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Role of Hormones in the Pregnancy and Sex-Specific Outcomes to Infections with Respiratory Viruses

Orlando Cervantes[1,2,*], **Irene Cruz Talavera**[1,3], **Emma Every**[4], **Brahm Coler**[2,5], **Miranda Li**[2,6], **Amanda Li**[2,7], **Hanning Li**[2], **Kristina Adams Waldorf**[1,2,*]

[1]Department of Global Health, University of Washington, Seattle, Washington, United States of America

[2]Department of Obstetrics and Gynecology, University of Washington, Seattle, Washington, United States of America

[3]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America

[4]University of Washington School of Medicine, Spokane, Washington, United States of America

[5]Elson S. Floyd College of Medicine, Washington State University, Spokane, Washington, United States of America

[6]Department of Biological Sciences, Columbia University, New York City, New York, United States of America

[7]Case Western Reserve, Cleveland, Ohio, United States of America

Summary

Pregnant women infected with pathogenic respiratory viruses, like influenza A viruses (IAV) and coronaviruses, are at higher risk for mortality, hospitalization, preterm birth and stillbirth. Several factors are likely to contribute to the susceptibility of pregnant individuals to severe lung disease including changes in pulmonary physiology, immune defenses and effector functions of some immune cells. Pregnancy is also a physiologic state characterized by higher levels of multiple hormones that may impact the effector functions of immune cells, such as progesterone, estrogen, human chorionic gonadotropin, prolactin and relaxin. Each of these hormones acts to support a tolerogenic immune state of pregnancy, which helps prevent fetal rejection, but may also contribute to an impaired antiviral response. In this review, we address the unique role of adaptive and innate immune cells in the control of pathogenic respiratory viruses and how pregnancy and specific hormones can impact their effector actions. We highlight viruses with sex-specific differences in infection outcomes and why pregnancy hormones may contribute to fetal protection but aid the virus at the expense of the mother's health.

[*]**Co-Corresponding Authors:** Orlando Cervantes, BS and Kristina Adams Waldorf, MD; University of Washington, Box 358070, 750 Republican Street, Seattle, WA, 98109; Telephone: 206-616-5258; Fax: 206-543-3915; adamsk@uw.edu and ocervant@uw.edu. Note that both co-corresponding authors have the same physical address and telephone numbers.

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Introduction

Although essential to human survival, pregnancy remains one of the most poorly understood biological and immunological events. High mortality rates of pregnant individuals during the coronavirus disease 2019 (COVID-19) pandemic have underscored how changes in immune function during pregnancy can leave young individuals extremely vulnerable to viral infections.[1–6] Pregnant people are also vulnerable to pandemic influenza A viruses (IAV) with increased rates of hospitalization, mortality, preterm birth, stillbirth and neonatal death.[7–17] How sex hormones impact immune function is understudied, but of paramount importance to understanding pregnancy- and sex-specific differences in respiratory infection outcomes. Pregnancy represents an extreme hormone milieu. Compared to the non-pregnant state, a pregnant individual will experience large increases in corticosteroids (20-fold)[18], progesterone (6–8-fold)[19], estrogen (estriol: 1,000-fold; estradiol/estrone: 6–100-fold)[20,21], prolactin (10–20-fold)[22], relaxin (>10-fold)[23] and human chorionic gonadotropin (hCG, only made during pregnancy). A woman will produce more estrogen in a single pregnancy than during the rest of her entire lifetime. This profound hormonal environment shapes immune cell function and is instrumental in driving both pregnancy- and sex-specific differences in the outcome of respiratory viral infections.

In pregnancy, many sex hormones function to promote immune tolerance to enable the mother to tolerate a semi-allogeneic fetus without rejection.[24–27] However, this tolerogenic state comes at the expense of antiviral immunity, as pregnant women are more vulnerable to many viral respiratory pathogens versus non-pregnant women. In this review, we explore the intersection between hormones, immunity, and pregnancy to provide insight into both pregnancy- and sex-specific differences in the outcome to respiratory virus infection.[1–17] First, we address the known pregnancy- and sex-specific differences in the outcome to respiratory virus infections, which may be related in part to differences in sex hormones. Secondly, we address the impact of hormonal changes on distinct immune cell subsets focusing on adaptive immunity (T and B cell subsets) with a more limited discussion of innate immunity. Finally, we discuss how sex steroids can impair adaptive immune function to specific respiratory viruses, focusing on IAV, respiratory syncytial virus (RSV) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Throughout the review, we discuss hypotheses linking hormone-mediated changes during pregnancy and the vulnerability of pregnant people to severe disease from respiratory viral infections.

Pregnancy- and Sex-Specific Differences in Outcomes to Respiratory Virus Infection

Many respiratory viral infections are associated with greater mortality and more severe lung disease in pregnant people. In this section, we focus on the pregnancy- and sex-specific differences in outcomes to influenza A viruses and highly pathogenic coronaviruses, for

which there is the most published data. We acknowledge that pregnancy-, sex- and gender-specific differences in health and disease outcomes are the result of numerous factors including sex hormones, genetics, sex-linkage of immune response genes, behaviors (e.g., hand washing), lifestyle, nutritional habits, occupation and perceived stress and pain; these factors may also modify epigenetics that modulates gene expression and biological phenotypes.[28] Although the foundation for these differences may be multi-factorial, they establish a framework for focusing on the impact of sex hormones on diverse immune cell populations.

Influenza A Viral Infections: Pregnancy- and Sex-Specific Differences in Outcomes

IAV is an orthomyxovirus, which evades adaptive immunity by rapidly acquiring mutations in its surface-proteins, neuraminidase (NA) and hemagglutinin (HA).[29] Changes in mutations can result in antigenic drift, which represent minor changes to the NA and HA proteins that may result in the need to annually revise the seasonal influenza vaccine. Occasionally, antigenic shift occurs, which describes larger changes in the NA and HA proteins occurring though genomic reassortment that can contribute to influenza pandemics. In all IAV pandemics since 1918, pregnant people have been described as a vulnerable population to IAV infection with higher rates of mortality, hospitalization, preterm birth and stillbirth.[7–17]

The first reports of pregnancy as a high-risk condition for severe IAV disease occurred during the 1918–1919 IAV pandemic (‘Spanish flu’). An analysis of death certificates in London found that the mortality rate for all women (15–49 years) was 4.9/1,000, but in pregnancy was 5.3–5.7/1,000.[30] As many pregnant women who died did not have their pregnancy noted on their death certificate, this is likely an underestimate. Similarly, in the U.S., reports of pregnancy mortality obtained from a questionnaire of obstetricians surveying 1,350 pregnancies found that 678 of these patients developed pneumonia (50%), 365 died (27%) and there were high rates of stillbirths.[31] Reports of higher mortality, hospitalization, preterm birth and stillbirth also occurred during the 1957 pandemic (‘Asian flu’) and the more recent 2009 H1N1 pandemic (‘swine flu’).[7,8,11,13–17,28,32–34] The postpartum period after delivery represents a particularly high-risk time for mortality due to IAV.[35] This is a time of rapid physiological changes, fluid shifts and a precipitous drop in sex hormones. In a systematic review of more than 610,000 participants identified the women less than four weeks postpartum as one of the few risk factors associated with a significantly increased risk of death from pandemic influenza [odds ratio: 4.43, 95% Confidence Interval (C.I.): 1.24–15.81].[35] The impact of changes in sex hormones and other physiological changes on the immunity and health of postpartum women is unknown.

Sex-specific differences in the outcomes to IAV infections have been observed throughout the last pandemics. Young adult women typically have a higher hospitalization rates and mortality to pandemic influenza and avian influenza (H5N1).[36–40] However, at the extremes of age, men have been reported to have higher IAV-mortality and morbidity. Japanese males younger than 20 and older than 80 were reported to have higher influenza morbidity during the H1N1 2009 pandemic than Japanese females.[41] These sex difference in IAV infection outcomes also translate to the immune response to IAV vaccination. In reproductive age

adults, women tend to develop higher antibody titers than men to the seasonal IAV vaccine, which has been attributed to higher estrogen levels and X-linked immune responses genes (e.g., toll-like receptor 7).[42,43] [44] In summary, sex-specific differences are age dependent and are reflected in both the IAV-associated mortality and vaccination efficacy.

Coronavirus Infections: Pregnancy- and Sex-Specific Differences in Outcomes

Although pregnant people tend to be young and healthy, they are highly vulnerable to severe COVID-19 from an infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19[1,5,45–49]. Although pregnant individuals were identified early in the IAV H1N1 2009 pandemic as a high-risk and vulnerable group in the U.S.[11,13], this was not recognized for the first, critical eight months of the COVID-19 pandemic. A broader view of the immunologic state of pregnant individuals, which is shaped in part by sex hormones, would suggest that pregnancy is a state that is likely to be more susceptible to viral infections. Indeed, pregnant individuals have a prolonged COVID-19 symptomatic course in comparison to reported outcomes in young adults; pregnant individuals reported 37 days (median time) until symptom resolution and 25% reported symptoms for more than 8 weeks.[50] In June of 2020, a population-based study by the U.S. Centers for Disease Control (CDC) found that pregnant patients with SARS-CoV-2 infections were at higher risk for hospitalization, mechanical ventilation and ICU admission, but mortality rates were similar between pregnant and non-pregnant reproductive age women (0.2%).[51] Subsequently, another CDC study including more cases found an increased risk of mortality among pregnant women versus non-pregnant women with SARS-CoV-2[52], prompting the CDC to revise public health guidance and indicate that pregnant women are at risk for severe COVID-19 disease.[45] Other population-based studies support that pregnancy is a vulnerable state for SARS-CoV-2 infection and linked to adverse maternal, pregnancy and neonatal outcomes.[4,6,49,53]

A male bias in COVID-19 mortality and intensive care unit admission has been reported in a meta-analysis of more than 3 million global cases of COVID-19.[54] Although there was no difference in the proportion of females and males with COVID-19 disease, males had a 2.8-fold higher odds of requiring intensive care and 1.4-fold higher odds of death. To understand how sex differences in COVID-19 outcomes might be explained immunologically, longitudinal blood samples from hospitalized men and women were studied to evaluate immunophenotypes, cytokines and SARS-CoV-2 viral load.[55] In males, a greater plasma IL-8 and IL-18 level and higher frequencies of activated non-classical monocytes were observed compared to females. However, females had greater T cell activation than males. A patient's age was correlated negatively with a poor T cell response associated with adverse outcomes in males, but not females. However, higher levels of cytokines were linked to worse disease in females, but not in males. Whether these sex-specific differences in immunologic correlates of disease are also linked to sex hormones is unknown.

