Published in final edited form as:

Obstet Gynecol Clin North Am. 2016 December ; 43(4): 679–698. doi:10.1016/j.ogc.2016.07.004.

Immune regulation in pregnancy: a matter of perspective?

Elizabeth A. Bonney, MD, MPH [Professor]

Department of Obstetrics, Gynecology and Reproductive Sciences, University of Vermont College of Medicine, Burlington Vermont, USA

Synopsis

The maternal immune system is complex and governed by multiple hormonal and metabolic factors, including those provided to her via the fetus. Understanding of the balance between maternal tolerance and protection of the fetus may require thinking from multiple theoretical approaches to general problem of immune activation and tolerance. The basics for this process are discussed here and may suggest both specific experiments in human and animal models and specific interventions in pregnant patients with immune system-related disease.

Keywords

Immune regulation; pregnancy; maternal tolerance

Why is understanding of the immune system in pregnancy clinically relevant?

The immune system matters. Several areas of clinical relevance should come to mind. First, regulation of the immune system is thought to play a role in both male and female fertility[1] and dysregulation of the immune system is still thought to play a role in recurrent miscarriage[2]. Women with asthma, autoimmune disease, immune deficiency and other derangements of the immune system are at risk for poor pregnancy outcomes[3] and it is clear that interactions between pregnancy and the immune system influence the woman post-partum and beyond[4]. Recent emergence of viruses such as pandemic influenza [5] Ebola[6] and Zika[7, 8] also underline the utility of focus on the immune system, particularly with regard to vaccine development for pregnant women. Finally, the implications of the interaction between the pregnant mother's immune system and infectious agents spill not only into the health of the woman but also the health of the embryo, fetus and neonate. Next is a brief overview of the immune system as relates to pregnancy.

Corresponding Author: Given Building Rm C-246, 89 Beaumont Avenue, Burlington Vermont 05405., Phone (802) 656 8677, ebonney@uvm.edu.

Disclosure: Nothing to disclose

Host defense

The importance of inherent protective mechanisms present in the reproductive track, including both barrier and antimicrobial actions, has been recognized[9]. Balance within the microbiome of various tissues can mean the difference between health and autoimmune disease[10]. The more than 1 billion organisms living in the vagina- are now thought to mediate both immune protective[11] and immune modulatory functions[12]. Moreover, alterations in the vaginal microbiome may be associated with increased risk of preterm birth[13]. While the association between altered vaginal microbiome and adverse pregnancy has been observed[14, 15], the interaction between pregnancy, the microbiome and subsequent disease or health has not been formally tested. In addition to bacteria existing in the vagina, there are viruses which interact with bacteria and the local immune system to support health or generate disease[16]. The microorganisms present in the vagina, in addition to other immune factors, are likely influenced by endogenously produced vaginal fluid and those agents such as lubricants and foreign objects (e.g. pessaries). While the cyclic nature of vaginal fluid in the non-pregnant state and the overall composition of the vaginal fluid and cervical mucous present during pregnancy has been evaluated, specific antimicrobial and immune modulating mechanisms are still under examination. For example, antimicrobial peptides such as defensins, reviewed elsewhere[17], are players in the composition of the cervico-vaginal fluid and are protectors against ascending infection.

Another important element of host defense during pregnancy is trophoblast. This is true in that these cells may present a physical barrier to prevent transmission of infection to the fetus[18, 19]. In addition, trophoblast expresses molecules that help to limit or prevent persistent infection[20–23]. However, persistent involvement of the placenta may be seen in several viral infections[24]. In this light it is interesting that it has been postulated that fetal cells are thought to be the source of persistent maternal infection with Zika virus[25].

Innate immunity

Inherent immune-protective/modulating properties of cells and products of the vagina and cervix are often spoken of differently from specific cells of the innate immune system. Characteristics attributed to the innate immune system are lack of specificity, rapidity, and lack of memory. The last of these three characteristics has come into question, however, since it is apparent that some innate immune cells, particularly NK cells are capable of being "educated" [26], possibly by interaction with trophoblast or decidual cells[27]. It is said that a hallmark of pregnancy is increased activation in systemic innate immunity[28, 29]. However, local innate immunity is said to be modified during gestation to be functionally active early in pregnancy in order to assist in implantation, down-regulated through most of gestation and then increased with parturition and labor.

Mast cells[30] play a sentinel role in tissues. Stimulation of mast cells by bacteria or other agents via surface-expressed pattern recognition receptors, generates mediators that enhanced blood flow, smooth muscle contraction and trafficking of neutrophils, basophils and eosinophils. Mast cell granules are packed with proteins, including interleukin (IL) IL-6, tumor necrosis factor (TNF), leukotrienes, and histamine [31]. Histamine exerts its actions

through four G protein-coupled receptors ($H_{1\text{-}4}R$). H_1R and H_4R are regulators of inflammatory, allergic and autoimmune disease[32, 33,32, 34–37], and recent evidence suggests that H_2R and H_4R support the generation of regulatory T cells (T_{reg}) that modulate immune responses[38–40].

Mast cells are present in the uterus and cervix[41]. Interactions between mast cells and other cells at the maternal-fetal interface mediate implantation(H_2R) [42] support angiogenesis[43, 44], and preserves quiescence [45] until-term when histamine from mast cells binds to H_1R and fosters uterine contractions [46, 47,48]. Type I sensitivity induces premature labor in humans[49] and in n animals[50] via histamine binding to H_1R in the uterus[51].

Neutrophils[52] are critical to the innate response through phagocytosis of bacteria and production of reactive oxygen species, lytic enzymes, and peptides that lead to activation of the inflammatory cascade. Activated neutrophils can pass from the blood through endothelial cells by the use of metalloproteinases that disrupt cellular membranes. Some organisms and stimuli induce neutrophils to undergo a unique form of death, “NETosis” which involves extrusion of chromatin and cytoplasmic contents which in turn can bind up and help immobilize bacteria. This process also generates tissue damage and more inflammation[53]. There exist phenotypic subsets of neutrophils, and some of these may have particular relevance to pregnancy. In the first trimester of human pregnancies, a unique sub population of neutrophils, so called “N2” becomes prominent[54]. This population may be supported by local expression of TGF-β and expresses proteins important to angiogenesis, including vascular endothelial growth factor (VEGF)-A. At term and in the context of preterm birth, inflammatory, or “N1” neutrophils traffic to the uterus in response to molecules such as IL-8, where they may express matrix metalloproteinases that help to dissolve fetal membranes. After delivery, neutrophils traffic to the cervix to participate in tissue repair[55].

Dendritic cells typically reside in a quiescent state in tissues. When activated, these cells mature and initiate protein antigen processing and traffic to the lymph nodes draining the tissue. Activated dendritic cells are considered to be the most proficient at processing antigenic protein and placing peptides from that protein into the cleft of major histocompatibility molecules and shunting the MHC-plus-peptide complexes to the surface for presentation to T cells. Presentation involves the binding of the MHC-peptide complex to the T cell receptor, binding of other surface molecules on dendritic cells to their receptors on T cells, and elaboration of soluble factors that can modify the T cell response. The result of this interaction can result in activation and proliferation of T cells specific for the protein whose peptide is in the MHC molecule. The dendritic cell population is likely to be slightly different depending on the tissue of residence, and this is true with regard to the placenta, uterus, uterine draining node and spleen[56]. It is possible that tissue-specific differences in the dendritic cell population are developmentally regulated. It has been observed that dendritic cells in the uterus are limited in their ability to traffic to the uterine draining lymph nodes during pregnancy[57] and that this supports tolerance of the fetus. Other possibilities of control of dendritic cell function may occur at the level of maturation[58, 59], as it has been proposed that “immature” dendritic cells support immune tolerance of tissue grafts[60] and

cancers[61]. However, inflammation can override these mechanisms and produce activation of dendritic cells from the uterus[56].

Macrophages[62, 63]

Members of the mononuclear phagocyte family includes monocytes and macrophages. In general, monocytes are generated in the bone marrow and circulate as diverse populations[31] until they traffic to tissues in response to specific developmental or environmental signals such as infection or inflammation[62]. Trafficking to tissues induces differentiation to macrophages. Inflammation or infection, including phagocytosis of bacteria and necrotic cells, causes activation and maturation of tissue-resident macrophages to full effector function[31]. Depending on the tissue type and local signals expressed, macrophages may form distinct phenotypes. One, the "M1" phenotype is considered to be the "inflammatory phenotype" and is marked by expression of inflammatory cytokines such as IL-1β, IL-6, IL-23 and IL-17 [31, 62]. The development of this phenotypic subset is driven by the local expression of gamma interferon (γIFN) produced by Th1 cells and NK cells and also by TNF expressed by activated dendritic cells[62]. Local expression of βIFN by trophoblast can also support generation of this phenotype[62]. A second group of phenotypes, "M2" includes M2a. These are generated by interaction with Th2-cell elaborated cytokines such as IL-4 and IL-13, and primarily participate in wound healing. Another M2 phenotypic subset, sometimes termed "regulatory" or "M2c can be activated in certain tissues by ligation of their toll-like receptors. Their development can be supported by the action of IL-10 expressed by T_{reg} and can in turn secrete IL-10 themselves and further support T_{reg} development [62]. Another suppressive offshoot of the monocyte lineage is terms the monocytic myeloid-derived suppressor cells, similar to tumor-associated macrophages that are said to suppress immune response in tumors and other tissues[64].

