity during the same respective time periods (see section *Developmental Influences of the Maternal Immune System Over Pregnancy*), suggesting common underlying mechanisms.

Fortunately, the third-trimester elevation in HCV viremia does not pose a major threat to maternal health. Influenza, by contrast, can be very severe during the third trimester, particularly for women with comorbidities such as asthma. Indeed, during the influenza pandemic of 1918, physicians noted a 10-fold higher fatality rate among pregnant (27%) versus nonpregnant (2%) women.[377] Increased influenza disease severity has also been observed in pregnant mice, whose lungs show more severe histopathology when compared to nonpregnant controls. These mice also show exaggerated innate responses with increased neutrophil and myeloid cell recruitment and increased production of inflammatory mediators,[378-380] whose adverse effects on the lung are likely compounded by the fact that pregnancy is associated with a reduced capacity for respiratory epithelial cell regeneration.[379] Additional immune deficits in infected pregnant mice include mild (<twofold) reductions in lung concentrations of type I IFN and other proinflammatory cytokines, costimulatory marker expression by lung APCs, lung *Cxcl9* and *Cxcl10* expression, with diminished CD8 T cell recruitment, CD8 T cell killing capacity, and anti-influenza antibody titers.[381] Similarly, influenza-infected pregnant women show reduced anti-influenza IgG2 titers[382] and diminished neutralization capacity of third-trimester serum,[383] while PBMCs from uninfected pregnant women show less types I and III IFN production following exposure to influenza virus particles *in vitro*.[384] To the extent they involve adaptive immune cells, these deficits are in-line with the more general defects in adaptive immunity seen in late pregnancy (see section *Systemic Changes to the Maternal Immune System During Pregnancy*) and likely foster further tissue damage by delaying viral clearance. Importantly, respiratory and cardiovascular adaptations of late pregnancy, including decreased pulmonary volumes, less effective clearing of pulmonary secretions, and increased oxygen demand predispose pregnant women to severe respiratory infection.[385]

Why Are Not All Systemic Infections Worse With Pregnancy?

As we discussed in section *Systemic Changes to the Maternal Immune System During Pregnancy*, work on mice and humans has suggested that systemic adaptive immunity is quantitatively depressed in certain ways during pregnancy. However, only in the cases of HCV and influenza have these deficits been consistently linked to altered disease course. Indeed, a comprehensive study on primary HCMV infection did not reveal appreciable differences in systemic T cell and antibody responses between pregnant and nonpregnant women.[386] Even pathogens such as *Listeria monocytogenes* (*L. monocytogenes*; discussed further below), LCMV, and *Fusobacterium nucleatum (F. nucleatum)*, which all robustly grow in the mouse decidua and then placenta, are effectively cleared from maternal liver, spleen, and lungs in the same hosts.[387-389] At present, there is no clear explanation for this pathogen-specific pattern, but it is important to note that a complete

dissection of immune responses to all pathogens over the course of gestation has not been undertaken. Thus, it remains possible that immune responses are modestly impaired to a larger number of pathogens than currently appreciated but that such deficits are clinically relevant in only certain cases.

It also bears emphasis that the nonimmunological physiologic changes of pregnancy might impact upon disease course for many pathogens even if the immune response is unaltered. In particular, respiratory infection might be more severe given the aforementioned changes in pulmonary function seen in late gestation.[390] The virulent and highly transmissible SARS-CoV, MERS-CoV, and SARS-CoV-2 viruses, which cause severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19, respectively, are thus potentially of great concern for the pregnant population. Unfortunately, our understanding of the pathogenesis of these viruses during pregnancy is still immature and only a limited number of cases have been reported. Vertical transmission appears to be rare for all three, and so far, data suggest adverse pregnancy outcomes for SARS and MERS are likely secondary to severe maternal illness.[391,392] The high case fatality rate for SARS in pregnant women suggests that illness might be more severe for this population. MERS, on the other hand, shows a similar fatality rate in pregnant and nonpregnant women.[393] Fortunately, thus far, COVID-19 does not appear to be more severe for pregnant women;[392] however, it remains to be determined if SARS-CoV-2 elicits adverse pregnancy outcomes.

Vaccines

Consistent with the quantitative depression of systemic immunity seen in late gestation, antibody titers in third trimester pregnant women given certain (but not all) inactivated influenza vaccine strains are somewhat diminished compared to nonpregnant women.[212,394] The elicited titers are nonetheless protective, as pregnant and nonpregnant women achieve similar levels of risk reduction.[395-397] Moreover, vaccination with inactivated influenza vaccine during pregnancy is safe,[398] and thus most guidelines recommend that pregnant women receive inactivated influenza vaccines as well as boosters against tetanus, diphtheria, and pertussis. Novel vaccines against other pregnancy and neonatal pathogens, including GBS, respiratory syncytial virus, HSV, and HCMV are currently under development (as reviewed in Ref. 399). Because of the risk of vertical transmission, live attenuated vaccines are generally not acceptable, with exceptions for endemic viral outbreaks.[400] Finally, because ZIKV is closely related to dengue virus, there is concern that antidengue antibodies could worsen ZIKV pathology via antibody-dependent enhancement (see Chapter 33). Although this has been seen in mouse models,[401] epidemiology studies suggest that preexisting immunity to dengue virus actually lowers the risk of ZIKV infection.[402]

Vaccination not only prevents infection during pregnancy, but the passive transfer of maternal IgG across the placenta to the fetus confers significant protection against influenza, rubella, tetanus, and pertussis in newborns and young infants.[403-407] A potential disadvantage of passively transferred maternal immunity is that maternal antibodies may inhibit the responses of infants to primary vaccination via immediate neutralization and clearance of the antigen or engagement of inhibitory Fc receptors on the infant's B cells (as discussed in Ref. 408). New research shows that novel vaccine design can somewhat overcome these barriers.[409]

Immune Defenses at the Maternal-Fetal Interface

The two main routes by which pathogens colonize the maternal-fetal interface are ascending spread from the cervicovaginal tract and hematogenous spread from the maternal bloodstream. Ascending infection is the most common route encountered clinically and is typically caused by bacterial and fungal commensals of the vagina and cervix. These include GBS,[410] which is present among the healthy rectovaginal flora in 30% of women, as well as *Mycoplasma hominis* and *Ureaplasma* spp.[411] and *Candida* spp.[412] Once they transverse the cervix, these organisms infect the abutting fetal membranes. By contrast, a wide variety of bacteria, fungi, protozoa, and viruses reach the maternal-fetal interface via the blood. These include *L. monocytogenes*,[413] *Salmonella typhi*,[414,415] *Treponema palladium*,[416] *F. nucleatum*,[417] *Toxoplasma gondii*,[418] *Trypanosoma cruzi*,[419] Hepatitis E virus,[420] ZIKV, and rubella virus,[421] which all primarily seed and multiply within the decidua before spreading to the placenta via anchoring villi. Notably, most of these pathogens have intracellular life cycles and so access the decidua via trafficking within maternal blood-borne monocytes.[422] In addition, *Plasmodium falciparum* (*P. falciparum)*[423] accumulates at the syncytiotrophoblast layer of the villous tree, while HCMV[421] can directly infect the villous tree as well as the decidua.

Ascending and hematogenous pathogens possess virulence mechanisms that promote seeding and growth at the maternal-fetal interface.[415,424-427] However, vertical transmission to the fetus is the exception rather than the rule, and in the case of viruses occurs only for a subset of quasispecies present in the mother.[428,429] These observations support the existence of uteroplacental defense mechanisms,[430] which are currently thought to be lower reproductive tract defenses for ascending pathogens and the syncytial barrier of the placental villi and innate immunity within the decidua for hematogenous pathogens. We, therefore, focus the following discussion on these defenses and highlight important facets of certain pathogens as they relate to the immune response, but we refer the reader to the comprehensive reviews cited above for more details on the pathogenesis of each organism.