The Changing Hormonal Landscape Across Pregnancy

The receptors for pregnancy hormones can be found on most immune cells, enabling immunomodulation to be tightly coupled to reproduction and pregnancy.[56] Dramatic changes to the hormonal milieu during pregnancy are designed to enhance survival and tolerance of the semi-allogeneic fetus. One of the earliest physiologic changes in pregnancy is the rise in the hormone hCG, which acts to quickly promote an immunologic state conducive to fetal survival and growth. hCG is produced initially by the blastocyst and begins to rise at the time of embryo implantation, doubles approximately every 2–3 days reaching peak levels in the first trimester followed by a gradual decline until term. Relaxin, a hormone that follows a similar trajectory to hCG peaks in the first trimester and then slowly declines until term. In contrast, there is a gradual rise in estrogen (90% is estriol), progesterone and prolactin into the third trimester. Progesterone plays two critical roles in pregnancy by preparing the endometrial lining for implantation of the embryo and maintaining uterine quiescence until the time of birth. Progesterone is initially produced by the ovaries and then taken over by the placenta after 10 weeks gestation. During pregnancy, the production of progesterone gradually increases from non-pregnant levels of 1–50 nmol/L (depending on menstrual cycle phase) to serum concentrations between 175 and 811 nmol/L in the third trimester of pregnancy.[57] Although variation in some hormone levels have been linked to the timing of labor onset (i.e., preterm birth or post-term birth)[58,59], whether pregnant individuals at the extremes of sex hormone production might be susceptible to viral infections due to differences in immunomodulation are unknown. The estradiol level significantly increases during pregnancy ranging from 110 to 440 pmol/L during the follicular phase, up to 1800 pmol/L during the first trimester, up to 75,000 pmol/L during the second trimester, and up to 136,000 pmol/L during the third trimester.[60] In a murine model, the increased morbidity due to influenza infection was shown to correlate with levels of circulating estrogen, which are highest in the third trimester and correlate with the period of greatest disease severity in pregnant women.[61]

T cells: Intersection of Hormones, Pregnancy and Immune Function in Distinct T Cell Subsets

T cells provide cross-reactive cellular immunity to various pathogens via recognition of conserved antigens presented by antigen-presenting cells. CD4+ effector T cells, also known as T helper cells, play a major role in mediating cellular immunity and also suppressing immune functions of some cells in their environment to limit tissue damage. Helper T cells are classified into several distinct subsets, only some of which are covered in this review that have key roles in pregnancy tolerance, viral respiratory infections and are affected by sex hormones: Treg, Th17, Th1, and Th2. CD4- and CD8- γδ T cells are another key cell type that plays important roles in immune protection in mucosal tissues. These T cell subsets are distinguished by their master transcription factors and respective cytokine secretomes.[62,63] The balance among these subsets is of critical importance to favor fetal tolerance, which requires a modulation of maternal immunity in the periphery and at the maternal-fetal interface. However, a shift in the balance of these subsets, driven in part by sex hormones, may be detrimental to clearing viral infections. Here, we synthesize literature

on the hormonal impact on immunity in pregnancy and how this secondarily may impair antiviral immunity.

Regulatory T Cells

Role of CD4+FoxP3+ Regulatory T cells in Immunity and Pregnancy

Regulatory T cells (Tregs) are essential for self-tolerance, prevention of autoimmunity, regulation of inflammatory immune responses, and for the establishment and maintenance of pregnancy (Fig. 1). Regulatory T cells (Tregs) are a subset of $CD4^+$ T cells characterized by their expression of the transcription factor forkhead box P3 (FoxP3) and their ability to regulate inflammatory responses, establish self-tolerance, and suppress effector T cells and other immune cells.[64,65] FoxP3 is essential for Treg's immunosuppressive function and is the master regulator of Treg development, function, and differentiation.[66,67] Tregs are critical immune mediators of tolerance, as patients suffering from fatal immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) and scurfy mice lacking functional expression of FoxP3 suffer from severe autoimmunity and dysregulated effector T cell responses.[68,69] Tregs have been most extensively studied in the thymus where they develop, and in peripheral lymphoid organs. However, there is a growing body of work characterizing phenotypically distinct tissue Tregs with unique roles in non-lymphoid tissue compartments such as visceral adipose tissue, skin, muscle, intestines, lungs, and genitourinary tract.[70–74] There are two main subsets of Tregs: natural $Helios^+$ $NRP1^+$ Tregs (nTreg) develop in the thymus and primarily involved in tolerance to self and environmental antigens, whereas induced $Helios^-$ Tregs (iTreg) arise in periphery from $CD4^+$ $FoxP3^-$ T cells in response to high inflammation or after antigen-exposure, often in the context of infection.[75–78] The differentiation of iTreg is dependent on many factors, including the strength of TCR signaling, signals from APCs, inflammatory responses, and the local cytokine environment.[75–77,79] Though distinguishing these subsets *in vivo* and *ex vivo* has proven difficult, as knowing which markers should be used to differentiate them has been unclear.[80]

Tregs utilize various mechanisms of immune suppression to regulate immune responses and control inflammation (Fig. 1). They express anti-inflammatory cytokines, such as TGF-β and IL-10.[81,82] Tregs can also suppress interleukin 2 (IL-2) T cell consumption through high expression of the IL-2 receptor (CD25) and directly kill target cells in a contact-dependent manner through the expression of granzyme B.[83,84] Importantly, granzyme B^+ Tregs have been shown to play a critical role in controlling lung inflammation and tissue damage during acute RSV infection in mice.[85] In addition to their immunosuppressive capabilities Tregs also contribute to tissue healing and integrity through the expression of epidermal growth factor receptor ligands, such as amphiregulin and keratinocyte growth factor, during viral infection and or tissue injury.[86–89] Not only are Tregs essential for self-tolerance, preventing autoimmunity, and regulating inflammatory immune responses, but they are also required at the maternal-fetal interface during implantation and throughout pregnancy.

Changes in Treg Frequency in Response to Pregnancy and Sex Hormones

hCG, produced by the blastocyst and syncytiotrophoblast during pregnancy, has been shown to increase Treg frequency, promote recruitment to the endometrium, and enhance suppressive Treg function in mice and humans[90–93]. The location and number of Tregs fluctuates first in response to seminal antigens and the blastocyst during implantation, and later due to changing hormonal levels throughout pregnancy with a rapid decrease systemically in the third trimester before birth[94–96]. Tregs are actively recruited and accumulate locally in the female reproductive tract and draining lymph nodes, as early as first exposure to sperm and male seminal fluid antigens, to mediate tolerance to the fetus.[97,98]. In fact, depletion or decrease of Tregs, locally and systemically, before implantation results in a failure of gestation and immunological rejection of the fetus in mice and humans.[99,100] The number and frequency of Tregs in peripheral blood also fluctuates throughout the menstrual cycle and peaks just before ovulation, correlating with serum estrogen levels, before dramatically decreasing in the luteal phase.[99–101] Once pregnant, maternal FoxP3$^+$ Tregs greatly increase in circulating blood and locally at the maternal-fetal interface in the placenta during healthy pregnancies[102,103]. Tregs are known mediators of fetal tolerance crucial for implantation and successful pregnancy.[100]

There is increasing evidence that sex hormones induce expansion and differentiation of Tregs and promote their strong immunosuppressive functions. Estra enhances the expansion of Tregs, their ability to effectively suppress the activation and proliferation of effector T cells, increases *FoxP3* expression, and decreases production of IL-17 by Th17 cells in mice.[26,104] Estriol, which is not present in non-pregnant females and produced at high concentrations by the placenta in the first trimester, also increases the frequency of Tregs, suppresses Th17 cell expansion, and enhances the generation of iTreg *in vitro*.[105] Progesterone has been found to promote the differentiation of iTreg with improved stability *in vitro*.[106] However, elevated levels of progesterone during the second and third trimesters have been correlated with reduced activity and expansion of Tregs in humans, though the opposite has been reported in mice.[27,104,107] Progesterone is also present at high levels in human cord blood where it has been shown to drive a shift towards immunosuppressive Tregs while simultaneously preventing differentiation of Th17 cells.[106] These findings demonstrate the importance of sex-specific hormones in the localization and expansion of Tregs.

The large systemic expansion of Tregs during pregnancy suggests that many may be peripherally induced iTregs. A couple of mouse studies proposed that both nTregs and peripheral iTregs are important in pregnancy, as adoptive transfer of pregnancy induced or TGF-β induced iTregs prevented abortion during allogenic pregnancy in mice.[108,109] One study found that in normal human pregnancies clonally expanded iTregs are induced by CD14$^+$DC-Sign$^+$ antigen presenting cells and are the dominant subset located in the decidua. Additionally, this process of iTreg induction was defective in pre-eclampsia cases resulting in poor iTreg cell induction in the decidua.[110] Similarly, another research group found that clonally expanded antigen-specific effector memory Tregs were found in the decidua, but not in peripheral blood in humans. Furthermore, these decidual clonally expanded effector Tregs were highest in third trimester in healthy women, and lower in pre-eclampsia

cases.[111,112] Taken together, these reports indicate that iTreg induction plays a large role in the systemic and local increase of Tregs during pregnancy, and in maintaining tolerance to the fetus.

Tregs and Viral Respiratory Infections

Despite their ability to suppress pro-inflammatory anti-viral responses, Tregs play a crucial role in healing tissue damage, orchestrating antigen-specific responses, and controlling systemic and local inflammatory responses during viral respiratory infections.[88,113–115] During influenza A infection in mice, amphiregulin-expressing lung Tregs play a major role in tissue repair of cell-mediated damage early in infection resulting in lower lung pathology scores than mice with amphiregulin-deficient Tregs, despite no difference in viral load and clearance.[88] Interestingly, another study showed that estriol treatment of female mice following influenza A infection resulted in a skew towards Th2 responses and an increase of Treg frequencies in lung tissue and associated with decreased disease severity, though viral replication and clearance was unaffected.[116] Tregs have also been shown to promote influenza specific Tfh and germinal center responses by controlling IL-2 availability.[117,118] Additionally, the Tregs that accumulate in the lung during influenza infection seem to persist in the tissue after resolution as long-lived antigen-specific memory cells.[72] However, the presence of Tregs does not always correlate with better disease outcomes, as one study observed that the altered increase and expansion of suppressive Tregs following influenza infection in aged mice when compared to young mice, resulted in delayed and decreased antigen-specific CD8 T cell responses.[119] Therefore, in addition to gender, age is also an important factor in the function and expansion of Tregs during infection.

In respiratory syncytial virus (RSV), disease severity and tissue damage of the lungs has been linked to functional and phenotypic differences in the Treg population. In RSV infected mice, CTLA-4$^+$ Tregs rapidly accumulate and proliferate in draining lymph nodes and lungs. Furthermore, *in vivo* depletion of Tregs prior to infection resulted in delayed viral clearance, exacerbated disease, delayed recruitment of antigen specific T cells to the lung, and increased frequency of IFN-γ and TNF (Tumor Necrosis Factor)-α expressing cytotoxic T cells.[115] In another study, Treg depleted mice had enhanced viral clearance but also experienced increased weight loss, increased cytokine and chemokine levels, and increased T cell activation and cellular infiltration of the lungs. In the same study, when Treg numbers and activity was boosted using IL-2 immune complexes, inflammation was decreased and lung Tregs from infected mice expressed granzyme B. Furthermore, selective loss of granzyme B expression in Tregs resulted in higher cell infiltration into the lungs.[85] In humans, children with severe RSV infection have significantly reduced activated Tregs in peripheral blood and decreased IL-33 protein in nasal washes, a cytokine crucial in maintaining Tregs in mucosal tissues.[120]

Like in RSV infection, disease severity and lung pathology in SARS-CoV2 have been associated with dysregulated immune responses, including a deficit of Tregs at the site of infection. A recent study showed that an increased frequency of activated Tregs in peripheral blood was associated with severe disease in hospitalized COVID-19 patients, but not in RSV or influenza patients. Furthermore, they found that increased levels of

CXCL10 and CXCL9 in peripheral blood might retain CXCR3$^+$ Tregs in the periphery from homing to the lungs.[121] Another study also reported that COVID-19 patients had decreased frequency and number of Tregs in peripheral blood samples that were negatively correlated with CD4 and CD8 T cell frequencies.[122] Similarly, others revealed that an increased frequency of circulating Tregs characterized by overexpression of immunosuppressive markers and reduced amphiregulin expression correlated with severe disease and predicted mortality.[123,124] Others have shown that severe COVID-19 airways have reduced Treg frequencies compared to healthy airways.[125] Additionally, elevated pre-infection Treg frequencies at steady-state correlated with better protection and lower viral load upon SARS-CoV2 infection in a mouse model.[126] Therefore, it is reasonable to speculate that defective trafficking, localization, and reduced tissue healing function in Tregs correlates with worse disease outcomes during viral respiratory infections.