During pregnancy, hormonal changes can alter the presence and phenotype of circulating monocytes[63]. In the decidua, macrophages are present and assist with implantation[65]. Through gestation, they are present at relatively constant numbers in the uterus. The presence of macrophages increases in the cervix at term[66] and in preterm labor[67, 68]. Macrophage subsets[63] may contribute to the mechanisms leading to disruption of the fetal membranes, due to expression of matrix metalloproteinases[69], uterine contractions due to expression of prostaglandins[70], and softening and dilation of the cervix due to expression of collagenases[71].

Given the capacity and complexity of macrophage subsets, it is easy to imagine that macrophages also assist with healing and remodeling of the epithelium over the implantation site, and with cervical and uterine remodeling in the post partum[72]. Further, data suggests that T cells can modify the phenotype of macrophages or monocytes in secondary lymphoid organs draining the uterus[73]. This suggests that macrophages may play a part in regulatory circuits that modify inflammation-induced poor pregnancy outcomes.

NK cells are grouped within the ILC1 subset of innate lymphoid cells, and represent a population of cells that can augment inflammation in many sites. While initially thought to be mostly involved in killing of abnormal cells including virally infected[74] and cancer[75] cells, over time it has been recognized that distinct subpopulations of NK cells exist. These

subpopulations express decreased ability to kill but increased ability to provide factors that modify the growth or differentiation of other cells. Adding complexity to the evolving picture of NK cells are the observations that NK cells can "learn" from exposure to cells and factors from their environment. The complexity of NK cells is highlighted by their presence and function at the maternal-fetal interface where they can collaborate with trophoblast and endothelial cells to remodel decidual vessels and increase blood flow through the placenta. In other sites lack of or alteration in MHC tends to cause NK cell killing. However, it appears that at the maternal-fetal interface, NK cells may "learn" and retain the ability to limit trophoblast killing despite the relative lack of MHC expression in the placenta. NK cell function is regulated by an array of *inhibitory* receptors, including killer Ig-like receptors (KIRs), and *activating* receptors[76] Thus relative expression of inhibitory versus activating receptors might regulate the level of cytotoxicity expressed by these cells. The ILC2 innate lymphoid subset express cytokines such as IL-4[77], but little is known about their presence in decidua or placenta[78]. Within the ILC3 group are the lymphoid tissue inducer (LTi), and NK22 cells. In human decidua, LTi produce γ–interferon and IL-17 both thought to be important in the response to infection, and NK22 cells- those that are phenotypically similar to NK cells, but also secrete the cytokine IL-22, which can be a growth factor for trophoblast[79].

NK T cells have limited specificity but several of the effector functions of classical T cells. NKT cells were originally shown to be inherently capable of producing cytokines such as IL-4[80]. Invariant NKT cells recognize lipid ligands bound to the "MHC-like" molecule CD1 [81]. Within the reproductive track, activated NK T cells have been shown to mediate pregnancy loss and preterm birth in mouse models[82]. In contrast, the tumor environment can generate NKT cells that down-regulate immune responses[83] which may occur at the maternal-fetal interface [84].

γδ T cells

During development a proportion of T cell lineage cells generate T cell receptor chains gamma (γ) and delta (δ), instead of alpha (α) and beta (β). These cells develop and populate tissues earlier than their αβ counterparts, have a limited repertoire and in addition tend to populate mucosal surfaces[85]. This places them in a unique position to sample the environment in which the animal exists and be a first line of defense. The exact nature of the antigens recognized by γδ cells is unknown, but it has been suggested that they, like NKT cells, respond to certain lipids in the context of CD1[85]. In addition, this cell type plays a potential regulatory role as they express the capacity to kill activated T cells [86]. These cells are present in the reproductive tract, where they may modify local immunity[87]. Sex steroids influence the development of these cells[88]. They expand during pregnancy and are found in placental villi in humans[89] and in mice[90]. Although genetic deficiency in γδ T cells does not inhibit successful pregnancy it may be that pregnancies deficient in γδ T cells are more susceptible to infection[91].

Adaptive immunity

T cells

T cells bearing αβ T cell receptor chains comprise the primary regulation of the adaptive immune response. T cells express either the CD4 or CD8 Co-receptor that restricts its ability to recognize peptide bound to MHC class II or class I, respectively. Naïve T cells of either type leave the thymus to circulate between blood and lymph node draining various organs. When a naïve T cell interacts productively with an activated dendritic cell that presents the MHC-plus-peptide complex recognized by the T cells' receptor, the T cell begins to change its developmental status. If the correct mix of other signals is also received by the T cell it can begin to divide and produce daughter cells. The "other signals" include signaling through molecules such as CD28 and T cell-generated cytokines such as IL-2. Further, the cells that present antigen to T cells can produce cytokines and other factors that can modify the T cell subset that is generated by activation. Finally, T cells can directly or indirectly provide signals that support or suppress the kind of effector function in other T cells.

For CD4 T cells, the many possibilities for effector function have not been clearly delineated. Expression of cytokines such as IL-4, IL-5, and IL-13 constitute a population of CD4 T cells, "Th2", important in the production of antibody and protection against some parasites. Over-activity of such cells is a hallmark of allergy and asthma. In contrast, expression of cytokines such as γINF and TNF constitute a population, Th1, which supports cytotoxic immune responses. The Th2-Th1 paradigm has been the focus of interest with regard to maternal tolerance of the fetus, as many observations suggested that pregnancy caused a shift in the maternal immune system towards Th2 versus Th1 responses[92]. However, the idea that pregnancy is critically dependent on this shift waned because deficiency in critical Th2 cytokines results in grossly normal pregnancies in animal models (for example[93]).

With regard to the conundrum defined by the competing needs of maternal tolerance of the fetus and maternal and fetal immune protection, a newer paradigm has arisen. This one is focused on the presence and function of two other CD4 T cell subsets: T_{reg} on the one hand and Th17 cells on the other. The hallmark cytokines of the T_{reg} subset are TGF-β and IL-10, both produced by cells of the placenta. It is now said that T_{reg} are the primary suppressors of immune responses. T_{reg} lineages include those that are thymus-derived (tT_{reg}) and developmentally inhabit tissues, in contrast to those that arise after activation by antigen in the periphery (pT_{reg}). This later group, it is said, prevents over activation and supports the re-establishment of a quiescent state. In mouse pregnancy, even when mother, father and offspring are all the same genotype ("syngeneic") there is evidence that the hormonal milieu of pregnancy supports the expansion of Treg capable of suppressing local immunity[94]. In addition, exposure to semen can cause the induction of fetal/paternal antigen specific T_{reg}[95]. Further exposure to fetal antigens during the course of pregnancy expands this population, thus creating a regulatory pool bearing immunologic memory to fetal antigens which can then support maternal tolerance in subsequent pregnancies. However, exposure of T_{reg} to inflammatory signals such as ligands for the Toll-like receptor and IL-6 can shift T_{reg} to a potent and highly inflammatory subset, Th17, known for its expression of IL-17. Th17 are

induced during the inflammatory response to agents such as listeria[96] and influenza[97] and a potential mediator of infection-related abortion and premature labor[98]. Other CD4 T cell subsets invoked in regulation of immunity in the maternal-fetal interface include the Th9 subset, which may be important in the local inflammatory response that supports parturition[99].

CD8 T cells also can express varying classes of responsiveness, depending on innately expressed genes and exposure to particular signals and cytokines from other T cells[100] or antigen presenting cells[101]. CD8 T cells produce molecules, such as granzyme and perforin that assist in killing virally infected cells[102]. They also can assist in the disruption of transplanted organs[103]. CD8 T cells are present at the maternal-fetal interface[104], particularly during viral infection[24]. While CD8 T cells and be modified by pregnancy, they still can attack fetal cells in the maternal blood and lymphoid organs[105, 106]. In contrast, and adding to the paradigm that T_{reg} support maternal tolerance, is the observation that pregnancy can support the generation of CD8 T_{reg}[99, 107], which may modify CD8 T cell cytotoxicity during pregnancy.

Memory

At some point after immune activation in response to antigen, the proliferative response ends, and a significant proportion of the population of antigen specific effector cells generated die. The result of this process is a pool of memory T cells. On a population level, memory T cells arise from a linearly differentiated subset of antigen specific T cells[108]. Pregnancy generates a pool of memory T cells that are specific for fetal antigen[4, 105]. Moreover, evidence suggests that vaccination or infection during pregnancy does not impair immunologic memory[24, 109].

Recent observations have focused on a new class of “tissue resident’ T cells that are thought to be critical in the rapid response of mucosal surfaces to viral or other pathogens. Infection in mucosa generates this pool which can rapidly circulate back to the index tissue with subsequent infections. Both CD4 and CD8 tissue resident T cells have been observed in the vagina[110, 111] and in uterine[112113, 114] tissues.