Lower Reproductive Tract Defenses

Physical and molecular barriers prevent vaginal and cervical organisms from traveling upward to the uterus.[431] An important first line of defense is provided by the numerous, short, amphipathic antimicrobial peptides (AMPs) that are produced by cervicovaginal immune and epithelial cells and that interact with and specifically disrupt bacterial membranes.[432] Antiviral protection is provided by epithelial-derived type III IFN.[433] In addition, the "cervical mucous plug" (CMP), which is a dense viscoelastic substance comprised mainly of

mucinous glycoproteins produced by secretory cervical glandular cells, sterically excludes bacteria and may have antiviral properties.[434] The mouse CMP, produced upon copulation, falls out within 1-day, while the human CMP, produced upon fertilization, remains over the course of gestation. The CMP also contains immunoglobulins, complement proteins, live phagocytes, the glycosaminoglycan hyaluronan, and various AMPs including lysozyme, lactoferrin, and calprotectin.[434] The importance of hyaluronan, in particular, is evident from the exacerbation of ascending infection-induced PTB in mice lacking cervical hyaluronan[435] and the association between ascending infection in humans and GBS strains that express the virulence factor hyaluronidase, which digests hyaluronan.[436]

Villous Syncytiotrophoblast and Cytotrophoblast Defenses

The villous tree is very resistant to direct bacterial and protozoal infection in large part due to the lack of pathogen entry receptor expression by syncytiotrophoblasts and this layer's dense actin cytoskeleton that physically resists the distortion needed for bacterial entry.[437-440] The syncytium also resists viral infection due to its constitutive expression of type III IFN that contrasts with the inducible nature of type III IFN expression by gastrointestinal and respiratory tract epithelia.[441,442] Type III IFN protects the mature syncytium from ZIKV infection, but primitive, undifferentiated trophoblasts do not produce type III IFN and are thus vulnerable to ZIKV.[443] As a consequence, ZIKV infection during early gestation shows a high risk of vertical transmission and severe congenital infection.[444] The layer of mononuclear cytotrophoblasts that lies immediately beneath the syncytiotrophoblast layer also possesses antiviral defense properties and can resist infection by a variety of DNA and RNA viruses.[440,445,446] Although underlying mechanisms have yet to be defined, this ability is at least in part conferred by expression of C19MC, a primate-specific microRNA cluster.[445] C19MC can also confer protection upon other villous cells via its packaging into exosomes.[446] Importantly, once pathogens breach the cytotrophoblast layer and reach the villous stroma, the main immune cells they will encounter before reaching the fetal circulation are Hofbauer cells. As compared to monocyte-derived macrophages, the M2-polarization of Hofbauer cells and their tendency to elaborate regulatory cytokines like IL-10 and TGF-β is believed to underlie their ability to limit HIV replication.[447] However, it is not clear how well these cells resist the spread of other viruses as vertical transmission of ZIKV, in particular, is thought to occur through infection of Hofbauer cells.[147]

Despite its many defenses, placental villi are important direct sites of infection for at least two pathogens. First, HCMV can gain access to the villous stroma during a primary infection because the initial set of induced antibodies, while too low avidity to effect viral neutralization, are nonetheless capable of transferring HCMV across the syncytiotrophoblast layer via the neonatal Fc receptor.[448] Second, *P. falciparum* specifically targets syncytiotrophoblasts during malaria infection by altering the expression of a family of *P. falciparum*-encoded clonally variant adhesion proteins (*var* genes, PfEMP1 protein family) in infected RBCs. In nonpregnant hosts, these PfEMP1 variants mediate adhesion of parasitized RBCs to endothelial cells. During pregnancy, however, an atypical variant (VAR2CSA) is induced that specifically binds to chondroitin sulfate A on the syncytial surface and thus allows infected RBCs to sequester within the placenta.[427,449] Unfortunately, the signals that trigger expression of VAR2CSA during pregnancy are not yet known. Multigarous women living in malarial-endemic regions usually do not suffer severe placental malaria because they maintain protective antibodies against VAR2CSA.[450] However, placental malaria in women lacking anti-VAR2CSA antibodies progresses to a chronic stage in which monocyte, macrophage, B cell, and fibrin accumulation in the intervillous space impairs nutrient transport and leads to poor outcomes.[451-453]

Decidual and Extravillous Trophoblast Defenses

Much of our knowledge about the immune response to decidual infection comes from work on *L. monocytogenes.* This facultative intracellular gram-positive bacterium causes a foodborne self-limited gastrointestinal illness in healthy nonpregnant individuals but can cause severe disease in pregnant women because of its ability to colonize and grow rampantly in the decidua. Consistent with this notion, work on *L. monocytogenes* infection during mouse pregnancy indicates that systemic disease is driven by the reseeding of bacteria from the decidua back to other maternal organs.[454]

L. monocytogenes grows rampantly within the decidua because of the decidua's deficits in cellular immunity. Thus, as studied in mice, the infected decidua is unable to accumulate macrophages and CD8 T cells at foci of bacterial growth, nor can it recruit Ly6C^{hi} inflammatory monocytes from the blood.[80,87,389,455,456] These deficits are consistent with the unique limits DSCs place over the trafficking and population dynamics of macrophages, monocytes, and T cells described in sections *Immune Cells of the Pregnant Uterus* and *Mechanisms of Effector Phase Tolerance to the Conceptus* and stand in stark contrast to the ease by which macrophages, monocytes, and T cells accumulate around infectious foci and control bacterial growth in nondecidual tissues, including the undecidualized endometrium.[389,456-458] As a result, the decidual immune response to *L. monocytogenes* falls to neutrophils, dNK cells, and trophoblasts.[389,456,459,460] The function of neutrophils in this regard is canonical (ie, production of reactive oxygen species etc. and NET generation),[461-463] but dNK cells show an unusual ability to kill *L. monocytogenes* organisms within infected EVTs via nanotube-mediated granulysin transfer in a way that keeps the EVTs alive.[460] Moreover, EVTs have an intrinsic capacity to restrain *L. monocytogenes* intravacuolar replication.[464] Neutrophils are also the main inflammatory cell recruited to the human amniotic cavity, fetal membranes, intervillous space, and villi once infection spreads to the placenta.[465] However, despite the ability of *L. monocytogenes* to grow rapidly within the decidua, infection during pregnancy is rather rare, and this correlates with the difficulty faced by the organism in initially colonizing the decidua.[87] Since blood-borne *L. monocytogenes* dissemination occurs within

infected mononuclear cells, one important bottleneck is the inability of the decidua to recruit Ly6C^{hi} monocytes.[466]

The decidual immune response to HCMV provides a second example of how pathogens take advantage of the unique immunologic environment of this tissue. In the absence of high anti-HCMV neutralizing antibody titers, the decidua becomes a local reservoir of active infection[467] likely exacerbated by the local constraints on T cells, which would otherwise control the virus.[468] Indeed, the stroma of infected placental villi shows prominent T cell accumulation,[469] unlike areas of decidual HCMV infection.[470] In the absence of T cells, antiviral defense within the decidual falls to other cell types, including dNK cells, which eliminate HCMV-infected decidual fibroblasts.[362,365] dNK and macrophages also protect against decidual HIV-1 infection. Thus, while decidual macrophages and Hofbauer cells are the main local targets of HIV-1 infection,[123] they are less permissive to infection and better at restricting replication when compared to blood monocyte-derived macrophages.[123,447,471] Moreover, dNK cells augment the resistance of decidual macrophages to HIV infection in an IFNγ- and contact-dependent manner.[472] Although not yet addressed directly, it seems unlikely that decidual DCs would be able to initiate adaptive immune responses to decidual pathogens given their low tissue densities in mice and humans and inability to migrate to the uterus-draining LN in mice (see section *Immune Cells of the Pregnant Uterus*). Lastly, the extent to which decidual infection is fostered by local immune suppression, potentially mediated by T_{reg} cells or IL-10 (see section *Immune Cells of the Pregnant Uterus*), is currently unknown.