During pregnancy, there is a general attenuation of the maternal immune system skewing towards anti-inflammatory responses. Dysregulation of the Th1/Th2 and Th17/Treg balance and an increase in pro-inflammatory responses during viral respiratory infection is associated with worse disease outcomes and complications in pregnant people.[127] A mouse study found that pregnant mice infected with IAV 2009 pH1N1 had increased mortality and displayed signs of reduced epithelial regeneration and impaired lung repair, as well as elevated levels of Tregs in the lungs despite no significant increase in viral load. There was an increased infiltration of pulmonary neutrophils and macrophages strongly correlated with elevated mortality, as well as increased nitrites and several proinflammatory cytokines involved in cell recruitment to the lungs.[128] It is reasonable to consider that this dysregulated inflammatory immune response is likely what caused increased mortality in pregnant mice and recruited an already expanded Treg population to the lungs. In the case of SARS-CoV2 infection in pregnancy, several recent studies have shown that COVID-19 patients have a significant reduction in Treg numbers and frequencies, causing an imbalance in the Treg/Th17 ratio.[129–131] Therefore, severe disease outcomes in pregnant people during viral respiratory infection could be due to uncontrolled systemic inflammation and a disruption of the Treg/Th17 balance rather than a Treg-driven inhibition of anti-viral immune responses.

Sex Differences in the Treg Population in Non-pregnant Women and Men

In humans, the fact that females have a lower frequency of circulating Tregs than men has been suggested as a reason for an increased predisposition to autoimmune disease.[132] Androgens have been implicated in modulating Treg responses in the context of autoimmune disease. One study showed that testosterone replacement therapy in male mice inhibited the development of autoimmune orchitis, had an immunosuppressive effect on the immune system, significantly reduced the number of CD4 conventional T cells, and induced a significant increase in the number of Tregs in the testis. Additionally, *in vitro* testosterone treatment of naïve T cells led to the expansion and differentiation of an iTreg subset with suppressive functions.[133] The same research group later showed that androgen stimulation of Tregs leads to increased transcription and expression of FoxP3 through modification of histone H4 acetylation. This androgen-dependent increase in FoxP3 expression occurred in T cells from ovulating women but not from men, indicating sex-specific androgen signaling.[134] Another recent study showed that testosterone significantly increased FoxP3

expression in Tregs from females with systemic lupus erythematosus and that plasma concentrations of testosterone positively correlated with higher FoxP3 Treg expression.[135] In male mice, visceral adipose tissue was found to be enriched for Tregs in comparison to females. Additionally, increased inflammation in male visceral adipose tissue facilitated recruitment and expansion of Tregs cells via the CCL21-CCR2 axis and an androgen-regulated IL-33 stromal cell population, respectively.[136] Interestingly this phenomenon is different in obesity, wherein in visceral adipose tissue the obese male mice have reduced Tregs, and obese female mice have increased Tregs. This increase in female visceral adipose tissue Tregs was abrogated in ovariectomized obese mice but restored upon estrogen supplementation, suggesting that estrogen may attenuate obesity-associated chronic inflammation. Furthermore, chemokine expression revealed a different localization system for female visceral adipose tissue Tregs which trafficked to the tissue via CCL24, CCR6, and CXCR3 signaling.[137]

In summary, Tregs control pro-inflammatory effector T cell responses, aid in preventing tissue injury, and are essential mediators of tolerance to self and fetal-alloantigens. Their localization, expansion, and immunosuppressive functions are influenced by fluctuating hormone levels during pregnancy. Importantly, the expansion of Tregs locally and systemically is required for a healthy and successful pregnancy. Dysregulated Treg responses or an imbalance in the Treg/Th17 ratio may be a significant factor in pregnancy complications and adverse outcomes to viral respiratory infections.

Th17 Cells

Th17 Cells and the Influence of Sex Hormones

Th17 cells are a CD4+ T helper lineage that are characterized by retinoic acid receptor-related orphan receptor transcription factors (RORγt and RORα) and the production of pro-inflammatory cytokines (IL-17, IL-21, IL-22; Fig. 2).[138,139] Naive CD4+ T cells differentiate into Th17 cells after stimulation with IL-6 and TGF-β. However, there has also been a subpopulation of CD39+ CD73+ Th17 with immunosuppressive functions known as supTh17. The supTh17 cells help produce adenosines from extracellular nucleotides with ectonucleotidases.[140,141] Progesterone has been found to promote the proliferation of supTh17, which may play a role in lung repair in influenza-infected mice.[142]

Hormones crucial for a successful pregnancy impact the function and proliferation of Th17 cells. Work with progesterone showed a suppressive role in inflammation and as an element for milder disease outcomes. Within the umbilical cord, progesterone can bias the naive CD4+ T cells towards differentiation into Tregs and away from their natural bias towards Th17.[106,143] Progestogens can downregulate the secretion of pro-inflammatory cytokines tied to a Th1/Th17 response whilst supporting Th2 cytokine secretion in peripheral blood from patients with unexplained recurrent spontaneous miscarriages, which already have a pro-inflammatory immune environment.[144] In pregnant cows, progesterone decreased the expression of RORγt and IL-17, but upregulated IL-4 (Th2 differentiation) creating conditions necessary for a successful pregnancy.[145] Medroxyprogesterone acetate, a synthetic progestogen, suppresses the expression of RORγt, IL-22, and IL-17, all key to Th17 function.[144,146] Estradiol at estrus levels in mice was enough to downregulate the

Th17 immune response to extracellular pathogens and sperm.[147,148] However, it's possible that both estradiol and progesterone may synergistically promote IL-17 and IL-23 secretion, especially in the context of a runaway Th2 immune environment.[149] A possible mechanism for this could be dendritic cells stimulated by estradiol secrete IL-1 which in turn can signal for the proliferation of Th17 cells to combat infection.[150] Estradiol at pregnancy levels suppresses the differentiation of Th17 cells from CD4+ via a PD-1 signaling pathway.[151] Estrogen deficiency can have deleterious effects in the nervous system as Th17 cells can promote aneurysm formation and rupture.[152] Estrogen can thus have a regulatory role in Th17 localization.[153] Pregnancy and pregnancy-like levels of estrogen can downregulate Th17 transcription factors and cytokines and upregulate Treg/Th2 transcription factors.[154] Estriol, at pregnancy-like levels, dampens Th17 responses by increasing the Treg/Th17 ratio and IL-10 secretion while inhibiting IL-17 secretion and neutrophil function.[105,155] There is also evidence that estradiol can enhance the population of tissue resident memory-like Th17 in the female reproductive tract during an antiviral immune response.[156] Also, deficiencies in estrogen receptor alpha (ERα) reduce Th17 differentiation which correlates with IL-17 and IL-23 secretion reduction.[157] However, estradiol can trigger the formation of an ERα-repressor complex which represses expression of RORγt.[158]

Regulation of the Treg/Th17 Balance During Pregnancy

Studying the "seesaw" between Treg/Th17 frequencies has yielded new knowledge about how recurrent pregnancy loss and other complications can arise that put the wellbeing of both parent and fetus at risk. In healthy pregnancies, the Treg/Th17 favors the proliferation of Tregs and the development of a tolerogenic immune profile, though Th17 levels may be proportionally higher in the decidua than in the parent's peripheral blood.[159] In patients with pre-eclampsia, a pregnancy complication featuring high blood pressure and organ dysfunction in the liver or kidneys, the ratio is skewed in favor of Th17.[103] A similar phenomenon has been observed in the peripheral blood and decidua of patients with unexplained recurrent pregnancy loss when compared to healthy pregnancies[160]. It should be noted that Th17 cells also fulfill an important part in protecting pregnancies from infection hence the observed role that pregnancy-specific glycoprotein 1a plays in stimulating dendritic cells to enrich the circulation of Th17, among other lymphocytes.[161] Another potential effect of healthy Th17 presence is that IL-17 has been shown to stimulate trophoblasts towards the production of progesterone *in vitro*.[162] Th17 cells can also be recruited by decidual stromal cells and prevent trophoblast apoptosis in the first trimester of healthy pregnancies.[163] However, chronic infusion of IL-17 in pregnant rats yielded physiological complications, hypertension and impaired uterine artery reactivity, and increased cytotoxic NK cell activity.[164] IL-17 and Th17 cells were also suggested to be in part responsible for maternal immune activation and subsequent fetal cortical abnormalities in line with an autism phenotype.[165]

Th17 as a Mediator of Viral Immunity

The role of Th17 cells and their effectors in influenza, especially in the context of pregnancy, is an evolving field of study. In a murine model of H3N2 infection during pregnancy, IL-17 was elevated in circulation and RORγt levels were upregulated in the intestines in parallel with maternal pulmonary inflammation and dam weight loss.[166] In

line with this, higher levels of IL-17 and Th17-linked cytokines (IL-6, IL-8) were found in human patients infected with the 2009 H1N1 strain.[167] Also, mice who were also infected with this strain were relieved of acute lung injury reducing the circulation of IL-17. Another study suggested that elevation in the Th17 cytokine profile (IL-17, IL-6, IL-8, IL-9) is a hallmark of early, severe influenza disease.[168] IL-17RA deficient mice were found to have better survival, less weight loss, and lower levels of oxidized phospholipids, particularly relevant as an agent of lung injury during influenza infection.[169] On the other hand, in a study of an IAV H5N1 model of infection in mice, IL-17 knockout led to worse disease outcomes and impaired B cell localization to the lung over the course of infection.[170] As Th17 is typically considered as a crucial component of the immune defense against extracellular pathogens, research suggests that influenza A infection triggers interferon-mediated repression of Th17 immunity which impairs the clearance of subsequent bacterial co-infection.[171] Th17 immunity against influenza may also be impaired during pregnancy because of the bias towards IL-10+ Tregs.[172] Of note as well is that Th17/Tc17 frequencies and IL-17 concentrations in circulation were depressed in humans infected with H7N9, an avian influenza strain of concern.[173] All these works come together to suggest that appropriate Th17 responses are crucial to overcoming influenza disease. However, conditions of pregnancy can result in a dampening of Th17 immunity, possibly alleviating lung injury and prolonging the disease course.

RSV, while predominantly a disease of concern for children, has yielded insights into Th17 behavior during viral respiratory infections. Nasal washes from infants with RSV infection revealed that IL-8 levels were lower than normal in these infants, which may tie into Th17 disruption, as neutrophil recruitment is a major downstream effect of their activity.[174] IL-27 downregulation may be at play during RSV infection and can lead to elevated IL-17 circulation, leading to an imbalance in the Th1/Th2 dynamic.[175] RSV infection in mice has suggested that Th17 are promoted during infection as signaling pathways leading to their differentiation were upregulated in the lungs.[176] Rat infants infected with RSV showed elevated presence of Th17 biomarkers and lower levels of Treg biomarkers in their lungs.[177] A possible mechanism for the skewering of the Th17/Treg seesaw could be that dysfunctional dendritic cells may be secreting more IL-6 and creating the conditions for Th17 polarization during RSV infection.[178] Furthermore, elevation of circulating levels of IL-17 may exacerbate symptoms and lower levels of IL-17 actually leads to milder disease outcomes and a stronger RSV-specific CD8+ T cell response.[179] RSV infection needs to be studied further to discern whether infections during pregnancy, especially if concurrent with offspring delivery, result in a pathogenic Th17 response.