B cells give rise to antibody producing plasma cells. They develop in the bone marrow and circulate to the periphery where they occupy specialized areas within lymph nodes. There, they can be exposed to antigen migrating from tissues into draining lymph nodes or present on lymph node-resident follicular dendritic cells[115]. For a subset of antigens with a particular structure, exposure to B cells may cause direct activation, proliferation and differentiation. For another set of antigens, binding to antigen specific B cell receptors causes antigen uptake, processing and presentation to T cells. This later process generates T cell production of soluble and cell-surface molecules that can bind to B cells and mediate immunoglobulin production, class switch, and differentiation to plasma cells[116]. Lineages of B cells include regulatory B cells that express IL- 10, down modulate the B cell response and thus repress autoimmune disease[117]. The B cell compartment undergoes homeostatic changes during pregnancy[118, 119], that may increase serum immunoglobulins during this time, as well as support distribution of immunoglobulins, including IgA and IgG, through tissues into their respective lumen (for example[120]). It also has been observed that pregnancy

expands regulatory B cells[121] and the strength and specificity of these B_{reg} may modify both maternal tolerance and protection against infection.

Do gonadal steroids affect immune function?

Gonadal steroids comprise the environment generated by the X and Y chromosomes by which gene-by-environment interaction produces health or disease[122]. The view that one hormone, estrogen is pro-inflammatory and the other, progesterone, is anti-inflammatory is too simplistic. For example, estrogen can support antiviral immunity in the reproductive tract[123], and this is thought to be dependent on an inflammatory cytokine. In contrast, estrogen can modulate immunity by supporting the presence of Treg[124], and is used to treat autoimmune disease. For another example, progesterone, long held to be critical to the apparent immune suppression of pregnancy, supports the expression of cytokines, such as IL-15, that enhance the homeostatic proliferation of immune cells[125126, 127]. The role of gonadal steroids in immune regulation is likely to be complex. The in vitro and in vivo effects of these molecules on immune cells have anchored the experimental evidence used to support idea that successful pregnancy requires immune modulation. What about the theoretical constructs addressing the immunology of pregnancy?

Theories and models of immune tolerance in the context of pregnancy

Tolerance is an active process by which the immune system does not respond to a given antigen

Despite the differences in placentation amongst mammalian species, the “problem of viviparity” is essentially one wherein the developing fetus is in intimate contact with the mother. In humans and rodents, there are at least four potential venues for such contact. The hemachorial placenta of these species, as the name implies, is such that blood from the mother directly bathes trophoblast which arises from the fetus and comprises the placenta. In addition, extra-villous trophoblast both anchors the placenta and replaces the endothelium of vessels in order to accommodate maternal blood flow into the intervillous space. Fetal cells migrate to the systemic circulation of the mother, and vice versa. This accounts for long-term micro-chimerism in both directions and may carry immunological consequences.

Self-non-self models of immunity[128]

Classically, recognition of that which is “non- self” initiates T cell activation[129130]. In these models regulation of the immune response, including tolerance of self-antigens, includes reliance on specific methods of suppression. By these models, another way to generate functional tolerance is to limit the specific class or brand of immune response possible. Thus, a harmful immune response that is mediated by cytotoxic T cells is “suppressed” by the shifting of this immune response to one that produces non-cytotoxic antibody. Further, classical models of immunity suggest that a final phase of immune tolerance is the limitation of trafficking or function of T cells generated in the course of activation by antigen.

With respect to pregnancy, classical models have, through interpretation of existing data, morphed over time to include highly complex underlying mechanisms. For example, early models suggested that maternal tolerance was simply a matter of failure of maternal T cells

to be exposed to fetal antigen[128]. As an extension of this idea, it has been proposed that there is specific limitation of the trafficking of dendritic cells from the uterus to the uterine draining nodes and that this limits presentation of fetal antigens to maternal T cells during pregnancy[57]. However, as previously mentioned, fetal and maternal cells can traffic in both directions[131, 132], and pregnancy produces systemic immunity to fetal antigens.

Many mechanisms have been put forth to provide the local become activated. The list of molecules thought to provide both global and local suppression of immunity includes molecules such as indoleamine 2,3-deoxygenase IDO[133, 134]. These molecules have been used to support the idea that the whole of pregnancy is a state of relative immune suppression, and thus susceptibility to infectious disease. Further, the presence of alternatively activated macrophages and NK cells begin the list of cells with immune-suppressive properties that exist within the uterus and placenta during pregnancy. This list of cells recruited into the immune suppression paradigm culminated with the regulatory T cell, both in its CD4 and possibly CD8 formats.

The ‘Danger’ model [135, 136]

This model is the major alternative to classical models of maternal tolerance of the fetus. This model has been discussed in detail in the context of adverse pregnancy outcomes[137]. The critical pieces of this model state that T cell, and therefore immune system activation, is not reliant on recognition of “non-self” but on recognition of “Danger”. Although this may appear to some as a matter of semantics, it does represent a major shift in how one might think about diseases, including infectious diseases, which occur during pregnancy. According to the Danger model, the expression of paternal or unique fetal antigens during pregnancy does not necessarily generate T cell activation if Danger is not present. Danger is expressed in fetal tissues and in the decidua through dysregulation of critical metabolic processes, necrosis, and similar mechanisms which produces a signal that activates dendritic cells and possibly alters the processing of locally expressed antigens. Danger is tied to the activation of dendritic cells and their expression of the co-stimulatory signals needed for T cell activation. According to the model, recognition of fetal antigen in the absence of co-stimulation leads to T cell death. Even if a population of T cells is generated against fetal antigens, they do not necessarily generate fetal loss and this is dependent on the structural integrity, growth and lack of continued expression of Danger in fetal tissues. Like the liver, the remaining placenta and related tissues, if healthy simply out runs or out grows any insult by potential attacking T cells. In this context, the expansion of antigen nonspecific or fetal antigen specific regulatory T cells may represent a “bystander effect” that supports the placenta’s normal growth or the ability to “out run” potentially harmful T cells. The fact that disruption of this population of T cells leads to loss of “semi-allogeneic” fetuses neither proves nor disproves the validity of self- non-self- recognition as the basis for immune activation. Through this model, the expression of molecules or the expansion of cells with immune-suppressing characteristics are non-critical to successful fetal antigen-specific maternal immune tolerance. What is critical is metabolic or physiologic health of fetal cells. This model is also consistent with the idea that some diseases of pregnancy carry a maternal component. For example, in pregnancies marked by pre-eclampsia, if maternal decidual or endothelial cells are rendered dysfunctional by some insult, this may lead to local or

systemic maternal dendritic cell activation and processing of local (e.g., source is placental) or systemic (e.g., source is trafficking fetal cells) fetal antigens and presentation of the relevant peptides to maternal T cells. This may lead to specific anti-fetal immunity. In other pregnancies, trafficking of T cells into the decidua can occur in the context of infection and not lead to abortion[24]. Regulation of trafficking to this tissue by effector cells is a complex issue, and possibly not a default mechanism of tolerance.

With regard to the relationship between class of immune response and tolerance of the maternal-fetal unit, the Danger model suggests that every tissue has a specific tendency towards the type of immune response generated in that tissue[138]. The presence therefore of "foreign" or in the case of pregnancy, fetal/paternal antigen, as opposed to "self" antigen does not drive the class of the response. It may be that placental or intrauterine responses are geared towards certain classes as a result of early developmental programing. This may explain the observation of a tendency toward Th2-type immune responses in decidua or the systemic circulation during pregnancy. Moreover this model would support the idea that the pleotropic nature of cytokines and growth factors is such that pregnancy loss due to lack of expression of certain "Th2 cytokines, such as IL-10 may have more to do with the poor health of trophoblast than the failure of a class switch in maternal immunity. Further, the Danger model's likely interpretation of the fact that lack of expression of the "pro-inflammatory" cytokine IL-6 leads to increased gestational length[139] is that IL-6 is an important metabolic regulator of the time clock(s) leading to parturition, not that inherent mid-gestation suppression of inflammation is the primary goal of pregnancy-associated tissues.

"Evolutionary non-self" model[140]

Although not intended to deal with pregnancy transplantation, or allo-immune recognition in general, it might be useful to speculate, given current data, what evolutionary non-self and related models might say about maternal tolerance of the fetus. In this offshoot of classical immune models, the focus is on activation of the innate immune response as the critical mechanism for overall immune activation.

By this model, T cell receptor recognition of self-peptides in the context of MHC underlines the basis for development in the thymus and survival and initial activation in the periphery. However, full activation is reliant on a costimulatory signal delivered by an activated antigen presenting cell. The signal for activation of the antigen presenting cell constitutes the point at which self is discriminated from non self. Three strategies for immune recognition are envisioned[141]:

- The first is recognition of "microbial non-self" which occurs through binding of innate immune cell receptors expressed by dendritic cells or macrophages to pathogen associated molecular patterns (PAMPS) on infecting agents.
- The second is recognition of "missing self", that is recognition of molecules that are evolutionarily expressed on cells of the body or immune cells, but not bacteria, for example.