Infection-Mediated Pregnancy Complications

Effects on Fetal Development

Pathogens that affect fetal development are easily recalled using the "TORCH" pneumonic, which stands for *Toxoplasma gondii,* Others (*Treponema pallidum,* Parvovirus B19, Varicella virus, ZIKV, *P. falciparum*), *Rubella, (H)CMV,* and *HSV*). Infection during early gestation, when organogenesis is occurring, is generally more damaging than infection later in gestation. For instance, ZIKV-induced microcephaly is caused by infection of neural progenitor cells in the developing CNS, which inhibits their growth and differentiation.[473-475] Other important clinical manifestations caused by direct infection include hydrops fetalis elicited by parvovirus B19-mediated destruction of fetal erythroid progenitors,[476] bone deformities in congenital syphilis,[416] and cataracts, deafness, and heart defects in congenital rubella syndrome.[477]

Transplacental transport of pathogen-associated molecular patterns (PAMPs) and the maternal immune response to infection can also affect fetal development even if the fetus is itself not infected. The fetal brain is particularly sensitive to inflammation since inflammatory mediators both damage neurons and activate microglia, which then produce more cytokines, glutamate, and oxidative free radicals. Ascending infection, modeled in mice by administration of either LPS or *E. coli*, is associated with TLR4-dependent fetal brain inflammation,[478,479] while bacterial peptidoglycan alters postnatal behavior after it crosses the placenta and engages TLR2 in the fetal brain.[480] In humans, there is a correlation between severe placental inflammation and brain injury,[481,482] while infection can affect oxygenation and cerebral blood flood to exacerbate neonatal hypoxic-ischemic injury.[483,484] *In utero* inflammation also affects the fetal lungs and immune system.[485]

Intriguingly, epidemiologic and experimental evidence supports a role for pregnancy infections in the development of schizophrenia and autism spectrum disorders. The "neurodevelopmental theory of schizophrenia" emerged from the observation that this disease is more common in babies born during the annual influenza season and from mother infected during the 1957 influenza pandemic.[486,487] Subsequent studies confirmed that maternal infection slightly elevates the risk of offspring developing schizophrenia or autism.[488-490] Proposed mechanisms include (1) transplacental transport of cytokines that directly bind to receptors on brain cells; (2) transplacental transport of antibodies that cross-react with proteins expressed in the brain; (3) pathologic reprogramming of the fetal adrenal axis secondary to maternal stress hormone exposure; and (4) infection-induced placental secretion of neurotransmitters such as serotonin.[491] Mouse experiments show that maternal Th17 cell-derived IL-17a can alter fetal brain development to elicit autism-like behaviors.[492]

Preterm Birth

Infection is the most commonly identified cause of PTB and accounts for an estimated 30% to 40% of cases. The most common pathogenic organisms are aerobic and anaerobic bacteria and fungi that typically colonize the genitourinary tract, oral cavity, and skin—such as GBS, *Mycoplasma hominis, Gardnerella vaginalis, Candida* spp., and *F. nucleatum*[493]. Altered microbiomes or infections at distant sites have also been suggested to increase the risk of PTB due to trafficking of these organisms to the maternal-fetal interface. Thus, there is an association between PTB and rectovaginal colonization with GBS, which is a commensal in 30% of healthy women,[494] between PTB and vaginal dysbiosis,[495] and a controversial association between PTB and oral cavity infections.[496]

The general paradigm for infectious PTB is that organisms gain access to the amniotic cavity and the local inflammatory response culminates in labor via mechanisms described in section *Parturition and PTL*.[497] GBS, for example, invades the amniotic epithelial cells of the fetal membranes via the action of the virulence toxin β-hemolysin/cytolysin and activates NF-κB to drive production of IL-6, IL-1β, and IL-8 leading to neutrophil recruitment.[426] In other cases, it is believed that GBS-derived toxin-containing membrane vesicles promote PTB in the absence of uterine colonization,[498] raising the possibility that infection underlies cases of PTB secondary to so-called "sterile" amniotic fluid inflammation.[499] Concurrent viral infection is thought to lower the threshold for an inflammatory response to bacteria.[500-502] For example, hematogenous infection with gammaherpesvirus 68 and vaginal infection with HSV-2 both sensitize the mouse uterus to

bacterial-driven PTB, possibly through upregulation of TLRs, inhibition of type 1 IFN-β production, and promotion of cervical remodeling.[500,502] This "two-hit" model helps to explain why vaginal infections with HSV-2 and *human papillomavirus* (HPV) are risk factors for PTB.

Fetal Loss

Infection underlies 10% to 25% of fetal losses in high-income settings and upward of 50% of losses in low-to-medium income settings.[503] A major immediate antecedent is congenital malformation, which as discussed above is a common consequence of TORCH organism infection. Influenza infection is also associated with higher rates of fetal loss, as well as PTL, fetal growth restriction, and perinatal mortality, but these outcomes are thought to be secondary to systemic inflammation since influenza infection of the maternal-fetal interface and vertical transmission are very rare in mice and humans.[504] In the cases of *L. monocytogenes* and *S. typhimurium* infection in mice, fetal loss is caused by both infection of the maternal-fetal interface as well as by systemic impairments in maternal T_{reg} cells, leading to systemic inflammation.[197] Finally, fetal loss can also occur secondary to disruptions in placental development and hence placental insufficiency. For example, HCMV dysregulates Wnt/β-catenin signaling in trophoblasts, interferes with trophoblast migration, and elicits increased collagen deposition around endothelial cells, thus impairing nutrient/oxygen exchange.[505-508] More generally, viral infections are associated with elevations in type I IFN and IFN-induced transmembrane proteins (IFITMs), whose normal role is to block viral entry into cells. But IFITMs also happen to block cytotrophoblast fusion and therefore syncytiotrophoblast formation, thereby disrupting placental architecture and function. Thus, type I IFN driven fetal loss is observed in WT but not *Ifitm*$^{-/-}$ mice,[509] and type I IFN underlies fetal loss in ZIKV-infection.[510]

Treatment Strategies

The incidence of several congenital infections, such as rubella and varicella, has decreased because of maternal vaccination. Unfortunately, vaccination against all pregnancy pathogens is not feasible, as some are healthy commensals. When administered to GBS-positive mothers, intrapartum antibiotics successfully prevent neonatal sepsis and meningitis and increase the time to delivery in cases of premature preterm rupture of the fetal membranes, a prelude to PTB.[511] Moreover, screening and treatment of pregnant woman during gestation for asymptomatic bacteriuria, bacterial vaginosis, *Trichomonas vaginalis*, and candida reduces the incidence of PTB.[512,513] However, global prophylactic antibiotic treatment of women already in preterm labor does not reduce adverse outcomes,[514] while nonsteroidal anti-inflammatory drugs (NSAIDs), which show efficacy in mouse models of PTB by preventing the generation of procontractile prostaglandins, are contraindicated during human pregnancy because of adverse fetal effects.[515] Newer targeted immune strategies, such as TLR4 antagonists, may be of use since these suppress uterine and placental inflammation in infection-induced PTB mouse models.[516,517]

The Role of Infection in Infertility and Ectopic Pregnancy

Sexually transmitted *Chlamydia trachomatis* and *Neisseria gonorrhea* both target epithelial cells of the female reproductive tract and are both associated with increased risk of infertility and ectopic pregnancy.[518,519] These organisms initially infect the vaginal canal, where they often fail to elicit symptoms. Left untreated, however, they may ascend into the upper reproductive tract, enter the fallopian tubes, and elicit local inflammation and scaring.[520,521] The consequent losses of beating ciliated epithelial cells, epithelial secretion, and muscular tubal contractions are thought to compromise the transit of both male and female gametes to the tube for fertilization, as well as the transit of the fertilized ovum into the uterus. The molecular mechanism for ovum attachment to the tubal epithelial in cases of ectopic pregnancy remain unknown. Infertility is also associated with plasma cell-rich chronic inflammation of the endometrium (ie, chronic endometritis) that likely has an infectious etiology since polymicrobial bacterial species are identified on biopsy, and antibiotics lead to not only resolution of inflammation but also improved fertility outcomes.[522]

DEVELOPMENTAL INFLUENCES OF THE MATERNAL IMMUNE SYSTEM OVER PREGNANCY

In addition to combatting infection, the maternal immune system also contributes to pregnancy outcome by regulating developmental events within the uterus. Here, we describe these contributions and how their disruption leads to pregnancy pathologies in mice and humans.