Numerous studies have sought to establish Th17 cells as crucial mediators of severe COVID-19. Previous reviews have speculated that adverse pregnancy outcomes in people with COVID-19 and pregnant people's susceptibility to respiratory illnesses could be in part explained by a Treg/Th17 imbalance contributing to a cytokine storm.[180] In the context of severely ill patients, researchers found high frequencies of Th17 cells, cytotoxic CD8+ cells, and levels of IL-17, suggesting a dysregulated pro-inflammatory Th17 response.[131,181,182] This phenomenon correlates to a decrease in the frequency of Tregs and expression of their biomarkers (TGF-β, IL-10) which could be disastrous in the context of pregnancy.[113] These findings are in agreement with earlier studies of Middle Eastern Respiratory Syndrome,

an earlier coronavirus epidemic.[183] Even after viral clearance, tissue resident memory-like Th17 cells were found in the respiratory and circulatory systems of patients, possibly playing a role in disease severity and lung injury. However, a single cell RNAseq study found that Th17 cells were underrepresented among CD4+ T cells taken from COVID-19 patients. Ultimately, the research in this area is ongoing, but most research points to a Th17 dysregulation that contributes to COVID-19's characteristic cytokine storm.

Th17 cells are a key mediator of the inflammatory response to pathogens by recruiting neutrophils to sites of inflammation. However, a strong Th17 response can be harmful to both the pulmonary and placental tissues. Estrogen and progesterone can downregulate the proliferation and function of Th17 cells to avoid this potential for harm during pregnancy. Furthermore, Th17 cells maintain a delicate ratio with Tregs, a ratio that may develop into a detriment in the initial immune response towards a viral respiratory infection. This leads to potential future research work into studying the interactions between the Treg/Th17 ratio, sex hormones, and the need to maintain an immunological landscape favorable for pregnancy.

γδ T cells

γδ T cells, Sex Hormones and the Impact on Respiratory Viral Infections

γδ T cells make up only 5–10% of peripheral T cells, but are most concentrated at mucosal tissues (i.e., skin, intestine, uterus). They fulfill an innate-like function between the innate and adaptive responses due to their localization (Fig. 3).[184] They can act to facilitate innate immunity, but also can persist as pathogen-specific T cells. Aside from their function, the major distinguishing feature of this group is that they come in combinations of Vγ1–9 chains with either Vγδ1 or Vγδ2 chains for their T cell receptors, in comparison to the alpha-beta chains of the rest of their T cell cousins. Regarding their role in innate immunity, there are two recognized groups of γδ T cells: those that produce IFN-γ and others that produce IL-17 (Fig 4).[185] The fate of T cells depends on either strong TCR signaling for IFN-+ or cytokine stimulation (IL-1β, IL-23, TGF-β) for IL-17+ T cells.[186,187] IL-17+ γδ T cells secrete some of the same cytokines as Th17 cells (IL-21, IL-22).[187] During early acute infection, IL-17+ γδ cells make up the primary source of IL-17 secretion, more so than the CD4+ Th17 cells.[188–190] In mucosal tissue, the frequency of γδ T cells is almost 40% and most of these display the Vδ1 chain, in contrast to the peripheral blood γδ T cells which typically display Vδ2.[191,192]

Sex Hormones Influence γδT Cell Frequencies

Sex hormones influence γδ T cell functions and localization in females.[193] Peripheral γδ T cell frequencies increase in healthy pregnancies and over 90% express progesterone receptors (PR), which connects to secretion of progesterone-induced blocking factor (PIBF), a protein that aids immune evasion of the developing embryo, and IL-10 secretion.[194] In patients with unexplained recurrent spontaneous abortion, PR+ decidual γδ T cells decreased significantly, correlating with a decrease in PIBF and co-stimulatory molecules. A high enough level of progesterone is necessary for high secretion of PIBF among γδ T cells, suggesting a hormone-mediated regulation of decidual γδ T cell function.[193] In

an interesting study using sheep, progesterone was found to prevent xenograft rejection and increase γδ T cell frequency in the uterus.[195] As progesterone levels increase during pregnancy, endometrial stromal cells recruit Vδ1+ γδ T cells to the endometrium, shifting the Vδ1/Vγδ2 ratio away from Vδ2+ γδ T cells, possible bad actors in unexplained recurrent spontaneous abortion.[196] Estrogen seems to selectively regulate IL-17+ γδ T cell migration from lymphoid tissue; possibly allowing a greater frequency of them to be diverted towards the uterine tissue during pregnancy.[197,198] Estradiol stimulates IL-17 secretion by γδ T cells in female reproductive tissue, which is then necessary to prime an adequate Th17 response.[199]

γδ T cells and Their Functions During Pregnancy

During pregnancy, γδ subsets maintain a delicate balance between those primed for responding to pathogens and those assisting a successful pregnancy. It has been shown that at the start of pregnancy, there is a pro-inflammatory bias among the uterine γδ T cell population, but as the pregnancy progresses, there arises a tolerogenic bias in the decidual γδ T cell population.[200–202] Furthermore, Vδ1 γδ T cells maintain cell-to-cell communication with trophoblasts, which may help, dictate expansion in their population in the later trimester of pregnancy.[203,204] Decidual γδ T cells produce TGF-β and IL-10, key cytokines for maternal tolerance of alloantigens, and produce little to no inflammatory cytokines such as TNF-α and IFN-γ. In addition, decidual γδ T cells may promote trophoblast proliferation and suppress apoptosis in trophoblasts, supporting early pregnancy.[205] Researchers have also found that decidual γδ T cells expressed memory cell markers (CD45RO) and cytotoxic markers, suggesting an early role in preventing unwanted infections.[206] Among the γδ T cells of the uterus and placenta/decidua there is a large frequency of IL-17+ γδ T cells, which may be critical for preparing the uterus for implantation after insemination.[205,207,208] These IL-17+ γδ T cells present a Vγ6 chain and may peak in frequency sometime in the second trimester.[209]

As opposed to other tissues, IFN-γ+ γδ T cells may be at lower frequencies in maternal tissues as their secreted cytokines may be harmful for pregnancy.[208,210] Furthermore, they can infiltrate the fetal nervous system after maternal immune inflammation.[211] It is also worth noting, there is evidence to suggest that inflammatory IL-17+ γδ T cells may also be responsible for negative pregnancy outcomes for patients with recurrent pregnancy loss.[212] An overabundance of cytotoxic γδ T cells during early pregnancy would be dangerous, as they are linked to patients with recurrent implantation failure.[213,214] Interestingly, work done in studying correlations between γδ chain combinations and pregnancy outcomes. Vγ9Vδ2 T cells were predominant in patients with recurrent spontaneous abortions, while Vγ1Vδ1 were more frequent in healthy pregnancies, probably because of their preponderance to produce IL-10 and suppress cytotoxic NK activity.[215,216] Vδ2 γδ T cells in peripheral blood of recurrent spontaneous abortion patients expressed more CD107 and IL-17, leading to the idea that this phenotype is in part responsible for recurrent spontaneous abortion.[217] Provocatively, a study in late gestation sows found that CD8+ IFN-γ+ cytotoxic γδ T cells were prevalent in maternal peripheral blood and gestational tissues.[218]

Role of γδ T cells in Viral Respiratory Infections

As a component of the innate immune response, γδ T cells secrete pro-inflammatory cytokines and their population expands, and the same functions hold true during respiratory viral infections. IL-17+ γδT cells are recruited at high frequencies to the upper respiratory tract as part of innate immunity against influenza virus infection.[219] These IL-17+ T cells express the Vγ4 chain, which can also be found in γδT cells in the uterus and become tissue resident memory-like cells in the aftermath of other respiratory infections.[208,219,220] This relation suggests that the IL-17+ γδT cell population may be impacted if influenza infection occurred during pregnancy. IL-21 plays a role in a negative feedback loop for the IL-17+ γδT cells in the respiratory tract during influenza infection.[218] Interestingly, IL-17+ γδT cells have a protective function for the lungs of neonates infected with influenza, which suggests this phenomenon may also occur during *in utero* infection.[169,221] Vγ9Vδ2 T cells fulfill a cytotoxic role, eliminating influenza-infected lung epithelial cells and monocyte-derived macrophages of the respiratory system.[222–225] Lung inflammation decreases when Vγ9Vδ2 T cells are stimulated thereby decreasing influenza disease severity, for both avian and seasonal human influenza.[226] Vγ9Vδ2, during influenza infection, secrete Th1 cytokines and chemokines and are classified as IFN-γ+ γδ T cells.[222,227,228] This subset also strongly relies on CD137 co-stimulation for ideal effector function and expresses high levels of CD69 activation marker in the context of influenza infection.[228–230]

In other respiratory viral infections, γδ T cells also form a fundamental portion of the antiviral innate immune response. During RSV infection, IL-17 expression is impaired in neonates and Vγ4+ γδ T cells adopt an IFN-γ+, proinflammatory cytokine secretome.[231,232] However, it has not been confirmed if there is a specific γδ T cell subset that handles IL-17 secretion during RSV infection. Increased frequencies of Vδ2+ γδ T cells were detected in neonates born from mothers with ongoing SARS-CoV-2 infection along with a cytokine secretion profile most likely derived from the maternal immune activation event.[233] Earlier work with SARS-CoV-1 identified that IFN-γ+ Vγ9Vδ2 T cells were an important portion of the effector memory T cell response to SARS-CoV-1.[234] This subset may also form a part of the immune response to SARS-CoV-2, localizing to the lung from peripheral blood and persist as tissue resident memory-like cells.[235] However, a study has shown that γδ T cell populations decrease during SARS-CoV-2 infection, possibly a result of exhaustion.[236]

However, most studies outline a transitional role for γδ T cell subsets as they aid in implantation via inflammation and must quickly adopt a support role in maternal immune tolerance. However, γδ T cells can also participate in a strong inflammatory response during a viral respiratory infection that can be harmful to the mother. An interesting research direction would be to investigate γδ T cell subset localization to the lung during pregnancy or under the influence of sex hormones. Understanding how γδ T cell subset frequencies change in these special immunological circumstances could be valuable in understanding the pulmonary host response to respiratory viral infection during pregnancy.

Th1 and Th2 Cells

Impact of Sex Hormones on Th1/Th2 Balance

A balance of Th1/Th2 subsets was an early immune mechanism proposed to explain tolerance of the semi-allogeneic fetus. Many studies followed demonstrating that maternal T cell mediated tolerance and T cell suppression as critical for a successful pregnancy. While compelling, many of these studies that support the Th1/Th2 paradigm were limited by use of experimental animal models, small human sample size, and a focus on recurrent spontaneous abortions, which in sum are not representative of the typical healthy human pregnancy.[201,237–239] Human pregnancy is now understood as a state of maternal-fetal immunomodulation, where hormones upregulate the innate and humoral immune response while downregulating the cell-mediated immune response, a stage-dependent shift in the maternal immune response that is largely mediated by Th1 and Th2 cells.[7] First, Th1 and Th2 cells play a key role in establishing and maintaining pregnancy (Fig. 4). During implantation, a Th1 cytokine profile dominates, producing a proinflammatory response during implantation and releasing TNF-α, which inhibits trophoblast cell mobility and adhesion.[240] Together with IFN-γ, these cytokines promote angiogenesis and uterine tissue remodeling to control trophoblast invasion at the implantation site.[240] Th1 cells also release IL-2, which stimulates the chorion to release PGE2, a prostaglandin critical for pregnancy maintenance.[241] After implantation, the maternal immune response shifts to a Th2 dominated profile. Uterine dendritic cells induce naïve CD4+ T cells to differentiate into Th2 cells, and the decidua releases cytokines to recruit Th2 cells to the maternal-fetal interface.[240,242] Th2 cells then promote a largely humoral immune response for the rest of the pregnancy.[243]

A shift from a Th1 to a Th2 profile in pregnancy was proposed to explain how the maternal immune response is sufficiently immunosuppressed to tolerate a semi-allogeneic fetus, while maintaining sufficient vigilance to defend both the mother and fetus from infection.[240,242 244]Indeed, the Th1/Th2 profile in human maternal blood has been demonstrated to decrease throughout the course of gestation in tandem with rising hCG, estrogen and progesterone sex hormones. At low concentrations, estradiol promotes Th1 cell-mediated immune response by enhancing IFN-γ transcription.[245] At high concentrations, estradiol promotes Th2-led humoral immunity.[246,247] Estrogen contributes to the Th2 immune profile by stimulating IL-4 secretion.[245] By decreasing levels of TNF-α, hCG also inhibits the Th1 pathway.[243,248,249] Progesterone also promotes a Th2 profile as shown *in vitro* and *in vivo*. In primary CD4+ T cells isolated from the PBMCs of non-pregnant women, progesterone suppressed CD4+ T cell activation, and downregulated gene targets associated with the STAT1 and STAT3 pathways including IL-2, IL-12b, IL-10.[250,251]Progesterone inhibits the Th1 pathway by decreasing TNF-α and IL-6 release, and stimulates the Th2 pathway by increasing IL-4 and IL10 release[243,252] High concentrations of progesterone also stimulate lymphocytes to synthesize progesterone-induced binding factor (PIBF).[253] PIBF in turn promotes naïve CD4+ T cell differentiation into Th2 cells, which then secrete high levels of anti-inflammatory cytokines.[252] Additionally, progesterone directly stimulates T cell activation: modulating TCR signaling, blocking PIBF-induced degranulation, and inhibiting cellular cytotoxicity.[254]

Overall, multiple sex hormones act on Th1 and Th2 cells to shift their ratios during pregnancy to favor fetal tolerance.