- The third is recognition of “altered self” which is said to occur when there is expression of new cellular markers or abnormalities in cellular markers in the wake of viral or other pathological infection.

“Tolerance” in this model is an indirect process that occurs because microbial non self is segregated from cells that could recognize it, by inhibitory signals expressed on the tissue of interest, by increased expression of unique “self” antigens and by pathogen-associated mechanisms to decrease expression of “altered self” after infection. Later versions of this model also rely on the activity of “suppressor cells” to limit the function of autoreactive T cells[142]. We could guess, according to this model, that the presence of fetal antigens at the maternal-fetal interface does not necessarily activate the immune system. However, when infection occurs, the pattern receptor mediated immune system occurs in order to protect the mother. This thinking supports interpretation obtained through experimental models of infection or inflammation-induced preterm birth[73, 143]. The fact that parasitic infection within the placenta leads to dire consequences[144] also fits within this model.

There are observations related to maternal tolerance that would be in line with the model’s focus on innate immune privilege. For example, the expression on the human zona pelucida of Sialyl-Lewis^x motifis which bind immune-suppressive ligands such as sieglec-9, expression of the immune modulating glycoprotein Glycodelin-A (reviewed in[9]) and expression of the mucinous glycoprotein MUC 16 (also known as CA 125) by the endometrium[9] are thought to suppress local activity of immune cells to protect the implanting embryo. For another example, the placenta expresses a number of small lectin molecules, the galectins, which are thought to be immune modulatory. The role of other unusual glycoproteins and their role in immune modulation in the reproductive track are being examined.

In the context of this model, the relatively low level of immune cell activation to the organisms present in the reproductive tract and uterus[145, 146] might be explained by reproductive tract cell modulation of sialic acid residues[147], or segregation of these organisms from the immune response by their retention intracellularly[145, 146]. Viral infection is common at the maternal-fetal interface, but the loss of pregnancy and other adverse outcomes occurs only in a portion of cases, and this may be related to a second “hit” that induces innate immune system activation[148]. An explanation consistent with this model is that certain viruses adapt to trophoblast in such a way that viral infection in trophoblast down regulates the expression of altered self and thus prevents immune system activation. Support for the idea of viral adaptation comes from the fact that evolutionary time has produced a placenta whose critical functions depend on genes taken from endogenous retroviruses[149].

Is the post-partum immune system important?

Pregnancy is a time of rapid shifting in physiology. Resolution and new adaptation occurs globally during the postpartum state. For example, some degree of pregnancy-induced vascular adaptation continues for weeks to months after delivery[150–153]. Elements of the physiology of pregnancy continue well into the woman’s post pregnancy life. Normal

pregnancies are generally associated with very low long-term cardiovascular risks while complicated pregnancies, including preeclampsia[154–156], preterm birth[157–159], gestational diabetes[160] and high multiparity[161], are associated with cardiovascular risk. The post-partum state is likely an important time to ask questions about what happens to the maternal immune system. For example, how does one explain fetal cell micro-chimerism after delivery? Classical models suggest that through micro-chimerism, the fetus becomes an extension of maternal "self"[162, 163] and that long-lived T_{reg}, impair reactivity to fetal cells. By the Danger model, there is another perspective on these cells. If the trafficking of these cells was not caused by necrosis or dysregulation of tissues within the uterus, and further if the trafficking cells settle in their new homes without causing damage or disruption, then no immune response would be expected, and this might lead to the long term micro-chimerism that has been reported. Another question is how to explain evidence of new-onset autoimmune disease, such as thyroiditis[164] or peri-partum cardio myopathy[165], overshoots over baseline in severity of autoimmune disease in the postpartum period? While classical models would suggest these findings are related to release from immune suppression in the post-partum state, the evolutionary-non-self and Danger models might suggest persistent underlying infection or dysregulation, respectively, of maternal tissues as driving long term disease risk. There may be other models however, based on what we know about immune cell homeostasis[166–170], and these will have to be explored.

References

1. Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. J Autoimmun. 2012; 38(2–3):J266–74. [PubMed: 22284905]
2. Bonney EA, Brown SA. To drive or be driven: the path of a mouse model of recurrent pregnancy loss. Reproduction (Cambridge, England). 2014; 147(5):R153–67.
3. Pantham P, Abrahams VM, Chamley LW. The role of anti-phospholipid antibodies in autoimmune reproductive failure. Reproduction (Cambridge, England). 2016; 151(5):R79–90.
4. Lissauer D, Piper K, Goodyear O, Kilby MD, Moss PA. Fetal-specific CD8+ cytotoxic T cell responses develop during normal human pregnancy and exhibit broad functional capacity. Journal of immunology (Baltimore, Md: 1950). 2012; 189(2):1072–80.
5. Raj RS, Bonney EA, Phillippe M. Influenza, immune system, and pregnancy. Reproductive sciences (Thousand Oaks, Calif). 2014; 21(12):1434–51.
6. Caluwaerts S, Fautsch T, Lagrou D, Moreau M, Modet Camara A, Gunther S, et al. Dilemmas in Managing Pregnant Women With Ebola: 2 Case Reports. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2016; 62(7):903–5. [PubMed: 26679622]
7. Duffy MR, Chen T-H, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika Virus Outbreak on Yap Island, Federated States of Micronesia. New England Journal of Medicine. 2009; 360(24): 2536–2543. [PubMed: 19516034]
8. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound in Obstetrics & Gynecology. 2016; 47(1):6–7. [PubMed: 26731034]
9. Clark GF, Schust DJ. Manifestations of immune tolerance in the human female reproductive tract. Frontiers in immunology. 2013; 4:26. [PubMed: 23407606]
10. Davis-Richardson AG, Triplett EW. A model for the role of gut bacteria in the development of autoimmunity for type 1 diabetes. Diabetologia. 2015; 58(7):1386–93. [PubMed: 25957231]
11. Anahtar MN, Byrne EH, Doherty KE, Bowman BA, Yamamoto HS, Soumillon M, et al. Cervicovaginal bacteria are a major modulator of host inflammatory responses in the female genital tract. Immunity. 2015; 42(5):965–76. [PubMed: 25992865]

12. Rizzo A, Fiorentino M, Buommino E, Donnarumma G, Losacco A, Bevilacqua N. Lactobacillus crispatus mediates anti-inflammatory cytokine interleukin-10 induction in response to Chlamydia trachomatis infection in vitro. International journal of medical microbiology: IJMM. 2015; 305(8): 815–27. [PubMed: 26372530]
13. Nelson DB, Shin H, Wu J, Dominguez-Bello MG. The Gestational Vaginal Microbiome and Spontaneous Preterm Birth among Nulliparous African American Women. American journal of perinatology. 2016
14. Baldwin EA, Walther-Antonio M, MacLean AM, Gohl DM, Beckman KB, Chen J, et al. Persistent microbial dysbiosis in preterm premature rupture of membranes from onset until delivery. PeerJ. 2015; 3:e1398. [PubMed: 26644969]
15. Jacob JA. Another frontier in microbiome research: Preterm birth. JAMA. 2015; 314(15):1550–1551. [PubMed: 26418197]
16. Wylie KM, Mihindukulasuriya KA, Zhou Y, Sodergren E, Storch GA, Weinstock GM. Metagenomic analysis of double-stranded DNA viruses in healthy adults. BMC biology. 2014; 12:71. [PubMed: 25212266]
17. Yarbrough VL, Winkle S, Herbst-Kralovetz MM. Antimicrobial peptides in the female reproductive tract: a critical component of the mucosal immune barrier with physiological and clinical implications. Human Reproduction Update. 2015; 21(3):353–377. [PubMed: 25547201]
18. McConkey CA, Delorme-Axford E, Nickerson CA, Kim KS, Sadovsky Y, Boyle JP, et al. A three-dimensional culture system recapitulates placental syncytiotrophoblast development and microbial resistance. Science advances. 2016; 2(3):e1501462. [PubMed: 26973875]
19. Zeldovich VB, Clausen CH, Bradford E, Fletcher DA, Maltepe E, Robbins JR, et al. Placental syncytium forms a biophysical barrier against pathogen invasion. PLoS pathogens. 2013; 9(12):e1003821. [PubMed: 24348256]
20. Penkala I, Wang J, Syrett CM, Goetzl L, Lopez CB, Anguera MC. LNCRHOXF1: a long noncoding RNA from the X-chromosome that suppresses viral response genes during development of the early human placenta. Molecular and cellular biology. 2016
21. Racicot K, Kwon JY, Aldo P, Abrahams V, El-Guindy A, Romero R, et al. Type I Interferon Regulates the Placental Inflammatory Response to Bacteria and is Targeted by Virus: Mechanism of Polymicrobial Infection-Induced Preterm Birth. American journal of reproductive immunology (New York, NY: 1989). 2016; 75(4):451–60.
22. Aldo PB, Mulla MJ, Romero R, Mor G, Abrahams VM. Viral ssRNA induces first trimester trophoblast apoptosis through an inflammatory mechanism. American journal of reproductive immunology (New York, NY: 1989). 2010; 64(1):27–37.
23. Zdravkovic M, Knudsen HJ, Liu X, Hager H, Zachar V, Aboagye-Mathiesen G, et al. High interferon alpha levels in placenta, maternal, and cord blood suggest a protective effect against intrauterine herpes simplex virus infection. Journal of medical virology. 1997; 51(3):210–3. [PubMed: 9139085]
24. Constantin CM, Masopust D, Gourley T, Grayson J, Strickland OL, Ahmed R, et al. Normal establishment of virus-specific memory CD8 T cell pool following primary infection during pregnancy. Journal of immunology (Baltimore, Md: 1950). 2007; 179(7):4383–9.
25. Driggers RW, Ho C-Y, Korhonen EM, Kuivanen S, Jaaskelainen AJ, Smura T, et al. Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities. New England Journal of Medicine.
26. Cooper MA, Yokoyama WM. Memory-like responses of natural killer cells. Immunological reviews. 2010; 235(1):297–305. [PubMed: 20536571]
27. Sharkey AM, Xiong S, Kennedy PR, Gardner L, Farrell LE, Chazara O, et al. Tissue-Specific Education of Decidual NK Cells. Journal of immunology (Baltimore, Md: 1950). 2015; 195(7): 3026–32.
28. Sacks GP, Studena K, Sargent K, Redman CW. Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. American journal of obstetrics and gynecology. 1998; 179(1):80–6. [PubMed: 9704769]