Implantation, Decidualization, and Early Pregnancy Failure

The maternal immune system first impacts upon pregnancy by influencing the events associated with embryo implantation. These events include the establishment of the receptive uterine state, the attachment reaction itself, and the subsequent generation of a fully decidualized endometrial stroma that can support embryonic and placental development. Importantly, implantation-associated events are primarily controlled by the endocrine system and uterus-intrinsic developmental pathways rather than by the immune system.[3] Indeed, virtually every mouse strain with an immunological deficit is able to become pregnant. For example, *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$, *Csf1*$^{-/-}$ (*op/op*), *Csf3r*$^{-/-}$, and *Flt3l*$^{-/-}$ mice are all overtly fertile, thus ruling out absolute reproductive requirements for lymphocytes, ILCs (including NK cells), macrophages, monocytes, neutrophils, and DCs. However, a few specific immune pathways are required for the establishment of early pregnancy in mice, as will be mentioned. Moreover, implantation in both mice and humans is associated with a transient wave of uterine inflammation that is thought, via ripple effects extending throughout gestation and beyond, to have profound negative consequences if over-exuberant or uncontrolled.[523,524]

Establishment of the receptive uterine state is driven by the ovarian hormones, estrogen and progesterone. In mice, copulation triggers a programmed hypothalamic-pituitary-ovarian response leading to tonically increased progesterone production that is overlaid, 3 days after mating, with a transient surge in estrogen production ("nidatory," ie, implantation estrogen). Together, these hormones induce gene expression changes in the endometrial stroma and epithelium that generate a "window of implantation" lasting for about 1 day. Importantly, nidatory estrogen induces uterine glandular epithelial cells to express leukemia inhibitory factor (LIF), a IL-6 cytokine family member that also fosters subsequent decidualization.[525] Nidatory estrogen also modestly elevates uterine levels of IL-1α/β, IL-6, and TNFα,[526,527] but this follows upon a more full-blown wave of inflammation that is induced by endometrial exposure to non-LPS TLR4 ligands present in semen and that becomes evident immediately after copulation.[528] This earlier wave is characterized by elevated uterine expression of multiple cytokines and chemokines together with endometrial accumulation of macrophages, lymphocytes, and neutrophil s.[143,528-531] In humans, rising progesterone levels in the secretory phase of the menstrual cycle create a similar window of implantation lasting ~2 days, also associated with increased endometrial LIF expression. Although inflammation is not an overt feature of the secretory phase, this period shows mild endometrial IL-1 and IL-6 upregulation together with mild increases in macrophage tissue densities.[48,127,134,136,532-534] These findings have raised the possibility that inflammation may promote implantation, an idea furthered by the observation that endometrial biopsies can increase implantation rates for *in vitro* fertilization patients in proportion to the extent of the induced inflammation.[523,535] Preimplantation inflammation must be under strict control, however, as even subtle but generalized endometrial inflammation (ie, chronic endometritis) is an established cause of repeated implantation failure.[536]

Blastocyst attachment to the uterine luminal epithelium and the immediate response of the epithelium and its underlying stroma induces further inflammation, in this case highly localized to the attachment site. This response cannot be studied in humans due to ethical considerations, but in Rhesus monkeys, it is associated with macrophage accumulation,[537] while in mice, it induces abutting uterine epithelial and stromal cells to express COX-2, which leads to the localized production of inflammatory prostaglandins, in particular, PGE_2 and PGI$_2$. These prostaglandins promote implantation and are critical for the formation of decidual tissue.[538-540] In addition, ESCs produce IL-11, another IL-6 family member, which drives decidualization in autocrine fashion.[541]

It is not surprising that embryo implantation would induce an inflammatory response in the endometrium, given that the process essentially generates a small wound. What is remarkable, however, is the short-lived nature of the response given that the wound never heals but rather keeps increasing in size as the conceptus grows and trophoblasts invade into the uterine stroma. In fact, the decidua assumes a decidedly noninflammatory state once the initial stages of implantation are complete. In mice, this state is characterized by an inability to recruit T cells and monocytes from the blood, to expand its resident macrophage pool, and to express various proinflammatory genes. We have already described these phenomena when we discussed DSCs, decidual leukocytes, and intrauterine mechanisms of fetomaternal tolerance (see sections *Anatomy, Development, and Microbiology*; *Immune Cells of the Pregnant Uterus* and *Mechanisms of Effector Phase Tolerance to the Conceptus*). Even prior to implantation, the copulation-induced accumulation of macrophages, lymphocytes, and neutrophils evident throughout the mouse uterus recedes within 2 days and does not reemerge in response to nidatory estrogen or the attachment reaction. In humans, the noninflammatory state of the early decidua is characterized by reduced T cell tissue densities and the polarization of resident macrophages to an IL-10-producing M2-like phenotype lacking the M1-like inflammatory features that are instead associated with spontaneous abortion.[94,123,125,127,128,134] In both species, the stereotypical inflammatory reaction to wounding, including the recruitment of neutrophils and monocytes followed by the formation of granulation tissue, is not apparent.

The uterus thus appears to actively transition to a noninflammatory state as it proceeds across the peri-implantation period. The mechanistic basis of this transition remains incompletely understood but is a subject of intense interest given its obvious importance for reproductive success. In mice, one likely mechanism specific to decidual tissue is the targeted accumulation of the repressive histone mark H3K27me3 on select genes within DSCs, which prevents them from expressing CSF-1 and T cell-attracting chemokines (see section *Anatomy, Development, and Microbiology*).[4,5] A second mechanism is IL-10 production by decidual macrophages (see section *Immune Cells of the Pregnant Uterus*), although it should be noted that IL-10-deficient mice are fertile.[126,295,542] Third, T_{reg} cells are thought to suppress inflammation throughout the uterus, with effect starting even before implantation.[524,543] In mice, T_{reg} cells increase in frequency in the uterine-draining LN immediately after copulation as a consequence of uterine exposure to seminal plasma components, and then increase in tissue density in the uterus by gd3.5, presumably as a result of their homing there from the LN.[120,266-269,297,544,545] Most of them are thymus-derived.[545] Their role in promoting early pregnancy is evident from the reproductive deficits caused by their experimental ablation during this period, namely implantation failure and the resorption of otherwise successfully implanted early-stage concepti.[156,193,196,264,267,546] Conversely, T_{reg} cell transfer attenuates early fetal loss in abortion-prone mating combinations.[264,265] In humans, RSA, a condition formally defined by repeated fetal loss prior to 20 weeks gestation for no otherwise identifiable reason is associated with decreased decidual T_{reg} cell and increased decidual Th17 cell frequencies.[297-302,341,342]

Together, these observations suggest that uterine T_{reg} cells tamp down inflammatory responses at multiple points across the peri-implantation period, following copulation and the nidatory estrogen surge (mice), during the secretory phase of the menstrual cycle (humans), and during the attachment reaction and its immediate aftermath. Importantly, uterine

T_{reg} cells, at least in mice, suppress the components of these inflammatory responses that are generated by effector T cells (and possibly B cells) since Rag-deficient mice, lacking both T_{reg} cells and effector T cells, do not show implantation defects or early resorptions. In other words, T_{reg} cells do not support early mouse pregnancy by suppressing inflammation caused by myeloid cells, innate immune cells, the parenchymal components of the uterus, or by complement. A major question thus remains concerning the antigenic specificity of both the T_{reg} cells and their effector T cell targets, including the extent to which either population recognizes paternal alloantigens in semen, semen-specific "tissue" antigens, and/or antigens expressed by the early conceptus. Complex results have come from the many studies that pertain to this issue[120,193,196,264,267-269,544,546]; indeed, it remains possible that many of the effector T cells that cause implantation or early pregnancy failure in mice following T_{reg} cell depletion or in women with implantation failure or RSA are merely uterus-resident T cells with specificities toward tissue antigens or commensal microbes that must be kept in check, as everywhere else in the body, by the constant actions of similarly self- or commensal-specific T_{reg} cells.