Impact of Pregnancy Hormones on Th1/Th2 Response to Respiratory Viral Pathogens

The maternal immune response during pregnancy is thus not simply suppressed but rather biased towards an antibody-based, anti-inflammatory profile that shapes disease pathogenesis and manifestation. In non-pregnant individuals, SARS-CoV-2 disease progression is characterized by a cytokine storm of pro-inflammatory, Th1 cytokines that include IL-2, IFN-γ, IL-1, and TNF-α.[255] Higher levels of IFN-γ were linked to a higher risk of mortality, suggesting that an ineffective Th1 response prevented successful elimination of the virus.[255] A reduction in Th1 responses during pregnancy may partially explain why pregnant women are more susceptible to severe SARS-Cov-2 and IAV disease.[256] In pregnant Sprague-Dawley rats, IAV infection further shifted the ratio of Th1/Th2 to favor Th2, which led to more severe disease.[257] Pregnant BALB/c mice infected with the 2009 pandemic IAV H1N1 virus exhibited lower levels of peripheral blood T cells and antibody responses than their non-pregnant counterparts.[257,258] Notably, a change in Th1/Th2 profiles in pregnant women does not seem to affect the efficacy of the inactivated influenza vaccine,[259] suggesting that more work must be done to characterize the impact of pregnancy hormones on the Th1/Th2 cytokine profiles, vaccine efficacy and outcome to respiratory viral infections.

Taken together, key pregnancy hormones regulate Th1 and Th2 activity to favor tolerance of the semi-allogeneic fetus. Severe maternal disease associated with respiratory viral infections has been attributed, in part, to the Th2 dominance in pregnancy, which is less adept at clearing viral infections. Much of the existing literature evaluates this relationship by measuring cytokine levels characteristic of either Th1 or Th2 cells in pregnant animal models and human subjects. However, to fully elucidate the regulatory role that pregnancy hormones like progesterone and estradiol play in the Th1/Th2 immune response, more studies are needed that directly target the reciprocal interactions between pregnancy hormones and effector lymphocytes.

B Cells

Immunologic Functions of B Cells

B cells serve numerous immunologic functions which include (1) displaying diverse immunoglobulin (Ig) surface receptors to bind, phagocytose, and present foreign antigens for cellular or complement activation, (2) differentiating into plasma cells that produce immunoglobulins (Ig) of unique affinity, specificity, and function, and (3) releasing cytokines (e.g., IL-6, IFN-γ, TNF-α, IL-10, IL-13, etc.) for coordination with other host immune cells including other antigen presenting cells (e.g., dendritic cells, macrophages, Langerhans cells) and T lymphocytes.[260] There are two subsets of B lymphocytes: B1 and B2 cells.[261,262] B2 cells are essential to the adaptive arm of the immune system, initially displaying IgM surface receptors for both antigen sampling and co-stimulation with splenic T lymphocytes.[261,262] Antigen-bound IgM surface receptors undergo internalization and subsequent Ig class-switching, somatic hypermutation, and affinity maturation.[260] Further

signaling stimulates B2 cells to differentiate into plasma cells and memory B cells capable of producing secretory Ig that underlie high-affinity, high-specificity antibody-mediated responses.[262] B1 cells, in contrast, produce 'natural antibodies' which are generated without antigenic stimulation and initially accumulate during fetal development to provide lower affinity and lower specificity Ig for broader neutralization of exogenous proteins or apoptotic self-cells.[263–265] The antibody-mediated protection conferred by B lymphocytes is tightly regulated to allow these cells to differentiate "self" from "nonself".

The Influence of Sex Hormones on B Cells

Sex steroids (e.g., estrogens, progesterone, and androgens) have been well established as potent regulators of humoral immune responses, notably contributing to upregulation, downregulation, and dysregulation of adaptive immune responses.[245,264–269] This complex interplay is best demonstrated through the actions of estrogen; elevated estrogen levels have been well established in the pathogenesis of certain autoimmune disorders (e.g., systemic lupus erythematosus, multiple sclerosis) while in tandem contributing to robust immune responses to infection or vaccination as well as diminished immune responses in the setting of marked hormonal fluctuations (e.g., pregnancy).[245,267,268,270] The potentially opposing impacts of estrogen on B cells comprise an area of ongoing research, however, the current literature highlights that estrogen confers up- and down-regulation of B cell production, maturity, and stimulation through interactions with unique receptors (estrogen receptors (ER): ERα or ERβ). Binding of ER shapes downstream gene expression and subsequent cell-to-cell interactions, most notably within the context of differing physiologic states (e.g., pregnancy, menopause, puberty).[245,266,268] The immunomodulation of B cell production and differentiation by sex hormones is best exemplified in pregnancy where sex hormones directly affect B cell differentiation and proliferation[271].

B Cells in Pregnancy

During pregnancy, the fetus expresses both maternal and paternal human leukocyte antigen (HLA) genes, presenting a mosaic of MHC receptors recognized as partially foreign by circulating maternal B cells. Activation of the maternal immune system against a semi-allogeneic fetus could have catastrophic consequences (e.g., pregnancy loss) in the absence of immunomodulation. Further downregulation of inflammatory and immunologic responses to infection are needed to prevent fetal injury due to infection.[272] Multiple mechanisms involving B cell subsets act to suppress maternal immune activation throughout pregnancy. Protective antibodies, produced by B2 cells, identify the paternal antigens present on the fetus and subsequently downregulate cytotoxic lymphocyte responses by trophoblastic cells in the placenta.[264] Regulatory B cells (Breg) further modulate the maternal immune response by secreting IL-10, an anti-inflammatory cytokine that suppresses pro-inflammatory responses by maternal effector T cells and activates anti-inflammatory cell lines.[264,272–274] Breg levels rise steadily throughout the first trimester of pregnancy; emerging research on estrogen and mechanisms of immunomodulation has identified hCG and estrogen receptors on Breg cells, implicating hormonal fluctuations in the Breg elevations characteristic to early pregnancy.[274] Through increased IL-10 signaling, levels of proinflammatory Th1 cells are gradually eclipsed by anti-inflammatory T helper

2 (Th2) cells which further upregulate IL-10 production and perpetuate maternal immune suppression.[264]

Although Breg subsets appear to increase in the first trimester, studies characterizing circulating B cell populations in pregnancy have shown that nearly all other B cell subsets are significantly diminished by the third trimester and throughout parturition, compared with non-pregnant or postpartum individuals.[263] Immature B cells are particularly affected due to suppressed lymphopoiesis in the bone marrow. A gradual rise in estradiol reduces IL-7 cytokine expression, which is critical for B cell differentiation and proliferation and contributes to lymphopoiesis (Fig. 5).[275,276] In effect, rising estrogen levels throughout pregnancy cause a marked decrease in B cell precursor cells and a gradual increase in specific subsets of mature B cells which are elevated throughout the third trimester and parturition.[263,274] B cell counts among postpartum and non-pregnant women are largely similar, indicating that lymphopenia in the third trimester resolves following delivery as estradiol levels decrease and B cell maturation resumes, and broader B cell populations rise to near-normal levels.[263] This unique finding was further confirmed by diminished levels of CD23, a marker of B cell differentiation from naïve to memory B cells, throughout the transition from third trimester into parturition with gradual returns to baseline in the postpartum period.[263] Despite these fluctuations, B cell levels remain within standard reference ranges throughout pregnancy, delivery, and the postpartum period. A selective increase in naïve mature B cells may be explained by the effects of progesterone, which reduces further differentiation to plasma cells or memory B cells.[263] Progesterone acts to suppress maternal immune responses by stimulating IL-10 production and modulating dendritic and natural killer cell functions to reduce interactions with B cells, dampening broader immune activation.[277,278] Studies employing murine models have identified that progesterone suppresses antigen presentation among B cells through the diminished expression of critical surface co-stimulatory receptors CD80 and CD86.[254] It is plausible that a steep decline in estrogen and progesterone levels following parturition may underlie increased lymphopoiesis and B cell differentiation to restore baseline mature B cell populations.

B cells serve a paramount role in protecting both the mother and fetus from infectious pathogens. Fetal B1 lymphocytes produce natural antibodies to supplement maternal immune responses.[261,279] Transplacental transfer of maternal IgG antibodies to the fetus, starting as early as 13 weeks, augments the newborn’s own developing immune system. This mechanism of passive immunity underlies an added benefit of maternal vaccination and presents a key area of further study to identify how maternal antibodies can be both beneficial and potentially harmful by way of the maternal-fetal interface.

Pregnancy Influences on B Cell Responses to Viral Infections

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections among infants; pulmonary infiltrates consisting of various B cell subsets reflect robust neonatal adaptive immune responses to the viral pathogen. RSV particles bind and infect fetal Breg in lung tissues, inducing the upregulation of Breg CX3CR1 chemokine receptors that interact with RSV G glycoproteins to stimulate IL-10 secretion and downstream anti-

inflammatory responses.[280,281] Profuse IL-10 release has been correlated with diminished T helper 1 (Th1) priming or activation. In conjunction with increased RSV-infected Breg cell frequencies, IL-10 elevations may be predictive for more severe outcomes in the setting of RSV infections during pregnancy.[281] Transplacental transfer of maternally produced IgG significantly contributes to fetal immunity against RSV and potential vaccines to induce maternal antibody responses are being evaluated.