29. Southcombe JH, Redman CW, Sargent IL, Granne I. Interleukin-1 family cytokines and their regulatory proteins in normal pregnancy and pre-eclampsia. Clinical and experimental immunology. 2015; 181(3):480–90. [PubMed: 25693732]
30. St John AL, Abraham SN. Innate Immunity and its Regulation by Mast Cells(). Journal of immunology (Baltimore, Md: 1950). 2013; 190(9):4458–4463.
31. Galli SJ, Borregaard N, Wynn TA. Phenotypic and functional plasticity of cells of innate immunity: macrophages, mast cells and neutrophils. Nature immunology. 2011; 12(11):1035–1044. [PubMed: 22012443]
32. Simon T, Gogolak P, Kis-Toth K, Jelinek I, Laszlo V, Rajnavolgyi E. Histamine modulates multiple functional activities of monocyte-derived dendritic cell subsets via histamine receptor 2. Int Immunol. 2012; 24(2):107–16. [PubMed: 22232416]
33. Case LK, Moussawi M, Roberts B, Noubade R, Huber SA, Teuscher C. Histamine H1 receptor signaling regulates effector T cell responses and susceptibility to coxsackievirus B3-induced myocarditis. Cellular Immunology. 2012; 272(2):269–274. [PubMed: 22078271]
34. Sirois J, Menard G, Moses AS, Bissonnette EY. Importance of histamine in the cytokine network in the lung through H2 and H3 receptors: stimulation of IL-10 production. J Immunol. 2000; 164(6): 2964–70. [PubMed: 10706683]
35. Botturi K, Lacoeuille Y, Vervloet D, Magnan A. Histamine induces Th2 activation through the histamine receptor 1 in house dust mite rhinitic but not asthmatic patients. Clin Exp Allergy. 2010; 40(5):755–62. [PubMed: 20184607]
36. Meretey K, Fekete MI, Bohm U, Falus A. Effect of H1 and H2 agonists on the chemiluminescence of human blood mononuclear cells induced by phytohaemagglutinin. Immunopharmacology. 1985; 9(3):175–80. [PubMed: 3160680]
37. Teuscher C, Subramanian M, Noubade R, Gao JF, Offner H, Zachary JF, et al. Central Histamine H_3 Receptor Signaling Negatively Regulates Susceptibility to Autoimmune Inflammatory Disease of the CNS. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104(24):10146–10151. [PubMed: 17548817]
38. del Rio R, Noubade R, Saligrama N, Wall EH, Krementsov DN, Poynter ME, et al. Histamine H4 Receptor Optimizes T Regulatory Cell Frequency and Facilitates Anti-Inflammatory Responses within the Central Nervous System. The Journal of Immunology. 2012; 188(2):541–547. [PubMed: 22147765]
39. Dijkstra D, Leurs R, Chazot P, Shenton FC, Stark H, Werfel T, et al. Histamine downregulates monocyte CCL2 production through the histamine H4 receptor. J Allergy Clin Immunol. 2007; 120(2):300–7. [PubMed: 17507084]
40. Emerson MR, Orentas DM, Lynch SG, LeVine SM. Activation of histamine H2 receptors ameliorates experimental allergic encephalomyelitis. Neuroreport. 2002; 13(11):1407–10. [PubMed: 12167763]
41. Menzies FM, Higgins CA, Shepherd MC, Nibbs RJ, Nelson SM. Mast cells reside in myometrium and cervix, but are dispensable in mice for successful pregnancy and labor. Immunol Cell Biol. 2012; 90(3):321–9. [PubMed: 21577230]
42. Zhao X, Ma W, Das SK, Dey SK, Paria BC. Blastocyst H(2) receptor is the target for uterine histamine in implantation in the mouse. Development. 2000; 127(12):2643–51. [PubMed: 10821762]
43. Bosquiazzo VL, Ramos JG, Varayoud J, Munoz-de-Toro M, Luque EH. Mast cell degranulation in rat uterine cervix during pregnancy correlates with expression of vascular endothelial growth factor mRNA and angiogenesis. Reproduction (Cambridge, England). 2007; 133(5):1045–55.
44. Woidacki K, Meyer N, Schumacher A, Goldschmidt A, Maurer M, Zenclussen AC. Transfer of regulatory T cells into abortion-prone mice promotes the expansion of uterine mast cells and normalizes early pregnancy angiogenesis. Scientific reports. 2015; 5:13938. [PubMed: 26355667]
45. McNeill JH, Verma SC. Histamine2 receptors in rat uterus. Res Commun Chem Pathol Pharmacol. 1975; 11(4):639–44. [PubMed: 1179032]
46. Castelli MC, Vadora E, Bacchi Modena A, Molina E. In vitro effects of histamine on human pregnant myometrium contractility. Boll Soc Ital Biol Sper. 1993; 69(12):783–9. [PubMed: 8003294]

47. Willets JM, Taylor AH, Shaw H, Konje JC, Challiss RA. Selective regulation of H1 histamine receptor signaling by G protein-coupled receptor kinase 2 in uterine smooth muscle cells. Mol Endocrinol. 2008; 22(8):1893–907. [PubMed: 18511496]

48. Bytautiene E, Vedernikov YP, Saade GR, Romero R, Garfield RE. IgE-independent mast cell activation augments contractility of nonpregnant and pregnant guinea pig myometrium. International archives of allergy and immunology. 2008; 147(2):140–6. [PubMed: 18520159]

49. Romero R, Kusanovic JP, Gomez R, Lamont R, Bytautiene E, Garfield RE, et al. The clinical significance of eosinophils in the amniotic fluid in preterm labor. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2010; 23(4):320–9.

50. Bytautiene E, Vedernikov YP, Maner WL, Saade GR, Romero R, Garfield RE. Challenge with ovalbumin antigen increases uterine and cervical contractile activity in sensitized guinea pigs. American journal of obstetrics and gynecology. 2008; 199(6):658e1–6. [PubMed: 18722575]

51. Bytautiene E, Vedernikov YP, Saade GR, Romero R, Garfield RE. Degranulation of uterine mast cell modifies contractility of isolated myometrium from pregnant women. American journal of obstetrics and gynecology. 2004; 191(5):1705–10. [PubMed: 15547545]

52. Giaglis S, Stoikou M, Grimolizzi F, Subramanian BY, van Breda SV, Hoesli I, et al. Neutrophil migration into the placenta: Good, bad or deadly? Cell adhesion & migration. 2016; 10(1–2):208–25. [PubMed: 26933824]

53. Brinkmann V, Zychlinsky A. Neutrophil extracellular traps: is immunity the second function of chromatin? The Journal of cell biology. 2012; 198(5):773–83. [PubMed: 22945932]

54. Amsalem H, Kwan M, Hazan A, Zhang J, Jones RL, Whittle W, et al. Identification of a novel neutrophil population: proangiogenic granulocytes in second-trimester human decidua. Journal of immunology (Baltimore, Md: 1950). 2014; 193(6):3070–9.

55. Mahendroo M. Cervical remodeling in term and preterm birth: insights from an animal model. Reproduction (Cambridge, England). 2012; 143(4):429–38.