Spiral Artery Remodeling, IUGR, and Preeclampsia

Spiral artery remodeling is the next major event in pregnancy under the influence of the maternal immune system (Fig. 41.8). The process takes place late in the first trimester of human pregnancy and commences with apoptosis of the arteries' smooth muscle cells. Trophoblasts (EVTs in humans) then undergo a process termed endovascular invasion whereby they migrate into the vessels' lumens and replace the vessels' endothelial cell linings.[68,548] High resistance, low flow vessels thus transform into low resistance, high flow vessels that are capable of supplying the placenta with the large volumes of blood required for fetal growth and development. Critically, perfusion of the human placenta is inadequate if spiral artery remodeling does not extend deeply enough into the uterus, a situation considered to be the root cause of many important pregnancy complications, including preeclampsia, IUGR, and others of the so-called "great obstetrical syndromes" that manifest themselves in the second and third trimester.[549] Impaired spiral artery remodeling, if severe enough and associated with a general defect in EVT invasion into the decidua, has also been linked to pregnancy loss in the first and early second trimester.[345]

Unlike the case with implantation, where the role of the maternal immune system is less well defined, there is direct evidence that the maternal immune system contributes to spiral artery remodeling. In mice, the process occurs between gd8.5 to gd12.5 and is initiated by dNK cells, which closely associate with uterine spiral arteries. In their absence (eg, in *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ or *Il15*$^{-/-}$ mice), the vessels retain their smooth muscle cells, display thick walls and narrow lumens, and fail to undergo the hemodynamic adaptations described above.[63,80,81,550] In humans, dNK cells also accumulate around uterine spiral arteries as the vessels shed their smooth muscle coating,[78] with functional evidence for dNK cells driving such shedding based upon immunogenetic studies that link the expectation of dNK cell activation deficits with impaired spiral artery remodeling and its clinical consequences. Understanding these studies requires us to remind the reader that NK cell activation state is determined, in general, by the aggregate level of signaling induced by an NK cell's set of activating and inhibitory receptors (see Chapter 18). In humans, these include activating and inhibitory killer Ig-like receptors (KIRs), which engage class I HLA ligands. Thus, by taking advantage of the polymorphic nature of the KIR locus, which determines the set of KIR molecules that can be expressed by each of the mother's dNK cells, together with the polymorphic nature of HLA-C molecules (and thus KIR ligands) expressed by trophoblasts, researchers were able to link increased incidences of preeclampsia, IUGR, and RSA with combinations of the maternal KIR haplotype and the paternally inherited HLA-C haplotype of the conceptus that predicts lower aggregate dNK cell activation.[77,243,551-554] This kind of combinatorial influence is further supported by data in mice showing that spiral artery remodeling is impaired when paternal MHC-I expression is experimentally manipulated to inhibit maternal dNK cell activation.[555] Presumably, relevant dNK cell activation states are established when dNK cells directly interact with invading trophoblasts, although whether this interaction occurs in areas of incipient vascular remodeling remains controversial.[78,243,556]

How dNK cells actually induce spiral artery remodeling has remained unclear. As alluded to in section *Immune Cells of the Pregnant Uterus*, induction of vascular smooth muscle cell apoptosis in mice is thought to be more a function of the conventional NK cell subset recruited to the decidua starting at gd8.5 rather than the tissue-resident subset.[51] The process has also long been known to depend upon the cells' production of IFNγ although target cell types and downstream events have remained undefined.[63] A recent study has demonstrated an additional requirement for dNK cell production of VEGF-C and its action on decidual endothelial cells.[86] First trimester human dNK cells also disrupt the smooth muscle cell lining of heterologous vessels *in vitro*, similar to what is seen with remodeling spiral arteries *in vivo*, and these effects can be mimicked by purified IFNγ and VEGF-C.[557]

Preeclampsia is the obstetrical complication in humans most classically associated with inadequate spiral artery remodeling. It affects ~5% of all pregnancies and occurs when the underperfused placenta systemically releases substances in the late second and third trimesters that are toxic to maternal endothelial cells.[68,558] These substances include the VEGF decoy receptor soluble Flt1. Ensuing systemic vascular dysfunction causes the two cardinal characteristics of the disease—severe hypertension and proteinuria—but the syndrome can also affect other organ systems and even cause death. By contrast, inadequate spiral artery remodeling does not cause these phenotypes in mice but rather only IUGR, with decreased fetal weights seen following manipulations that either deplete dNK cells or cause deficits in their activation, including alterations to paternal MHC class I expression.[80,86,555,559,560] The phenotypic disparity between mice and