In pregnancy, the maternal adaptive immune response is attenuated through the decreased production of specific cytokines (IFN-α and IFN-γ) as well as the impaired maturation of antibodies critical to neutralizing pathogenic respiratory viruses, like IAV.[271] Whether increased morbidity is due to prolonged viral insult or damage from dysregulated maternal immune activation is often uncertain. The inflammatory state that follows IAV infection, however, has been closely linked with the development of neurocognitive disorders in children.[282] Although further research is needed to evaluate immune responses to influenza in pregnancy, an inactivated influenza vaccine has been well established as a safe method of protecting pregnant mothers against infection. The vaccine has been shown to promote robust serologic immune responses in pregnancy and maternal vaccination primes the fetus to elicit its own B cell response.[283,284]

B cell-mediated antibody responses have been shown to assist in neutralization and clearing of SARS-CoV-2 as with most other viral infections in pregnancy.[285] Estrogen- and progesterone-mediated actions on lymphopoiesis reduces the population of maternal B cells capable of responding to SARS-CoV-2 infection in pregnancy and pregnant women are less likely to have detectable antibody titers against SARS-CoV-2 compared to non-pregnant counterparts. Correlational analysis of differentially expressed genes representing cellular activity identified diminished expression of IL-6 and elevations in gene expression among naive B cell or memory B cell populations for IL-1β among pregnant women compared with non-pregnant women[286]. The cytokine storm characteristic of COVID-19 disease is partially produced through the broad antibody and cytokine release by activated B cells; this cascade of immune activation appears to be attenuated during pregnancy.[287,288]

Hormonal Influences on B Cells Beyond Pregnancy

One of the most significant immunological modifications during pregnancy is the increase of B cell responses due to the increased levels of progesterone and estrogen during pregnancy, which both reach their peak levels in the third trimester of gestation (Fig. 5).[247] Outside of obstetrical models, the hormonal influence over B cell production and function is further exemplified through androgen-derived immunomodulation. Like estrogen and progesterone, testosterone reduces B cell lymphopoiesis in the bone marrow through attenuation of stromal cell differentiation.[266,289,290] One mechanism for this androgenic marrow immunosuppression is exemplified in androgen receptor knock-out murine models wherein the absence of androgen receptors on osteoblast cells led to increased B cell precursor subsets, implicating osteoblasts in androgenic influences over B cell precursor production.[289] These knock-out studies, however, found no significant change in splenic B cell counts, despite an established role of testosterone in suppressing splenic B cell populations.[289] An alternative mechanism of testosterone-

regulated splenic immune suppression has been suggested to involve the cytokine BAFF, which serves as a critical survival factor for splenic B cells and is negatively regulated by testosterone.[266,289,290] [266,289,290]

B cells comprise a critical arm of the adaptive immune response, contributing both a myriad of receptor-mediated antibody responses and regulatory anti-inflammatory functions to the modulation of healthy immunity. Pregnancy represents a dynamic hormonal milieu, whereby the specific impacts of sex hormones on B cell function can be best evaluated. Estrogen and progesterone contribute significantly to the upregulation of specific mature B cell lines (e.g., Breg) and the suppression of numerous other B cell populations which aids the attenuation of maternal immune responses against fetal antigenicity. This modulation of maternal immunity further impacts maternal adaptive immune function in the setting of viral respiratory infections, contributing to higher morbidity and mortality risks among pregnant individuals.

Innate Lymphoid Cells

Innate lymphoid cells (ILC) refer to a broad category encompassing a variety of lymphoid lineage cells that respond rapidly to pathogen-associated molecular patterns (PAMPs) rather than specific antigens. Many subtypes with a wide variety of functions are classified within this broad category, but this review will focus on those that are involved in cytokine secretion during pregnancy and respiratory infections and that may respond to sex hormones. Here we highlight ILC subtypes and decidual natural killer (dNK) cells, as they have either a prominent role in pregnancy, defense against viral respiratory pathogens or are known to be influenced by sex hormones.

ILCs and Sex Hormones

A major class of cytokine secreting ILCs are helper ILCs. Helper ILCs are divided into 3 groups: ILC1s, ILC2s, and ILC3s, which are analogous to T-helper (Th) cell subsets Th1, Th2, and Th17, respectively.[291–293] They are often tissue resident cells, providing a broad first line of innate immune defense. Lymphoid tissue inducer cells are considered part of the ILC3 group but can be considered separately concerning respiratory virus response, as they are not functionally linked to antiviral immune responses and, instead, largely involved in lymphoid organ development.[294] Another subtype of ILC is the decidual natural killer cell (dNK). dNK cells are considered ILCs because they do not respond to specific antigens. Despite their name, dNK cells are non-cytotoxic, instead producing cytokines and chemokines like Th cells do. These cells become tissue residents within the uterus during pregnancy.[295]

Although the recent discovery of ILCs means that there is not much information on their response to pregnancy hormones, there are known sex differences in ILC numbers. Much of this early research has been done on mouse models, and the response of human ILCs to sex hormones is an area that remains to be explored. In mice, the ILC3 and ILC1 subgroups are not shown to express any sex hormone receptors, while ILC2 expresses androgen receptors, mediating the effects of testosterone and dihydrotestosterone.[296] Female mice have greater quantities of ILC2, and human studies have shown higher numbers of

ILC2 in women with asthma than in men with asthma.[296] Furthermore, mouse models demonstrate decreased ILC2 and eosinophil counts, both of which are implicated in respiratory inflammation, in response to testosterone.[297] The majority of ILC2 do not express estrogen receptors, but uterine ILC2 express both Esr1 and Esr2.[298] The effect of pregnancy hormones on ILCs is also not yet well researched, but some early findings suggest that the ability of ILC3 to present self-antigens on HLA is hormonally controlled. hCG downregulated HLA production in murine models, while VEGF, progesterone, and estradiol did not have any effect.[298,299] The effect of pregnancy hormones on ILCs is unknown, but some early findings suggest that the ability of ILC3 to present self-antigens on HLA is hormonally controlled. hCG downregulated HLA production in murine models, while VEGF, progesterone, and estradiol did not have any effect.[298,299]

Sex hormones and dNK cell function are tightly linked. Prolactin and IL-15 increase after ovulation in response to progesterone, inducing the proliferation of dNK.[295] These hormones continue to rise as the pregnancy continues. As the function of dNK cells changes throughout the pregnancy, so do the hormones they respond to. For example, dNK cells migrate to the spiral arteries to direct remodeling specifically in early pregnancy. This timing is associated with a rise in estrogen and progesterone.[300] Another sex hormone, estradiol, induces CXCL10 and CXCL11 expression in the endometrium, both of which are ligands for CXCR3 on dNKs.[301] The association between sex hormones and the increased numbers of dNK cells and dNK ligands suggests that the hormones may induce their migration and proliferation. Interestingly, though dNK cells respond to progesterone, they do not express a progesterone receptor, meaning that the effects of this sex hormone are mediated indirectly.[302]

ILCs in Pregnancy and in Viral Respiratory Infections

All ILCs have been found in the endometrium of the non-pregnant uterus. Though ILC2 is initially only present in low numbers, a shift in ILC expression occurs during pregnancy.[303] All helper ILC subtypes are also present within the decidual tissue in a pregnant person, with ILC2 representing the most abundant subtype and ILC1 making up a minor proportion of the uterine ILCs.[304] In general, ILCs produce the same cytokines in the decidua as they do in other tissues, though the relative numbers of cytokines produced can change as the fetal microenvironment changes.[304] For example, in preterm labor, ILC3 located in the decidua produce higher levels than ILC2 of cytokines, like IL-22. The amniotic fluid is another important location for ILC defense, as it protects the fetus from infection. Here, ILC3 predominates, producing IL-17 to fight amniotic infection.[305] The relative abundances of each ILC subtype, like the proportions of the cytokines, change throughout gestation, such as ILC3 levels remaining high until the second trimester of pregnancy, when they begin to wane.[305] Though the exact function of the maternal ILCs has not yet been elucidated, it is thought that they may play a role in both fetal tolerance and immune defense against pathogens.

ILCs have a major role in innate, first-line defense against respiratory viral pathogens due to their location at mucosal sites like the respiratory tract. The predominate ILC helper subtype in the respiratory tract is ILC3, and its production of IL-17 and IL-22 is key in

mediating immune defense against respiratory pathogens and allergens.[291,306] One study demonstrated that infection in mouse models of mouse adapted H1N1 influenza induced ILC response within the lungs and ILC depletion reduced lung function in the setting of influenza infection.[307] Studies of respiratory syncytial virus (RSV) and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) have shown similar ILC2 induction in the lungs.[308,309]

Though the research in this area is early and mostly correlative, these ILCs are thought to increase inflammation and contribute to lung remodeling, potentially leading to severe lung disease following respiratory virus infection.[306] One study showed that RSV activation of ILC2 leads to inflammation and eosinophilia in the lungs.[310]Though the research in this area is early and mostly correlative, these ILCs are thought to increase inflammation and contribute to lung remodeling, potentially leading to severe lung disease following respiratory virus infection.[306] One study showed that RSV activation of ILC2 leads to inflammation and eosinophilia in the lungs.[310] The inflammatory role of ILC2 in the respiratory system is also evident from the marked increase in ILC2 associated with non-viral pulmonary pathologies like asthma and chronic obstructive pulmonary disease.[311] Alternatively, ILCs also appear to be important in clearing respiratory viruses and reducing respiratory symptoms. Early studies of ILCs in SARS-CoV-2 patients showed an association between ILC2 reduction with increased severity of COVID-19 illness.[309] In this way, ILCs modulate a balance between respiratory immune defense and damage modulated by hyper-inflammation.

Essential Role for Decidual NK Cells in Pregnancy and the Influence of Sex Hormones

Another subtype of ILC that are important in pregnancy are decidual natural killer cells (dNKs). dNKs are uniquely implicated in both fetal development in a normal pregnancy and immune defense against pathogen infected decidual cells. dNK cells are the main lymphocyte in the decidua basalis.[295,312] In a healthy pregnancy, their main functions are to promote angiogenesis and vascular remodeling by secreting vascular endothelial growth factor (VEGF), direct migration of the fetal trophoblast by secreting chemokines IL-8 and IP-10 and induce fetal tolerance.[312,313] The presence of dNK cells has been shown to be essential for spiral artery modification in mouse models, and though their role in human angiogenesis is less clear, they remain in proximity to human spiral arteries, suggesting a relationship.[314] The invasive fetal trophoblast expresses CXCR1 and CXCR3, which are receptors for ligands IL-8 and IP-10, respectively. These chemoattractants direct the migration of the trophoblast by interacting with the fetal chemokine receptors.[315] Finally, since trophoblasts do not express the classic “self” labels like HLA-A/B that protect them from immune defense, they must have another mechanism inducing tolerance. Though the exact mechanism has not yet been elucidated, dNK cells are associated with decidual CD14+ cells that induce Tregs, which are known to have a role in fetal tolerance. Furthermore, spontaneous fetal abortion, potentially via maternal immune rejection, is associated with a reduced number of dNKs and decidual Tregs.[316]

dNK cells are not located in the lung tissue, so there is no currently known role in defense against respiratory viral pathogens. They have been shown to play a part in defending

against pathogens that infect the decidua, such as cytomegalovirus (CMV).[295] Studies have shown that when exposed to CMV, dNK cells exhibit plasticity and enhance lytic function to become cytotoxic and induce apoptosis in infected cells.[317] Studies with pregnancies infected with *Listeria monocytogenes* shows a similar ability to become cytotoxic in the presence of pathogens but notes that the mechanism of killing is not like the inflammatory perforin and granzyme secretion that peripheral NK cells use. Instead, dNK cells selectively deliver antimicrobial granulysin to infected cells via direct contact, thereby killing the *Listeria* without harming the trophoblast.[318] However, they are not currently known to have a direct role against preventing *in utero* infection by respiratory viruses. SARS-CoV-2 shows only rare vertical transmission, suggesting that there is some maternal-fetal barrier immune activity against the virus. Preliminary research documents an increased number of third trimester dNK cells, as well as T cells and macrophages, in those with symptomatic COVID-19.[319]

ILCs are a bridge between the innate immune response and the adaptive response to respiratory viral infections mounting a first line inflammatory response to viruses in the respiratory tract. dNK cells proliferate in response to sex hormones like prolactin to maintain healthy pregnancies and have a potential role in defending against *in utero* infections. Future directions for research on ILCs may include investigating ILC response to sex hormones that they exhibit receptors for, such as androgens and estrogens. This may help determine if uterine ILCs have a role in protecting the fetus from pathogens. Further research could also be done on dNK cells to determine the mechanism for the increased dNK cell count in pregnancies with symptomatic COVID-19 to examine whether they have a role in preventing vertical transmission. The potential transition of dNK cells from one facilitating immune tolerance to active immune defense is underexplored.