56. Bizargity P, Bonney EA. Dendritic cells: a family portrait at mid-gestation. Immunology. 2009; 126(4):565–78. [PubMed: 18778288]

57. Collins MK, Tay C-S, Erlebacher A. Dendritic cell entrapment within the pregnant uterus inhibits immune surveillance of the maternal/fetal interface in mice. Journal of Clinical Investigation. 2009; 119(7):2062–73. [PubMed: 19546507]

58. Kwan M, Hazan A, Zhang J, Jones RL, Harris LK, Whittle W, et al. Dynamic changes in maternal decidual leukocyte populations from first to second trimester gestation. Placenta. 2014; 35(12): 1027–34. [PubMed: 25449030]

59. Pomeroy B, Sipka A, Klaessig S, Schukken Y. Monocyte-derived dendritic cells from late gestation cows have an impaired ability to mature in response to E. coli stimulation in a receptor and cytokine-mediated fashion. Veterinary immunology and immunopathology. 2015; 167(1–2):22–9. [PubMed: 26163935]

60. Gao XW, Fu Y, Li WJ, Du AJ, Li X, Zhao XD. Mechanism of immune tolerance induced by donor derived immature dendritic cells in rat high-risk corneal transplantation. International journal of ophthalmology. 2013; 6(3):269–75. [PubMed: 23826517]

61. Scholz C, Rampf E, Toth B, Brunnhuber R, Weissenbacher T, Friese K, et al. Ovarian cancer-derived glycodelin impairs in vitro dendritic cell maturation. Journal of immunotherapy (Hagerstown, Md: 1997). 2009; 32(5):492–7.

62. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nature reviews Immunology. 2008; 8(12):958–969.

63. Ning F, Liu H, Lash GE. The Role of Decidual Macrophages During Normal and Pathological Pregnancy. American journal of reproductive immunology (New York, NY: 1989). 2016; 75(3): 298–309.

64. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. Trends in immunology. 2016; 37(3):208–20. [PubMed: 26858199]

65. Jasper MJ, Care AS, Sullivan B, Ingman WV, Aplin JD, Robertson SA. Macrophage-derived LIF and IL1B regulate alpha (1,2) fucosyltransferase 2 (Fut2) expression in mouse uterine epithelial cells during early pregnancy. Biology of reproduction. 2011; 84(1):179–88. [PubMed: 20864644]

66. Payne KJ, Clyde LA, Weldon AJ, Milford TA, Yellon SM. Residency and activation of myeloid cells during remodeling of the prepartum murine cervix. Biology of reproduction. 2012; 87(5):106. [PubMed: 22914314]

67. Gomez-Lopez N, StLouis D, Lehr MA, Sanchez-Rodriguez EN, Arenas-Hernandez M. Immune cells in term and preterm labor. Cellular & molecular immunology. 2014; 11(6):571–81. [PubMed: 24954221]

68. Yellon SM, Dobyns AE, Beck HL, Kurtzman JT, Garfield RE, Kirby MA. Loss of progesterone receptor-mediated actions induce preterm cellular and structural remodeling of the cervix and premature birth. PloS one. 2013; 8(12):e81340. [PubMed: 24339918]

69. Newby AC. Metalloproteinase production from macrophages - a perfect storm leading to atherosclerotic plaque rupture and myocardial infarction. Experimental physiology. 2016

70. Norwitz ER, Lopez Bernal A, Starkey PM. Tumor necrosis factor-alpha selectively stimulates prostaglandin F2 alpha production by macrophages in human term decidua. American journal of obstetrics and gynecology. 1992; 167(3):815–20. [PubMed: 1530044]

71. Ogawa K, Funaba M, Tsujimoto M. The effects of TGF-beta1 on the expression of type IV collagenases in mouse peritoneal macrophages. Molecular biology reports. 2011; 38(2):1451–6. [PubMed: 20845081]

72. Timmons BC, Fairhurst AM, Mahendroo MS. Temporal changes in myeloid cells in the cervix during pregnancy and parturition. Journal of immunology (Baltimore, Md: 1950). 2009; 182(5): 2700–7.

73. Bizargity P, Del Rio R, Phillippe M, Teuscher C, Bonney EA. Resistance to lipopolysaccharide-induced preterm delivery mediated by regulatory T cell function in mice. Biology of reproduction. 2009; 80(5):874–81. [PubMed: 19144956]

74. Orange JS. Natural killer cell deficiency. The Journal of allergy and clinical immunology. 2013; 132(3):515–25. quiz 526. [PubMed: 23993353]

75. Eguizabal C, Zenarruzabeitia O, Monge J, Santos S, Vesga MA, Maruri N, et al. Natural killer cells for cancer immunotherapy: pluripotent stem cells-derived NK cells as an immunotherapeutic perspective. Frontiers in immunology. 2014; 5:439. [PubMed: 25309538]

76. Vacca P, Montaldo E, Croxatto D, Loiacono F, Canegallo F, Venturini PL, et al. Identification of diverse innate lymphoid cells in human decidua. Mucosal Immunol. 2015; 8(2):254–264. [PubMed: 25052762]

77. Shih HY, Sciume G, Mikami Y, Guo L, Sun HW, Brooks SR, et al. Developmental Acquisition of Regulomes Underlies Innate Lymphoid Cell Functionality. Cell. 2016

78. Furcron AE, Romero R, Plazyo O, Unkel R, Xu Y, Hassan SS, et al. Vaginal progesterone, but not 17alpha-hydroxyprogesterone caproate, has antiinflammatory effects at the murine maternal-fetal interface. American journal of obstetrics and gynecology. 2015; 213(6):846.e1–846.e19. [PubMed: 26264823]

79. Wang Y, Xu B, Li MQ, Li DJ, Jin LP. IL-22 secreted by decidual stromal cells and NK cells promotes the survival of human trophoblasts. International journal of clinical and experimental pathology. 2013; 6(9):1781–90. [PubMed: 24040442]

80. Bendelac A, Hunziker RD, Lantz O. Increased interleukin 4 and immunoglobulin E production in transgenic mice overexpressing NK1 T cells. The Journal of experimental medicine. 1996; 184(4): 1285–93. [PubMed: 8879200]

81. Lawson V. Turned on by danger: activation of CD1d-restricted invariant natural killer T cells. Immunology. 2012; 137(1):20–7. [PubMed: 22734667]

82. Boyson JE, Nagarkatti N, Nizam L, Exley MA, Strominger JL. Gestation stage-dependent mechanisms of invariant natural killer T cell-mediated pregnancy loss. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103(12):4580–5. [PubMed: 16537414]

83. Huijts CM, Schneiders FL, Garcia-Vallejo JJ, Verheul HM, de Gruijl TD, van der Vliet HJ. mTOR Inhibition Per Se Induces Nuclear Localization of FOXP3 and Conversion of Invariant NKT

(iNKT) Cells into Immunosuppressive Regulatory iNKT Cells. Journal of immunology (Baltimore, Md: 1950). 2015; 195(5):2038–45.

84. Uemura Y, Suzuki M, Liu TY, Narita Y, Hirata S, Ohyama H, et al. Role of human non-invariant NKT lymphocytes in the maintenance of type 2 T helper environment during pregnancy. International immunology. 2008; 20(3):405–12. [PubMed: 18234691]
85. Adams EJ, Gu S, Luoma AM. Human gamma delta T cells: Evolution and ligand recognition. Cellular immunology. 2015; 296(1):31–40. [PubMed: 25991474]
86. Roessner K, Wolfe J, Shi C, Sigal LH, Huber S, Budd RC. High expression of Fas ligand by synovial fluid-derived gamma delta T cells in Lyme arthritis. Journal of immunology (Baltimore, Md: 1950). 2003; 170(5):2702–10.
87. Alcaide ML, Strbo N, Romero L, Jones DL, Rodriguez VJ, Arheart K, et al. Bacterial Vaginosis Is Associated with Loss of Gamma Delta T Cells in the Female Reproductive Tract in Women in the Miami Women Interagency HIV Study (WIHS): A Cross Sectional Study. PloS one. 2016; 11(4):e0153045. [PubMed: 27078021]
88. Chapman JC, Chapman FM, Michael SD. The production of alpha/beta and gamma/delta double negative (DN) T-cells and their role in the maintenance of pregnancy. Reproductive Biology and Endocrinology: RB&E. 2015; 13:73. [PubMed: 26164866]
89. Bonney EA, Pudney J, Anderson DJ, Hill JA. Gamma-delta T cells in midgestation human placental villi. Gynecologic and obstetric investigation. 2000; 50(3):153–7. [PubMed: 11014945]
90. Heyborne KD, Cranfill RL, Carding SR, Born WK, O'Brien RL. Characterization of gamma delta T lymphocytes at the maternal-fetal interface. Journal of immunology (Baltimore, Md: 1950). 1992; 149(9):2872–8.
91. Fujihashi K, McGhee JR, Kweon MN, Cooper MD, Tonegawa S, Takahashi I, et al. gamma/delta T cell-deficient mice have impaired mucosal immunoglobulin A responses. The Journal of experimental medicine. 1996; 183(4):1929–35. [PubMed: 8666951]
92. Krishnan L, Guilbert LJ, Russell AS, Wegmann TG, Mosmann TR, Belosevic M. Pregnancy impairs resistance of C57BL/6 mice to Leishmania major infection and causes decreased antigen-specific IFN-gamma response and increased production of T helper 2 cytokines. Journal of immunology (Baltimore, Md: 1950). 1996; 156(2):644–52.
93. Bonney EA, Onyekwuluje J. Maternal tolerance to H-Y is independent of IL-10. Immunological Investigations. 2004; 33(4):385–95. [PubMed: 15624697]
94. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nature immunology. 2004; 5(3):266–71. [PubMed: 14758358]
95. Moldenhauer LM, Diener KR, Thring DM, Brown MP, Hayball JD, Robertson SA. Cross-presentation of male seminal fluid antigens elicits T cell activation to initiate the female immune response to pregnancy. Journal of immunology (Baltimore, Md: 1950). 2009; 182(12):8080–93.
96. Curtis MM, Way SS. Interleukin-17 in host defence against bacterial, mycobacterial and fungal pathogens. Immunology. 2009; 126(2):177–85. [PubMed: 19125888]
97. Gopal R, Rangel-Moreno J, Fallert Junecko BA, Mallon DJ, Chen K, Pociask DA, et al. Mucosal pre-exposure to Th17-inducing adjuvants exacerbates pathology after influenza infection. The American journal of pathology. 2014; 184(1):55–63. [PubMed: 24183780]
98. Ito M, Nakashima A, Hidaka T, Okabe M, Bac ND, Ina S, et al. A role for IL-17 in induction of an inflammation at the fetomaternal interface in preterm labour. J Reprod Immunol. 2010; 84(1):75–85. [PubMed: 19969371]
99. Gomez-Lopez N, Olson DM, Robertson SA. Interleukin-6 controls uterine Th9 cells and CD8+ T regulatory cells to accelerate parturition in mice. Immunol Cell Biol. 2016; 94(1):79–89. [PubMed: 26073576]
100. Guerder S, Matzinger P. A fail-safe mechanism for maintaining self-tolerance. The Journal of experimental medicine. 1992; 176(2):553–64. [PubMed: 1386876]
101. Ridge JP, Di Rosa F, Matzinger P. A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper and a T-killer cell. Nature. 1998; 393(6684):474–8. [PubMed: 9624003]
102. Nguyen ML, Hatton L, Li J, Olshansky M, Kelso A, Russ BE, et al. Dynamic regulation of permissive histone modifications and GATA3 binding underpin acquisition of granzyme A