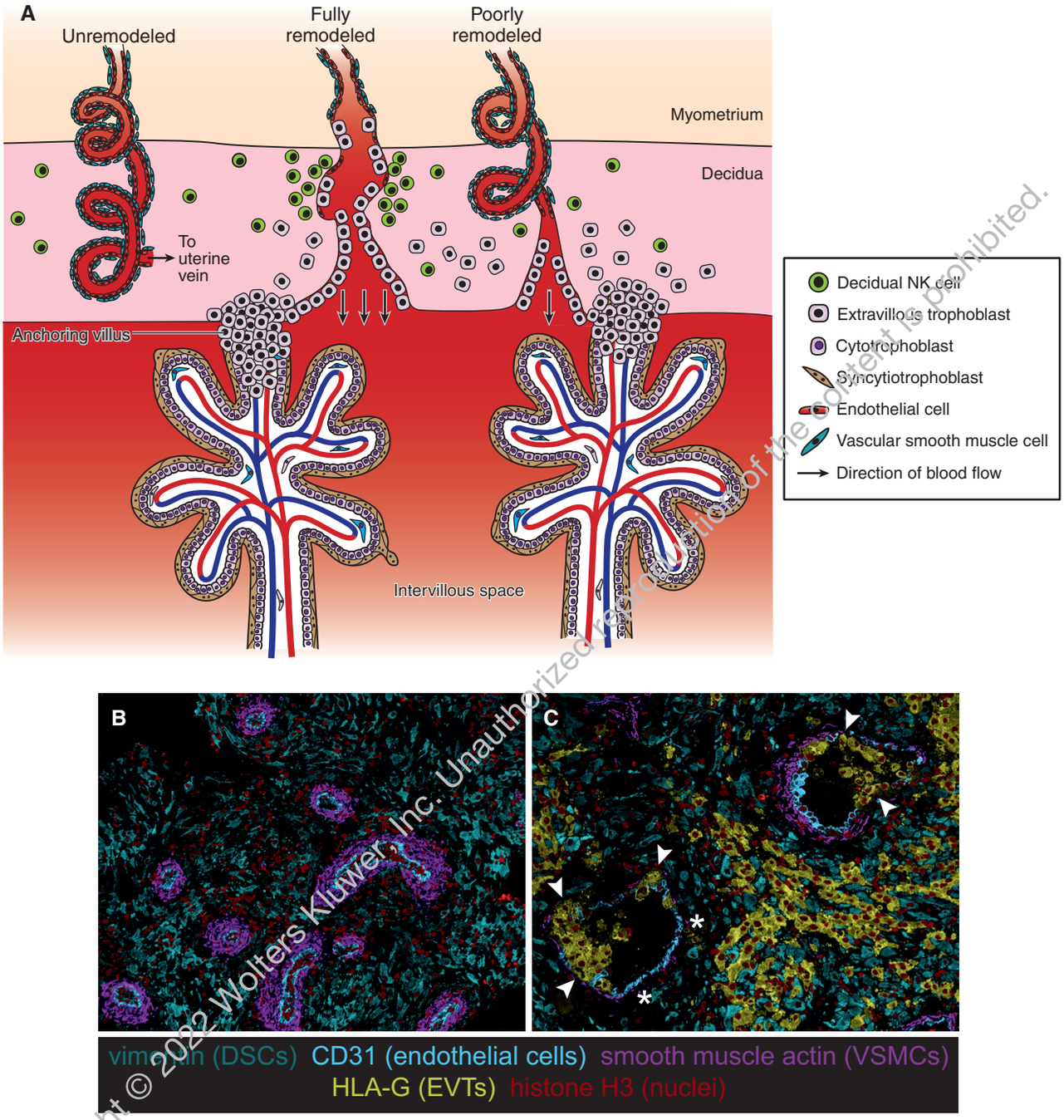

FIG. 41.8. Spiral artery remodeling. A: Schematic of normal and pathological remodeling in the pregnant uterus. The process occurs in the first trimester and early second trimester. The vessel on the left shows a normal spiral artery, replete with full endothelial cell and vascular smooth muscle cell lining, prior to being remodeled. Blood flow returns via a uterine vein (not shown). The vessel in the middle shows a fully remodeled spiral artery. The remodeled vessel has lost its smooth muscle cell lining, and its endothelial cells have been replaced by extravillous trophoblasts (EVTs) that had migrated out from anchoring placental villi into the decidua. The remodeling process extends all the way through the decidua and into the superficial layers of the myometrium, thus greatly reducing vascular resistance and increasing blood flow to the placenta. Decidual natural killer (dNK) cells, which aggregate at areas of ongoing remodeling, are also depicted. EVTs also invade into the uterine veins, thus providing an outlet for placental blood flow (not shown). The vessel on the right is a poorly remodeled spiral artery. It retains much of its own endothelial cell and vascular smooth muscle cell lining, and EVT invasion does not reach the myometrium. As a result, blood flow to the placenta is insufficient to meet the demands of the growing conceptus, which is thought to lead to preeclampsia, intrauterine growth restriction, and other maternal and fetal pathologies in the third trimester. Poor spiral artery remodeling is associated with inadequate dNK cell activation. In mice, the spiral arteries similarly lose their vascular smooth muscle cell lining, which by itself increases blood flow, but trophoblast invasion into the vessels is normally "shallow" and restricted to the decidua. **B and C:** Histology of human spiral arteries before **(B)** and during remodeling **(C)**. Both specimens were from second-trimester elective terminations. Sections were stained with antibodies toward the indicated proteins, and images were

acquired using a custom-designed MIBI-TOF mass spectrometer (Ion Path), as previously described.[547] The images were pseudocolored and further manipulated in Adobe Photoshop for instructional purposes. Note that the unremodeled vessels are covered with thick, continuous layers of vascular smooth muscle cells (VSMCs) and have narrow lumens, whereas the vessels undergoing remodeling have largely lost these cells and have wide lumens. VSMC loss is apparent in areas of the vessels that still possess endothelial cells (*asterisks*). EVTs can be seen invading interstitially throughout the decidua and into the vessels (*arrowheads*), where they replace the vessels' endothelial cells. Images provided courtesy of Shirley Greenbaum, Erin Soon, and Michael Angelo (Stanford University).

humans might reflect differences in the nature of endovascular invasion between the two species. In humans, endovascular invasion employs EVTs and normally spans the full thickness of the decidua up through the superficial layers of the myometrium. In mice, endovascular invasion employs a subtype of trophoblast giant cell and is much more shallow. Intriguingly, endovascular invasion in rats extends all the way to myometrium and thus is more similar to humans than to mice.[561] In all three species, and again in a species-specific fashion, dNK cells control the extent of endovascular invasion, a function seemingly independent of their function in inducing vascular smooth muscle cell apoptosis. In humans, dNK cells promote EVT migration via their production of various chemokines and cytokines, as visualized *in vitro*,[77,562,563] whereas mouse and rat dNK cells (and more likely the tissue-resident subset in mice) appear to inhibit trophoblast invasion, as evidenced by the over-invasion of the spiral arteries *in vivo* when the cells are absent or functionally deficient.[64,564] Importantly, trophoblast over-invasion is just as problematic for pregnancy as under-invasion since it adheres the placenta too tightly to the uterine wall. This pathology, termed placenta accreta, increta, or percreta, depending upon the extent of over-invasion, can cause severe hemorrhage during delivery. Thus, dNK cells could be considered to be critical for normal pregnancy by determining the overall "set-point" of trophoblast invasion into the uterus.

Macrophages, mast cells, T_{reg} cells, and complement have also been implicated in spiral artery remodeling,[78,121,137,168,524,565,566] but specific pathways have remained elusive. Akin to their contributions to implantation discussed in the prior section, T_{reg} cells might foster the process by dampening excessive inflammation.[567] Consistent with this possibility, systemic inflammation and decreased blood T_{reg} cell frequencies are evident in first-trimester pregnant women destined to develop preeclampsia.[568] Decreased decidual T_{reg} cell frequencies and altered decidual macrophage and APC phenotypes have also been observed in the third trimester in women with preeclampsia, but the causal relevance of these observations to the remodeling events of the first trimester is unclear.[566,569-571] Another idea is that spiral artery remodeling might be impaired if there is an occult placental infection although recent deep analysis of the placenta microbiome argues against this possibility.[78]

Given the clinical importance of preeclampsia and the relative ease of obtaining peripheral blood, many studies have sought to identify systemic immune alterations that would help explain elements of the end-organ damage seen in affected women.[572-574] These studies have uncovered decreased T_{reg} cell frequencies, increased effector T cell frequencies (in particular of Th17 cells), increased proinflammatory cytokine levels, and increased complement and innate immune cell activation.[566,569,572,573,575-577] However, these findings have been inconsistent and relatively subtle; moreover, the positive associations so far uncovered might only reflect additional manifestations of underlying disease processes rather than underlying causes since they virtually all come from analyses of women in their third trimester who already have the disease. Indeed, women in the second trimester either experiencing early-onset preeclampsia or destined to develop preeclampsia in the third trimester do not display decreased T_{reg} cell frequencies.[172,578] End-organ damage in preeclampsia has also been linked to the generation of agonistic autoantibodies toward the angiotensin II type 1 receptor, a receptor that is broadly expressed by multiple cell types, including endothelial cells, vascular smooth muscle cells, and syncytiotrophoblasts.[579] These antibodies are apparent not only in human pregnancies with placental underperfusion but also in a rat model of preeclampsia in which uterine arteries are surgically occluded, thus reducing placental perfusion.[580-582] When injected into nonpregnant mice, the antibodies cause hypertension, and when injected into pregnant mice cause hypertension, kidney and other end-organ damage, and the release of endothelial cell modulators from the placenta.[583] Several inflammatory mediators have been identified that connect activation of the angiotensin II type 1 receptor to placental dysfunction[579]; in fact, systemically induced type 1 inflammation in mice, by itself, can cause an otherwise normal placenta to adversely impact maternal endothelial cell and renal function.[584] Together, these results suggest a complex interplay between placental under-perfusion, immune activation, autoantibody production, and end-organ damage. Interestingly, the antiangiotensin receptor antibodies are natural antibodies produced by B-1a cells but why they are produced in pregnancies with placental under-perfusion remains unknown.[585]

Parturition and PTL

The molecular basis of parturition (ie, the act of giving birth) remains one of the great mysteries of reproductive biology. Not only is it unknown how gestation length is timed, but it is unknown what, exactly, is being timed. Presumably, the approach of term gestation (37 weeks in humans) sets in motion a sequence of events that ultimately causes the uterus, which has otherwise remained in a quiescent, noncontractile state for the entirety of gestation, to abruptly shift toward a state of high contractility. Similarly, the cervix undergoes a "ripening" process that opens it up to allow passage of the conceptus. In recent years, there has been a great deal of interest in how the maternal immune system might contribute toward or even drive these processes.[586] This interest has been further fostered by the clinical problem of PTL. PTL currently has

no effective treatment yet affects over 10% of all pregnancies around the world and is showing a steady increase in incidence.[587] PTB, the consequence of PTL, not only increases the risk of neonatal infection and other short-term complications stemming from the immaturity of multiple organ systems but also has long-term sequelae, including neurocognitive, visual and auditory impairments.