Conclusions

Pregnant people infected with pathogenic respiratory viruses, like IAV and SARS-CoV-2, are at a higher risk for hospitalization, preterm birth, stillbirth, Cesarean section and maternal mortality due to severe lung disease.[1–3,5–8,10–12,17,34,46,320,321] In our review, we summarize the literature regarding the effect that sex hormones have on distinct lymphoid immune cell populations, the ways these immune cells behave during pregnancy, and how they act over the course of viral respiratory infections. The picture that emerges is that there is a tradeoff between the hormonal and immune environment needed to promote fetal tolerance to support a successful pregnancy and an immunologic state that is optimally equipped to clear a pathogenic respiratory virus. Immune cell populations are in balance with one another to control the trajectory of the immune response. A combination of higher Treg and Breg populations, impaired B cell lymphopoiesis and Th17 differentiation are ideal modifications to prioritize immune tolerance of the fetus but leave the pregnant individual disadvantaged to mount a rapid immune response. However, the area of confluence between sex hormones of pregnancy, such as estrogens and progestogens, and immune responses to viral respiratory infections remains understudied. This is in part due to a lack of animal models that recapitulate the natural progression of human IAV disease, endocrinology, and pregnancy. Nonhuman primates are an excellent model of pregnancy[322] and viral respiratory infections[322–328], but most have differences in the hormonal cascade associated

with parturition (labor onset). A combination of *in vitro* and *in vivo* models is necessary to dissect the complex interactions between sex hormones, pregnancy and the pathogenesis of viral respiratory infections.

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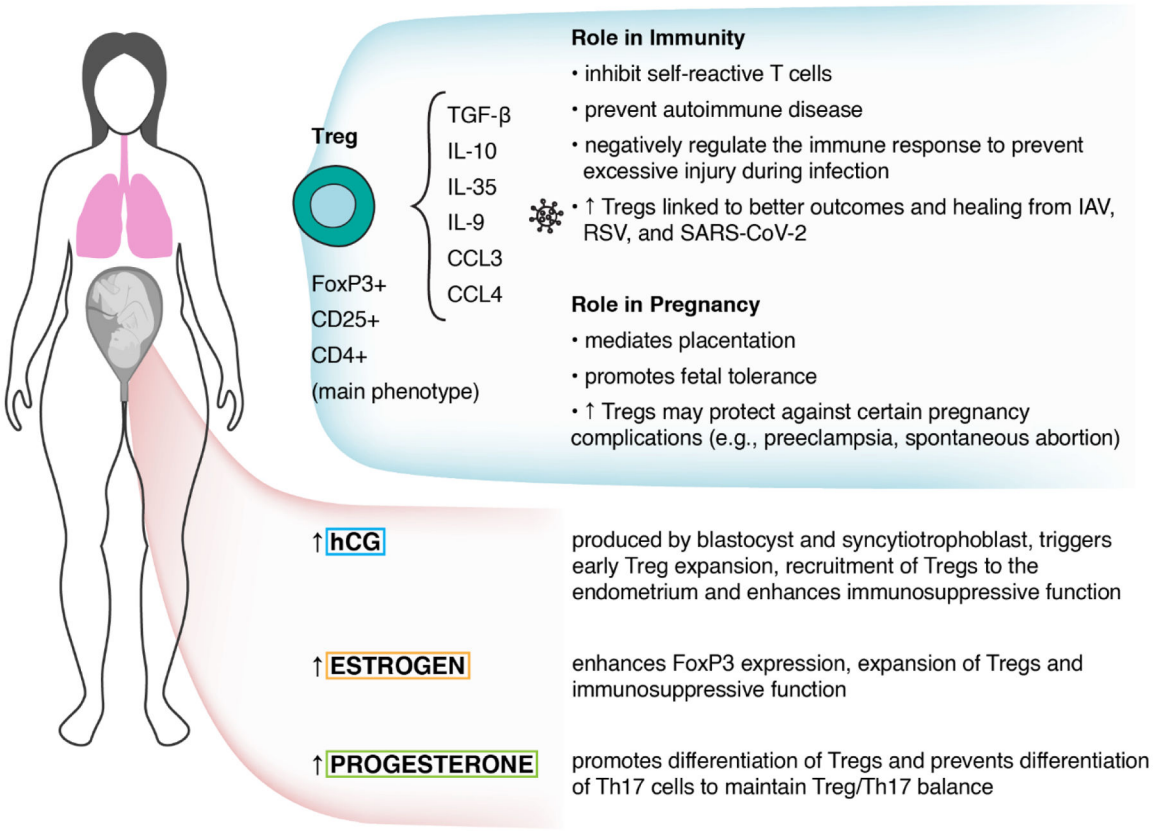

Figure 1. Treg cell role in immunity and pregnancy and the influence of sex hormones.

This figure illustrates the critical role of Tregs in early pregnancy to mediate placentation and promote fetal tolerance. All the major sex hormones in pregnancy support either the proliferation, differentiation, or immunosuppressive function of Tregs. Although there are many Treg phenotypes, the main phenotype is characterized by expression of CD4, CD25 and Forkhead box P3 (FoxP3+). Abbreviations: CD, cluster of differentiation; CD25, also known as the IL-2 receptor alpha chain, CCL3, C-C Motif Chemokine Ligand 3; CCL4, C-C Motif Chemokine Ligand 4; FoxP3, forkhead box P3; IL, interleukin; and TGF-β, transforming growth factor beta.

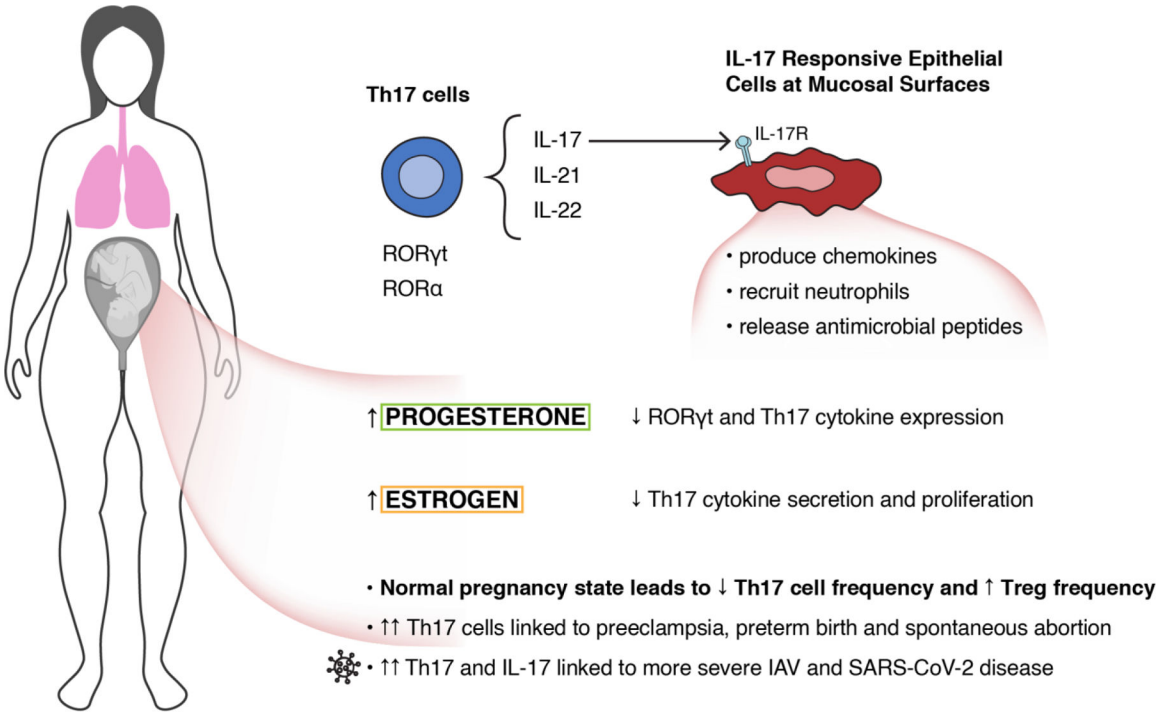

Figure 2. Pro-inflammatory Th17 cells are downregulated during pregnancy.

This figure outlines the pro-inflammatory immune function Th17 cells have in the epithelial and mucosal tissue. Estrogen and progesterone, key sex hormones in pregnancy, dampen the function and decrease the frequency of Th17 cells. Th17 cells are characterized by RAR-related (retinoic acid receptor) orphan receptor (RORγt and RORα) transcription factors and expression of interleukin (IL) cytokines IL-17, IL-21, and IL-22. Abbreviations: IL, interleukin; ROR, RAR-related orphan receptor.

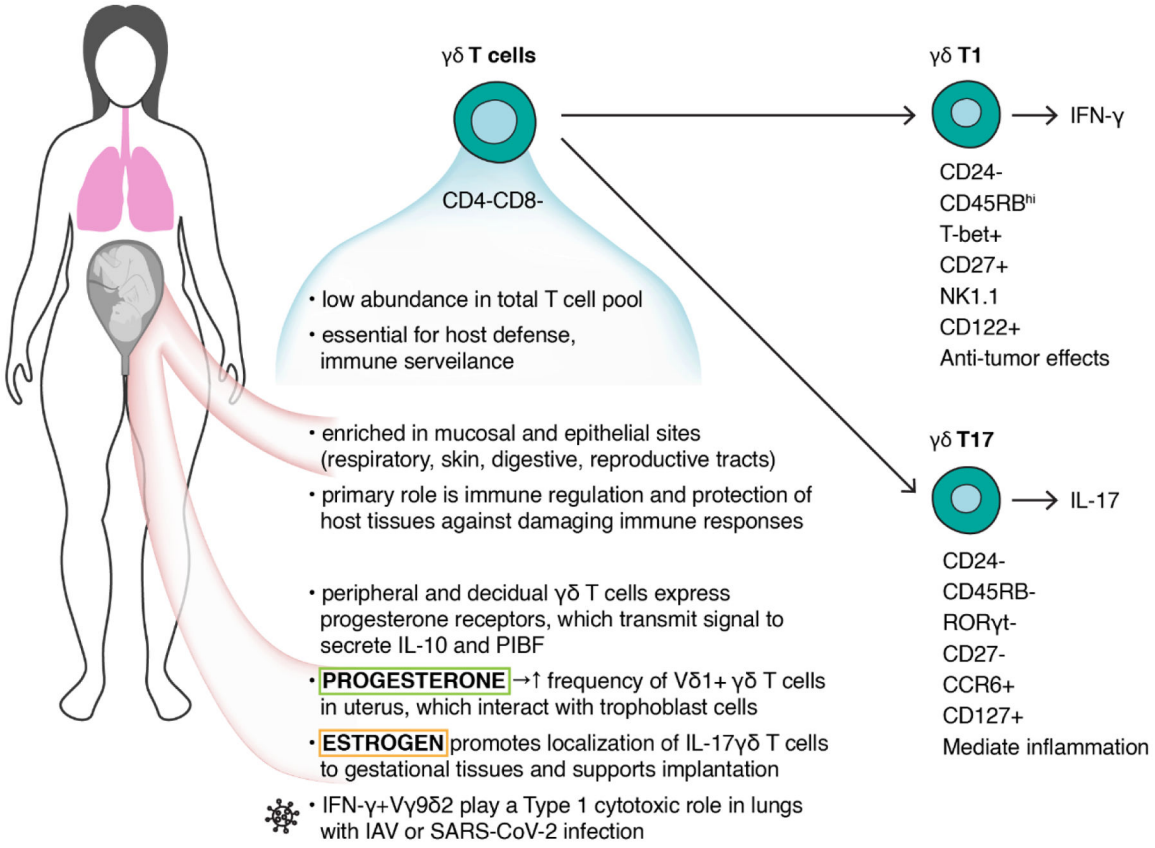

Figure 3. γδ T cell function and localization are influenced by sex hormones

γδ T cells are enriched mucosal and epithelial tissue and instrumental in innate immunity and immune regulation. They can be generally divided into IL-17+ and IFN-γ+ subsets with distinct functions in immunity and pregnancy. Progesterone stimulates the production of tolerogenic biomolecules such as IL-10 and progesterone induced blocking factor (PIBF). Estrogen and progesterone also promote localization of Vδ1 and IL-17+ γδ T cells to the gestational tissue. IFN-γ+ γδ T cells, on the other hand, fulfill a Type 1 cytotoxic role during viral respiratory infections that can be detrimental in the gestational environment. Abbreviations: CCR, C-C chemokine receptor; CD, cluster of differentiation; IFN, interferon; IL, interleukin.