expression by virus-specific CD8(+) T cells. European journal of immunology. 2016; 46(2):307–18. [PubMed: 26519105]

103. Valujskikh A, Lantz O, Celli S, Matzinger P, Heeger PS. Cross-primed CD8(+) T cells mediate graft rejection via a distinct effector pathway. Nature immunology. 2002; 3(9):844–51. [PubMed: 12172545]
104. Tilburgs T, Strominger JL. CD8+ effector T cells at the fetal-maternal interface, balancing fetal tolerance and antiviral immunity. American journal of reproductive immunology (New York, NY: 1989). 2013; 69(4):395–407.
105. Bonney EA, Onyekwuluje J. The H-Y response in mid-gestation and long after delivery in mice primed before pregnancy. Immunological Investigations. 2003; 32(1–2):71–81. [PubMed: 12722943]
106. Norton MT, Fortner KA, Oppenheimer KH, Bonney EA. Evidence that CD8 T-cell homeostasis and function remain intact during murine pregnancy. Immunology. 2010; 131(3):426–37. [PubMed: 20553337]
107. Wang SC, Li YH, Piao HL, Hong XW, Zhang D, Xu YY, et al. PD-1 and Tim-3 pathways are associated with regulatory CD8+ T-cell function in decidua and maintenance of normal pregnancy. Cell death & disease. 2015; 6:e1738. [PubMed: 25950468]
108. Jelley-Gibbs DM, Strutt TM, McKinstry KK, Swain SL. Influencing the fates of CD4 T cells on the path to memory: lessons from influenza. Immunol Cell Biol. 2008; 86(4):343–52. [PubMed: 18362946]
109. Kay AW, Blish CA. Immunogenicity and Clinical Efficacy of Influenza Vaccination in Pregnancy. Frontiers in immunology. 2015; 6:289. [PubMed: 26089824]
110. Iijima N, Iwasaki A. T cell memory. A local macrophage chemokine network sustains protective tissue-resident memory CD4 T cells. Science. 2014; 346(6205):93–8. [PubMed: 25170048]
111. Cuburu N, Graham BS, Buck CB, Kines RC, Pang YY, Day PM, et al. Intravaginal immunization with HPV vectors induces tissue-resident CD8+ T cell responses. The Journal of clinical investigation. 2012; 122(12):4606–20. [PubMed: 23143305]
112. Yeaman GR, Collins JE, Fanger MW, Wira CR, Lydyard PM. CD8+ T cells in human uterine endometrial lymphoid aggregates: evidence for accumulation of cells by trafficking. Immunology. 2001; 102(4):434–40. [PubMed: 11328377]
113. Tabanelli V, Valli R, Righi S, Nucera G, Zecchini Barrese T, Pileri S, et al. A unique case of an indolent myometrial T-cell lymphoproliferative disorder with phenotypic features resembling uterine CD8+ resident memory T cells. Pathobiology: journal of immunopathology, molecular and cellular biology. 2014; 81(4):176–82.
114. van Egmond A, van der Keur C, Swings GM, Scherjon SA, Claas FH. The possible role of virus-specific CD8(+) memory T cells in decidual tissue. J Reprod Immunol. 2016; 113:1–8. [PubMed: 26496155]
115. Heesters BA, Myers RC, Carroll MC. Follicular dendritic cells: dynamic antigen libraries. Nat Rev Immunol. 2014; 14(7):495–504. [PubMed: 24948364]
116. Dienz O, Eaton SM, Bond JP, Neveu W, Moquin D, Noubade R, et al. The induction of antibody production by IL-6 is indirectly mediated by IL-21 produced by CD4+ T cells. The Journal of experimental medicine. 2009; 206(1):69–78. [PubMed: 19139170]
117. Menon M, Blair PA, Isenberg DA, Mauri C. A Regulatory Feedback between Plasmacytoid Dendritic Cells and Regulatory B Cells Is Aberrant in Systemic Lupus Erythematosus. Immunity. 2016; 44(3):683–97. [PubMed: 26968426]
118. Muzzio DO, Soldati R, Ehrhardt J, Utpatel K, Evert M, Zenclussen AC, et al. B cell development undergoes profound modifications and adaptations during pregnancy in mice. Biology of reproduction. 2014; 91(5):115. [PubMed: 25210132]
119. Norton MT, Fortner KA, Bizargity P, Bonney EA. Pregnancy alters the proliferation and apoptosis of mouse splenic erythroid lineage cells and leukocytes. Biology of reproduction. 2009; 81(3): 457–64. [PubMed: 19369644]
120. Schaefer K, Brown N, Kaye PM, Lacey CJ. Cervico-vaginal immunoglobulin G levels increase post-ovulation independently of neutrophils. PloS one. 2014; 9(12):e114824. [PubMed: 25479383]

121. Rolle L, Memarzadeh Tehran M, Morell-Garcia A, Raeva Y, Schumacher A, Hartig R, et al. Cutting edge: IL-10-producing regulatory B cells in early human pregnancy. American journal of reproductive immunology (New York, NY: 1989). 2013; 70(6):448–53.
122. Ober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. Nat Rev Genet. 2008; 9(12):911–22. [PubMed: 19002143]
123. Anipindi VC, Bagri P, Roth K, Dizzell SE, Nguyen PV, Shaler CR, et al. Estradiol Enhances CD4+ T-Cell Anti-Viral Immunity by Priming Vaginal DCs to Induce Th17 Responses via an IL-1-Dependent Pathway. PLoS pathogens. 2016; 12(5):e1005589. [PubMed: 27148737]
124. Spanier JA, Nashold FE, Mayne CG, Nelson CD, Hayes CE. Vitamin D and estrogen synergy in Vdr-expressing CD4(+) T cells is essential to induce Helios(+)FoxP3(+) T cells and prevent autoimmune demyelinating disease. Journal of neuroimmunology. 2015; 286:48–58. [PubMed: 26298324]
125. Okada H, Nakajima T, Sanezumi M, Ikuta A, Yasuda K, Kanzaki H. Progesterone enhances interleukin-15 production in human endometrial stromal cells in vitro. The Journal of clinical endocrinology and metabolism. 2000; 85(12):4765–70. [PubMed: 11134140]
126. Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. Journal of Experimental Medicine. 2005; 202(7):907–12. [PubMed: 16203864]
127. Oelert T, Papatriantafyllou M, Pougialis G, Hammerling GJ, Arnold B, Schuler T. Irradiation and IL-15 promote loss of CD8 T-cell tolerance in response to lymphopenia. Blood. 2010; 115(11): 2196–202. [PubMed: 20075162]
128. Medawar PB. Some Immunological and Endocrinological Problems Raised by the Evolution of Viviparity in Vetebrates. Symposia for the Soc Exp Biol. 1954; 7:320–328.
129. Burnet FM. The immunological significance of the thymus: an extension of the clonal selection theory of immunity. Australasian annals of medicine. 1962; 11:79–91. [PubMed: 13874950]
130. Bretscher P, Cohn M. A theory of self-nonself discrimination. Science. 1970; 169(3950):1042–9. [PubMed: 4194660]
131. Bonney EA, Matzinger P. The maternal immune system's interaction with circulating fetal cells. Journal of immunology (Baltimore, Md: 1950). 1997; 158(1):40–7.
132. Mold JE, Michaelsson J, Burt TD, Muench MO, Beckerman KP, Busch MP, et al. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science. 2008; 322(5907):1562–5. [PubMed: 19056990]
133. Bonney EA, Matzinger P. Much IDO about pregnancy. Nature medicine. 1998; 4(10):1128–9.
134. Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B, et al. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science. 1998; 281(5380):1191–3. [PubMed: 9712583]
135. Matzinger P. Tolerance, danger, and the extended family. Annual review of immunology. 1994; 12:991–1045.
136. Anderson CC, Matzinger P. Danger: the view from the bottom of the cliff. Semin Immunol. 2000; 12(3):231–8. discussion 257–344. [PubMed: 10910744]
137. Bonney EA. Preeclampsia: a view through the danger model. Journal of Reproductive Immunology. 2007; 76(1–2):68–74. [PubMed: 17482268]
138. Matzinger P, Kamala T. Tissue-based class control: the other side of tolerance. Nat Rev Immunol. 2011; 11(3):221–230. [PubMed: 21350581]
139. Robertson SA, Christiaens I, Dorian CL, Zaragoza DB, Care AS, Banks AM, et al. Interleukin-6 is an essential determinant of on-time parturition in the mouse. Endocrinology. 2010; 151(8): 3996–4006. [PubMed: 20610570]
140. Janeway CA Jr. The immune system evolved to discriminate infectious nonself from noninfectious self. Immunology today. 1992; 13(1):11–6. [PubMed: 1739426]
141. Medzhitov R, Janeway CA Jr. Decoding the patterns of self and nonself by the innate immune system. Science. 2002; 296(5566):298–300. [PubMed: 11951031]
142. Medzhitov R. Approaching the Asymptote: 20 Years Later. Immunity. 2009; 30(6):766–775. [PubMed: 19538928]