The possibility that the immune system is involved in human parturition grew out of the long-recognized importance of prostaglandins in driving parturition across all mammalian species.[588] These molecules, in particular PGE_2 and PGF2α, are produced at high levels by decidual tissues upon labor onset and are potent and direct inducers of myometrial contraction. It has also long been known that ascending infection, and hence inflammation of the fetal membranes with associated neutrophil influx (ie, chorioamnionitis), is a frequent trigger for PTL in women (see section *Infection-Mediated Pregnancy Complications*). This link led to the discovery that amniotic fluid concentrations of inflammatory cytokines typically made by immune cells (IL-1β, IL-6, and TNFα) are frequently elevated not only in women with chorioamnionitis-triggered PTL, as might be expected, but also in women experiencing normal labor.[589,590] These descriptive studies have been robustly extended over the last 20 years to document increased expression of inflammatory chemokines and cytokines by various uterine tissue layers and cells in both term and PTL.[92,140,591-594] A recent single-cell RNA-Seq analysis has suggested that many of the gene expression changes occur in macrophages[57] and indeed decidual macrophages show a small degree of CD80 upregulation with both spontaneous term and PTL onset.[141] At the histological level, monocytes accumulate within the cervix during its ripening,[595] while after labor onset macrophages and neutrophils accumulate within the myometrium and macrophages accumulate in the fetal membranes.[138-140] Lastly, immune cells not only produce agents that are directly contractile for the myometrium (eg, PGE_2, histamine, serotonin)[588,596] but also cytokines (eg, IL-1β, IL-6) can indirectly promote myometrial contractility by a variety of mechanisms, including inducing higher myometrial smooth muscle cell expression of connexin-43, a gap junction protein that promotes cell-cell electrical coupling, as well as higher expression of receptors for both PGF2α and oxytocin, another contraction-inducing hormone that is released by the pituitary gland.[597,598]

Thus, although many nonimmunological processes also contribute to labor induction, the emerging consensus is that natural parturition at term gestation in part involves the activation of uterine immune cells (particularly within the decidua and fetal membranes) and their production of inflammatory mediators. In the case of PTL secondary to chorioamnionitis, which accounts for ~30% to 40% of all PTB,[599] the inflammatory response to the infection presumably feeds into the same inflammatory pathways that contribute toward normal parturition; in the case of "idiopathic" PTL, which accounts for ~45% of PTB,[599] inflammation of the fetal membranes or decidual tissue somehow spontaneously occurs, and this also feeds into the pathways that drive normal parturition. Such spontaneous inflammation might be associated with loss of T_{reg} cell function and the assumption of a more M1-like phenotype in macrophages.[141,600]

Despite this consensus, however, the precise ways that the maternal immune system and uterine inflammation contribute to labor induction remain unclear. The main difficulty in tackling this question lies in the inadequacy of current rodent models. With regards to natural parturition, rodents show features of uterine inflammation with approaching labor and labor onset, and IL-6–deficient mice show a 24 hours parturition delay.[145,601-603] However, parturition timing is unaltered in mice bearing complete or significant losses in T cells, B cells, NK cells, macrophages, monocytes, neutrophils, mast cells, and eosinophils.[130,145,146,559,604,605] Most likely, these negative results stem from the dominant role of the endocrine system in controlling parturition onset in rodents, for which the immediate antecedent to labor induction is cessation of progesterone production by the ovary (ie, "luteolysis").[606] In contrast, both term and preterm parturition in humans occurs without a decline in serum progesterone levels, instead emphasizing the primacy of uterus-intrinsic pathways. The upshot of this dichotomy is that the aforementioned studies that ostensibly rule out various immune cell populations in the control of parturition timing only rule out contributions to events that lie upstream or downstream of luteolysis and not necessarily contributions to the pathways that drive labor induction in humans. That such uterus-intrinsic pathways exist in mice is nonetheless clear from the fact that labor induction still occurs (albeit with delayed onset) when progesterone levels are kept experimentally high,[4] but roles for immune cells in this context have not been explored.

Rodent models have only been modestly more helpful in mechanistically dissecting the immunological and inflammatory pathways that potentially drive PTL. These models are typically based upon either inducing chorioamnionitis via direct uterine infection (typically using *GBS* or *E. coli*, sometimes in combination with local or systemic viral infection as we discussed in section *Infection-Mediated Pregnancy Complications*), or by simulating the inflammatory response to such infection via systemic or intrauterine injection of LPS.[607,608] Here too the difficulty has been that systemic inflammation, whether induced directly or secondary to intrauterine manipulations, is capable of inducing luteolysis and thus labor onset secondary to progesterone withdrawal.[609] Luteolysis and labor induction can occur as quickly as 24 hours following such manipulations, and unless the issue is directly addressed, render many studies difficult to interpret. Thus, studies demonstrating requirements for proinflammatory cytokines, such as IL-1, and the counter-regulatory influences of IL-10, T_{regs}, and B cells[610-613] could be seen more as confirming the general features of inflammation than revealing something specific to the pathways of labor induction. Importantly, studies that involve careful titration of LPS-dosing and direct assessments of serum progesterone levels have provided evidence that intrauterine inflammation per se can cause PTL in rodents.[614] Such results mimic observations with nonhuman primates that direct intra-amniotic injection of proinflammatory mediators such as IL-1β and TNFα induce PTL,[615] and together provide evidence that

intrauterine inflammatory processes are sufficient to induce parturition across many species. Key downstream pathways that link inflammation to increased myometrial contractility, including ones that might be targeted to prevent or forestall PTL, however, have yet to be determined.

PREGNANCY AND MATERNAL AUTOIMMUNE DISEASE

Pregnancy dramatically impacts preexisting maternal autoimmune disease, as many autoimmune conditions improve during gestation and then flare in the postpartum period. This pattern is perhaps most famously seen with RA, as ~60% of patients experience clinical improvement during pregnancy while ~50% experience a disease flare at roughly 6 weeks postpartum.[616] Similarly, the relapse rate for MS significantly decreases during pregnancy to below that seen even in patients on currently available treatments but then rises during the postpartum year above the prepregnancy rate.[617] The pattern is not uniform, however, as pregnancy does not have a beneficial effect on SLE.[219] Here, we will discuss these three autoimmune diseases and how their divergent responses might be explained by the intersection of respective pathogenic mechanisms with pregnancy-specific processes.

Rheumatoid Arthritis

One possible explanation for the effect of pregnancy on RA relates to the transient, pregnancy-induced increase in decorated (ie, highly galactosylated and sialylated) IgG species that possess less proinflammatory and more anti-inflammatory effector functions than their undecorated counterparts (see section *Systemic Changes to the Maternal Immune System During Pregnancy*). These undecorated counterparts, however, are known to increase in frequency in RA patients[618] (see Chapter 46) and have been implicated as a causal determinant of RA disease severity in mice.[619] Thus, pregnancy-induced IgG modifications run counter to the requirements for strong disease induction. Indeed, the proportion of highly galactosylated and sialylated IgG1 and IgG2 positively correlates with RA amelioration during pregnancy,[620,621] while the postpartum rise in agalactosylated IgG occurs in synchrony with the postpartum disease flare.[622]

Expanded T_{reg} cell function during pregnancy, as discussed in section *Treg Cells and the Attenuation of T Cell Priming to Trophoblast Antigens*, provides a second potential explanation for RA amelioration during pregnancy. This possibility emerged from the observation that disease activity inversely correlates with $CD4^+$ $CD25^+$ T cell frequencies in the blood of pregnant RA patients,[623] taken together with studies on the collagen-induced arthritis (CIA) mouse model of RA, in which T_{reg} cells are established suppressors of synovial inflammation.[624] This model recapitulates the human pattern of disease (ie, amelioration during pregnancy and increased severity postpartum)[625,626] and shows greater disease improvement with lower proinflammatory blood cytokines following allogeneic versus syngeneic mating.[627,628] Greater disease improvement thus parallels the greater expansion of T_{reg} cells in allogeneic pregnancies that we described in section *T_{reg} Cells and the Attenuation of T Cell Priming to Trophoblast Antigens*. In humans, the degree of mother/fetus HLA class II disparity also correlates with disease amelioration, thus somewhat paralleling the findings in mice, and further suggesting the involvement of a maternal immune response to paternal alloantigens.[629,630] Intriguingly, $CD4^+$ $CD25^+$ T cell transfer from pregnant mice into nonpregnant recipients decreases disease severity but only if the cell donors were collagen-immunized.[631] This observation supports a role for antigen-specific T_{reg} cells.