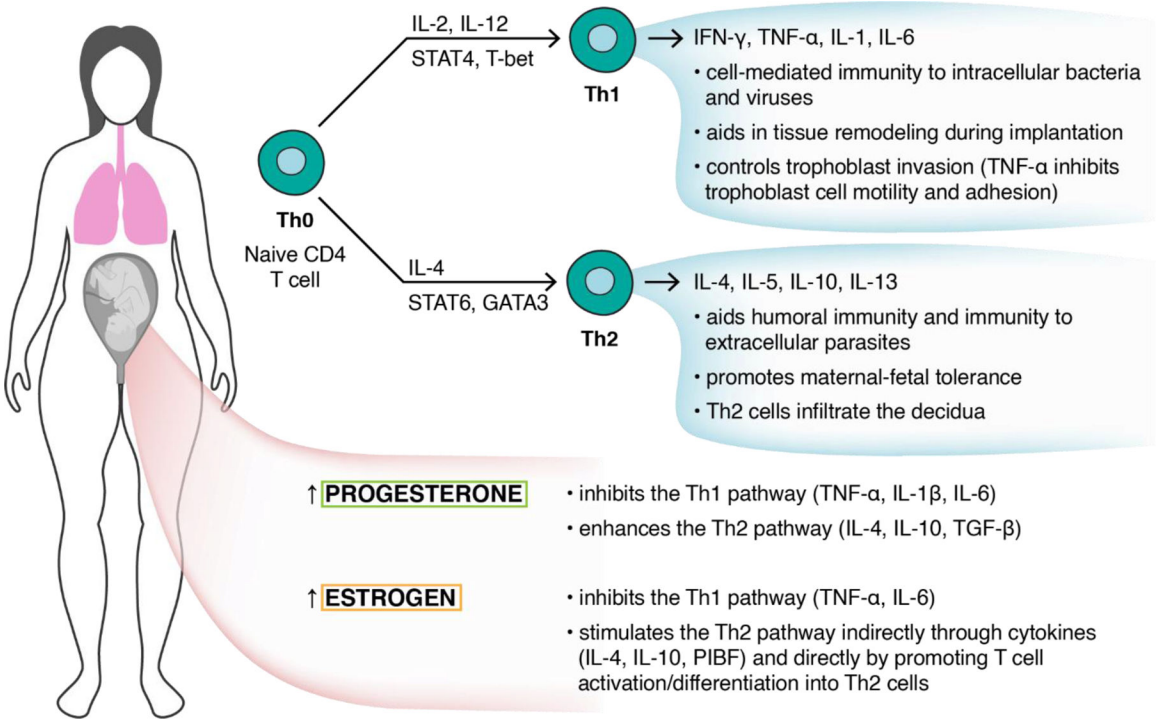

Figure 4. The maternal immune response shifts from a Th1 to a Th2 dominated cytokine profile during pregnancy.

Throughout the course of gestation, Th1 and Th2 cells regulate each other's activity and proliferation via signaling cytokine cascades to establish and maintain a healthy pregnancy. Progesterone and estrogen are key immunomodulators for this process. Abbreviations: CD, cluster of differentiation; GATA, GATA binding protein; IFN, interferon; IL, interleukin; PIBF, progesterone induced blocking factor; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor.

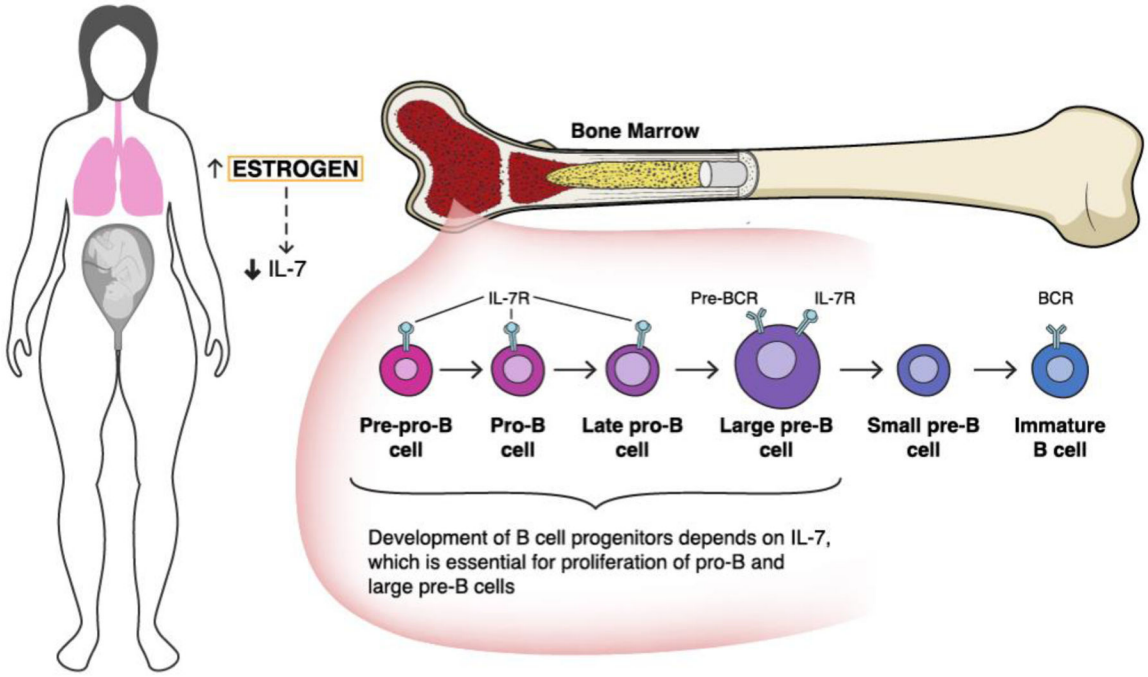

Figure 5. Influences of Sex Hormones on B Cell Production and Maturity.

This figure illustrates the critical role of estrogen in early B cell development to mediate cellular lymphopoiesis. Elevated levels of estrogen in pregnancy modulate B cell proliferation and differentiation through regulating the production and binding of critical cytokines such as IL-7. This serves to attenuate the humoral arm of the adaptive immune response, thereby suppressing overwhelming maternal immunity against an antigenic fetus. Abbreviations: BCR, B Cell Receptor; IL, interleukin.

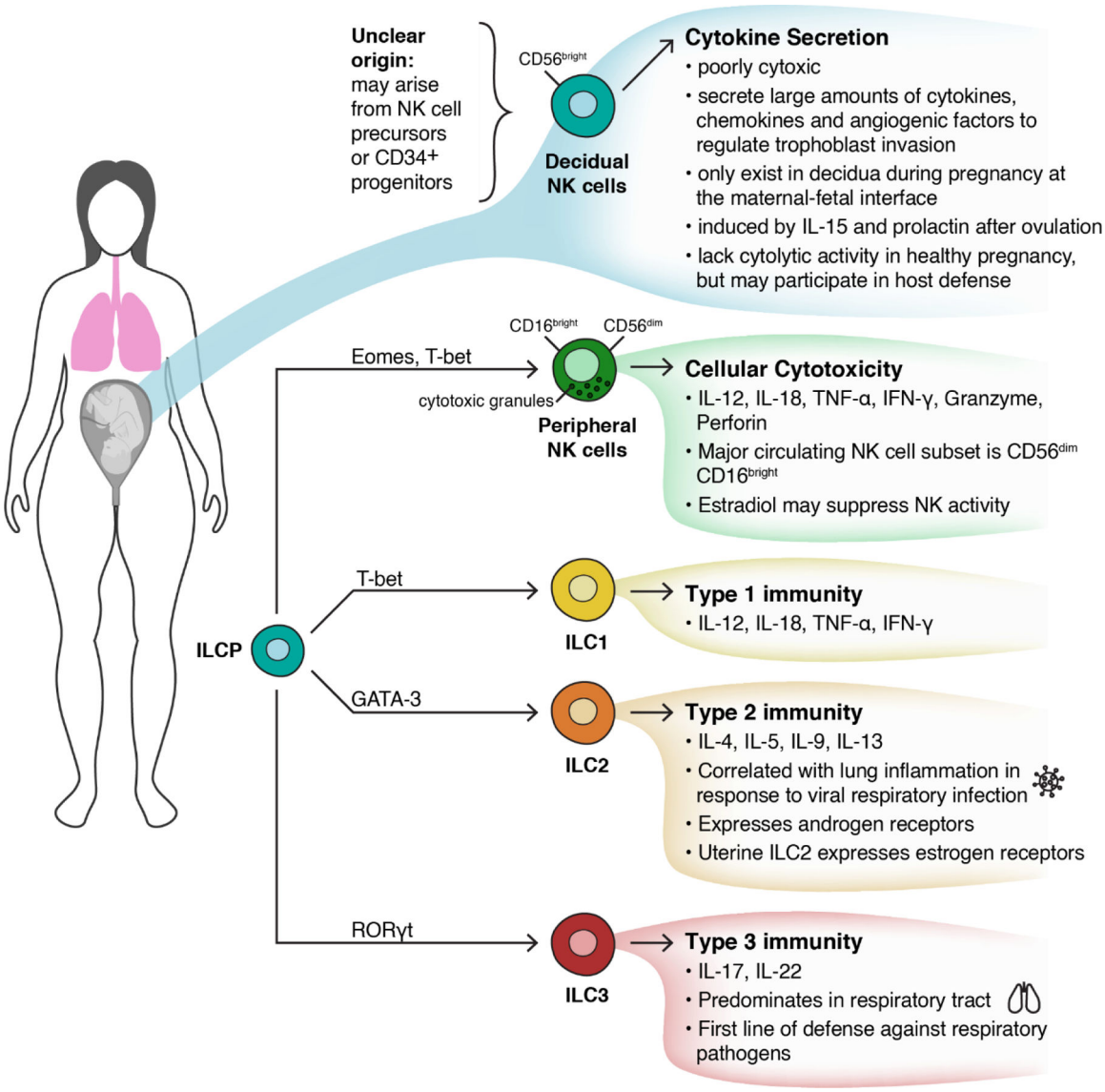

Figure 6. Impact of sex hormones on the function of ILC and dNK cells and their role in pregnancy and respiratory infections.

This figure demonstrates the ILC function of secreting cytokines in response to viral respiratory pathogens and the possible association between ILCs and sex hormones like androgen and estrogen. It also illustrates the role of dNK cells, which secrete cytokines to facilitate trophoblast migration in contrast to pNK cells, which are cytotoxic. dNKs are only found in decidual tissue during pregnancy and are induced by the sex hormone prolactin. Abbreviations: CD, cluster of differentiation; Eomes, eomesodermin; IFN, interferon; IL, interleukin; NK, natural killer; RORγt, RAR-related orphan receptor gamma; and TNF-α, tumor necrosis factor alpha.