143. Elovitz MA, Wang Z, Chien EK, Rychlik DF, Phillippe M. A new model for inflammation-induced preterm birth: the role of platelet-activating factor and Toll-like receptor-4. The American journal of pathology. 2003; 163(5):2103–11. [PubMed: 14578208]

144. Kabyemela E, Goncalves BP, Prevots DR, Morrison R, Harrington W, Gwamaka M, et al. Cytokine profiles at birth predict malaria severity during infancy. PloS one. 2013; 8(10):e77214. [PubMed: 24130857]

145. Stout MJ, Conlon B, Landeau M, Lee I, Bower C, Zhao Q, et al. Identification of intracellular bacteria in the basal plate of the human placenta in term and preterm gestations. American journal of obstetrics and gynecology. 2013; 208(3):226e1–7. [PubMed: 23333552]

146. Cao B, Mysorekar IU. Intracellular bacteria in placental basal plate localize to extravillous trophoblasts. Placenta. 2014; 35(2):139–42. [PubMed: 24439469]

147. Kline KA, Schwartz DJ, Gilbert NM, Hultgren SJ, Lewis AL. Immune modulation by group B Streptococcus influences host susceptibility to urinary tract infection by uropathogenic Escherichia coli. Infection and immunity. 2012; 80(12):4186–94. [PubMed: 22988014]

148. Cardenas I, Means RE, Aldo P, Koga K, Lang SM, Booth CJ, et al. Viral infection of the placenta leads to fetal inflammation and sensitization to bacterial products predisposing to preterm labor. Journal of immunology (Baltimore, Md: 1950). 2010; 185(2):1248–57.

149. Sugimoto J, Schust DJ. Review: human endogenous retroviruses and the placenta. Reproductive sciences (Thousand Oaks, Calif). 2009; 16(11):1023–33.

150. Morris EA, Hale SA, Badger GJ, Magness RR, Bernstein IM. Pregnancy induces persistent changes in vascular compliance in primiparous women. Am J Obstet Gynecol. 2015; 212(5): 633e1–6. [PubMed: 25576820]

151. Hilgers RH, Bergaya S, Schiffers PM, Meneton P, Boulanger CM, Henrion D, et al. Uterine artery structural and functional changes during pregnancy in tissue kallikrein-deficient mice. Arteriosclerosis, thrombosis, and vascular biology. 2003; 23(10):1826–32.

152. Clapp JF 3rd, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. The American journal of cardiology. 1997; 80(11):1469–73. [PubMed: 9399724]

153. Euser AG, Cipolla MJ. Resistance artery vasodilation to magnesium sulfate during pregnancy and the postpartum state. American journal of physiology Heart and circulatory physiology. 2005; 288(4):H1521–5. [PubMed: 15576433]

154. Bruckmann A, Seeliger C, Lehmann T, Schleussner E, Schlembach D. Altered retinal flicker response indicates microvascular dysfunction in women with preeclampsia. Hypertension. 2015; 66(4):900–5. [PubMed: 26283041]

155. Pruthi D, Khankin EV, Blanton RM, Aronovitz M, Burke SD, McCurley A, et al. Exposure to Experimental Preeclampsia in Mice Enhances the Vascular Response to Future Injury. Hypertension. 2015; 65(4):863–870. [PubMed: 25712723]

156. Garovic VD, Bailey KR, Boerwinkle E, Hunt SC, Weder AB, Curb D, et al. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. Journal of Hypertension. 2010; 28(4):826–33. [PubMed: 20087214]

157. Ngo A, Chen J, Figtree G, Morris J, Roberts C. Preterm birth and future risk of maternal cardiovascular disease – is the association independent of smoking during pregnancy? BMC Pregnancy Childbirth. 2015; 15(1):1–11. [PubMed: 25591791]

158. Robbins CL, Hutchings Y, Dietz PM, Kuklina EV, Callaghan WM. History of preterm birth and subsequent cardiovascular disease: a systematic review. American Journal of Obstetrics and Gynecology. 2014; 210(4):285–297. [PubMed: 24055578]

159. Bonamy A-KE, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth Characteristics and Subsequent Risks of Maternal Cardiovascular Disease: Effects of Gestational Age and Fetal Growth. Circulation. 2011; 124(25):2839–2846. [PubMed: 22124377]

160. Gunderson EP, Chiang V, Pletcher MJ, Jacobs DR, Quesenberry CP, Sidney S, et al. History of Gestational Diabetes Mellitus and Future Risk of Atherosclerosis in Mid-life: The Coronary Artery Risk Development in Young Adults Study. Journal of the American Heart Association. 2014; 3(2)

161. Ness RB, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, et al. Number of Pregnancies and the Subsequent Risk of Cardiovascular Disease. New England Journal of Medicine. 1993; 328(21):1528–1533. [PubMed: 8267704]

162. Adams KM, Yan Z, Stevens AM, Nelson JL. The Changing Maternal "Self" Hypothesis: A Mechanism for Maternal Tolerance of the Fetus. Placenta. 2007; 28(5–6):378–382. [PubMed: 16934327]

163. Adams KM, Nelson JL. Microchimerism: An Investigative Frontier in Autoimmunity and Transplantation. JAMA. 2004; 291(9):1127–1131. [PubMed: 14996783]

164. Lazarus JH, Parkes AB, Premawardhana LD. Postpartum thyroiditis. [Review] [55 refs]. Autoimmunity. 2002; 35(3):169–73. [PubMed: 12389641]

165. Ansari AA, Fett JD, Carraway RE, Mayne AE, Onlamoon N, Sundstrom JB. Autoimmune mechanisms as the basis for human peripartum cardiomyopathy. Clinical reviews in allergy & immunology. 2002; 23(3):301–24. [PubMed: 12402414]

166. Smith KA, Popmihajlov Z. The quantal theory of immunity and the interleukin-2-dependent negative feedback regulation of the immune response. Immunological reviews. 2008; 224:124–40. [PubMed: 18759924]

167. Schluns KS, Kieper WC, Jameson SC, Lefrancois L. Interleukin-7 mediates the homeostasis of naive and memory CD8 T cells in vivo. Nature immunology. 2000; 1(5):426–32. [PubMed: 11062503]

168. Sprent J, Surh CD. T cell memory. Annual review of immunology. 2002; 20:551–79.

169. Mueller SN, Ahmed R. High antigen levels are the cause of T cell exhaustion during chronic viral infection. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(21):8623–8. [PubMed: 19433785]

170. Gupta PK, Godec J, Wolski D, Adland E, Yates K, Pauken KE, et al. CD39 Expression Identifies Terminally Exhausted CD8+ T Cells. PLoS pathogens. 2015; 11(10):e1005177. [PubMed: 26485519]

Key points

- Elements of host defense, innate and adaptive immunity alter during pregnancy.
- The maternal immune system meets the needs for both tolerance and protection through complex regulation but not suppression.
- Classical as well as non-classical models of immune system activation and tolerance can explain elements of maternal tolerance.