Mechanistically, pregnancy hormones and/or placenta-derived soluble factors appear as upstream mediators of pregnancy-associated RA amelioration. Thus, pregnancy-like doses of estrogen and progesterone attenuate disease severity in the Zap70-mutant ("SKG" strain) mouse model of arthritis,[632] while exogenous estrogen protects against disease onset and the postpartum flare in the CIA model.[626,633] Moreover, estrogens promote IgG galactosylation in nonpregnant women and men.[634] Unfortunately, however, estrogen induces only minimal improvement in nonpregnant RA patients.[635] Other studies demonstrate decreased CIA severity in rats injected with placental supernatant,[636] while treatment with human pregnancy-specific glycoprotein 1a decreases CIA severity in mice with an associated decrease in systemic proinflammatory cytokines and expansion of splenic T_{reg} cells.[637] Finally, less common murine arthritis models, such as proteoglycan (PG)-induced and pristane-induced arthritis, also show improvement during pregnancy.[638,639] However, PG arthritis is unlike the other models in that it is independent of IL-17 and does not flare in the postpartum period, thus indirectly suggesting a role for Th17 cells in the postpartum flare.[639,640]

Multiple Sclerosis

In contrast to RA, efforts to understand why MS remits during pregnancy have focused more exclusively on active T cell suppression. Accordingly, TCR sequencing has revealed that the MS patient repertoire becomes less dominated by antigen-experienced (and possibly CNS antigen-reactive) $CD45RO^+$ CD4 and CD8 clones during the third trimester and that clonality reemerges in the postpartum period.[641] Additionally, decreased disease activity in pregnancy correlates with fewer IFNγ-producing CD4 cells and decreased inflammation-related transcripts in PBMCs.[642,643] Importantly, the experimental autoimmune encephalitis (EAE) animal model of MS (see Chapter 46 for basic details) recapitulates much of the human pregnancy phenotype, namely a delay in disease onset with decreased disease severity in animals administered CNS antigens before or soon after mating, but then severe disease in the postpartum period.[215,644] Using the EAE model in combination with mice bearing T cell-specific deficiencies in the glucocorticoid receptor, it was found that EAE protection requires the pregnancy-induced expansion/conversion of T_{reg} cells (see also section *Systemic Changes to the Maternal Immune System During Pregnancy*), in turn, the result of GR activation within T cells by pregnancy levels of progesterone.[215]

Although its relevance to disease improvement during pregnancy has yet to be directly established, estrogen likely provides additional protection since the administration of pregnancy-like doses of 17β-estradiol (the form of estrogen produced by the ovary) ameliorates EAE severity in nonpregnant mice.[219,633] The effect requires B cells (likely B_{reg} cells), PD-L1, and direct activation of ERα in CD4 T cells to inhibit Th1 and Th17 differentiation.[645,646] Estrogen also promotes T_{reg} cell differentiation, but this effect appears not to be required for EAE amelioration.[220,647] Lastly, ERα signaling in astrocytes is necessary for protection during the effector phase of EAE.[648] Consistent with estrogen's many effects, estriol, an estrogen that is uniquely produced by the conceptus, shows promise as an MS treatment in an early clinical study.[649]

EAE protection in nonpregnant mice can also be elicited by pregnancy-like doses of other factors, including glucocorticoids,[650] and conceptus-derived soluble factors;[644,651,652] however, their relative importance is not yet known. Additional intriguing but controversial clinical observations, such as whether breastfeeding decreases the risk of postpartum relapse[653] and whether parity decreases the risk of an initial MS diagnosis or severe disease later in life,[654] remain unconfirmed.

Systemic Lupus Erythematosis

In contrast to RA and MS, SLE does not show clinical improvement during pregnancy. Instead, pregnancy is a weak determinant of SLE disease flare, while having SLE reciprocally increases rates of pregnancy complications, including preeclampsia, PTB, fetal loss, and the antiphospholipid antibody syndrome described in section *Humoral Fetomaternal Tolerance*.[655] Importantly, estrogens are established positive modulators of SLE risk, and multiple studies have shown that estrogen enhances the type I IFN response (as reviewed in Ref. 656) and autoantibody production by B cells,[657] which are central to SLE pathogenesis. These effects likely explain why SLE patients do not show clinical improvement during pregnancy, unlike patients with RA or MS.[219]

THE LONG-TERM EFFECTS OF PREGNANCY ON THE IMMUNOLOGICAL HEALTH OF THE OFFSPRING

As discussed in section *Mechanisms of Fetomaternal Tolerance*, the maternal immune system responds to fetal blood cell alloantigens in an immunogenic fashion and to trophoblast antigens in a nonimmunogenic fashion. In contrast, tolerance is uniformly induced when the fetal immune system encounters noninherited maternal antigens (NIMAs). This latter effect underlies the improved immunologic acceptance of NIMA-matched organ grafts in humans[658-660] and mice[661-663] as well as the partial tolerance to Rh(D) antigen that is exhibited by the $Rh(D)^-$ offspring of $Rh(D)^+$ mothers.[664]

How fetal and neonatal lymphocytes come to engage NIMAs is not fully understood. Tolerance in murine systems appears to require both *in utero* and breast milk exposure.[663,665,666] In turn, *in utero* exposure involves the transplacental transport of both soluble maternal protein and rare maternal cells,[667-670] while breast milk exposure allows maternal protein and cells to access the neonatal gut.[671,672] Because they can live for long periods of time (a state known as "maternal microchimerism") and thus serve as persistent sources of antigens, the maternal cells that have crossed into the offspring appear more important for inducing tolerance to NIMAs. Mechanistically, NIMA exposure elicits antigen-specific T_{reg} cells in human fetuses[673] and neonatal mice,[661,662,666] as well as deletional tolerance of alloreactive T and B cells in neonatal mice.[663,674] Furthermore, the fact that 50% of "highly sensitized" human patients fail to develop antibodies against noninherited maternal HLA[675] suggests that B cell tolerance to NIMAs occurs in humans as well.

Investigators have also addressed the reciprocal situation, that is, whether the long-term persistence of fetal cells in the mother ("fetal microchimerism") influences the maternal immune system.[676] In particular, microchimeric fetal cells have been hypothesized to promote autoimmune diseases such as systemic sclerosis that arise in postreproductive years.[677,678] As of now, however, pregnancy is not an established risk factor for systemic sclerosis, and the biological relevance of microchimeric fetal cells to gravid women remains unclear.[679,680]

Importantly, the phenomenon of NIMA-induced tolerance adds to the ways researchers are beginning to appreciate how events during pregnancy influence the long-term immunological health of the offspring. Clearly, these also include the protection afforded the newborn as the result of transplacental maternal antibody transport and the fact that the offspring's first encounter with pathogens might occur during pregnancy.[681] In addition, recent work suggests that the occurrence of maternal allergic disease during pregnancy influences the offspring's risk of developing allergies.[682,683] Most generally, maternal health affects the developing fetus in its entirety, and this notion forms the basis of the "fetal/developmental origins of adult disease hypothesis," also called the "Barker hypothesis," for its initial proponent.[684] The extent to which such long-term effects, which include adult-onset hypertension and ischemic heart disease, might involve long-term alterations to the immune system instigated *in utero* is currently unknown.

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