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Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis

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Abstract

During pregnancy, it is evolutionary advantageous for inflammatory immune responses that might lead to fetal rejection to be reduced and anti-inflammatory responses that promote transfer of maternal antibodies to the fetus to be increased. Hormones modulate the immunological shift that occurs during pregnancy. Estrogens, including estradiol and estriol, progesterone, and glucocorticoids increase over the course of pregnancy and affect transcriptional signaling of inflammatory immune responses at the maternal-fetal interface and systemically. During pregnancy, the reduced activity of natural killer cells, inflammatory macrophages, and helper T cell type 1 (Th1) cells and production of inflammatory cytokines, combined with the higher activity of regulatory T cells and production of anti-inflammatory cytokines, affects disease pathogenesis. The severity of diseases caused by inflammatory responses (e.g., multiple sclerosis) is reduced and the severity of diseases that are mitigated by inflammatory responses (e.g., influenza and malaria) is increased during pregnancy. For some infectious diseases, elevated inflammatory responses that are necessary to control and clear a pathogen have a negative consequence on the outcome of pregnancy. The bidirectional interactions between hormones and the immune system contribute to both the outcome of pregnancy and female susceptibility to disease.

Keywords

autoimmunity; estrogen; IFN-γ; influenza; IL-10; malaria; multiple sclerosis; progesterone; Th1/Th2; regulatory T cell

Introduction

The state of pregnancy represents an extreme challenge for the immune system. From the perspective of the pregnant female's immune system, the fetus is an allograft that contains foreign antigens from the father. To support a successful pregnancy, it is evolutionarily

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advantageous for a pregnant female's immune responses to shift away from inflammatory responses that contribute to fetal rejection and toward anti-inflammatory immune responses that aid in passive transfer of antibodies to the developing fetus (Raghupathy, 1997). Hormones contribute significantly to the shift in immune function that occurs over the three trimesters of pregnancy (Figure 1). Importantly, pregnant females are not immunosuppressed, but rather their immune responses are biased toward an anti-inflammatory phenotype that influences not only the outcome of pregnancy but disease pathogenesis as well.

The hormonal and immunological changes that occur over the course of pregnancy are necessary to support a healthy pregnancy, but also dramatically affect female susceptibility to autoimmune and infectious diseases. While many studies of autoimmune and infectious disease pathogenesis report changes in immunological factors over the course of pregnancy, few studies consider the role that hormones play in orchestrating these immunological changes. The goals of this review are to: (1) evaluate the immunological shifts that occur during pregnancy; (2) determine the effects of pregnancy-associated hormones, in particular estrogens and progesterone (P4), on innate and adaptive immune responses; (3) provide relevant examples of pregnancy and pregnancy-associated hormones affecting the outcome of diseases caused by pathogens as well as recognition of self-antigens; and (4) identify general principles across diseases that might improve interpretation and treatment for immune-related diseases during pregnancy.

Inflammatory immune responses are skewed during pregnancy

Concentrations of steroid hormones, including estrogens and P4, are considerably higher during pregnancy than during other times in the female reproductive cycle and increase over the course of pregnancy, with highest levels achieved during the third trimester (Figure 1). Hormonal changes that occur during pregnancy underlie some of the distinct immunological changes associated with pregnancy. Elevated levels of P4 stimulate the synthesis of progesterone-induced binding factor (PIBF) by lymphocytes (Szekeres-Bartho and Polgar, 2010). In humans, PIBF increases over the course of pregnancy and drops significantly after birth, but in pathological pregnancies that result in preterm labor, abortion, or hypertension, concentrations of PIBF are low (Polgar et al., 2004). High concentrations of PIBF promote differentiation of $CD4^+$ T cells into helper T cell type 2 (Th2) cells that secrete high concentrations of anti-inflammatory cytokines, including IL-4, IL-5, and IL-10 (Szekeres-Bartho et al., 1996). The Th2 bias that occurs during pregnancy corresponds with a reduction in inflammatory Th1 responses (e.g., production of IFN-γ), both at the maternal-fetal interface and systemically in humans and animal models (Krishnan et al., 1996a; Lin et al., 1993; Marzi et al., 1996; Ostensen, 1999; Sacks et al., 2001; Veenstra van Nieuwenhoven et al., 2002). In vitro, splenocytes from pregnant female mice produce less Th1 cytokines and more Th2 cytokines than do cells isolated from non-pregnant females following stimulation (Dudley et al., 1993; Krishnan et al., 1996a). Successful pregnancies in humans are associated with elevated IL-4 and IL-10 and reduced IL-2 and IFN-γ production by peripheral blood mononuclear cells (PBMCs), with differences in cytokine production being greatest during the third trimester of pregnancy (Marzi et al., 1996). Inflammatory cytokines, like IFN-γ and TNF-α, can damage the placenta and developing fetus either directly or by activating cytotoxic cells, including natural killer (NK) or T cells (Raghupathy, 1997).

In addition to T cells, the anti-inflammatory polarization of immune cells during pregnancy is observed for macrophages. In an inflammatory environment (i.e., caused by the presence of inflammatory cytokines or exposure to inflammatory stimuli), uterine decidual macrophages develop an inflammatory phenotype (often referred to as M1 macrophages)

that is characterized by elevated secretion of the inflammatory cytokines, IL-12 and TNF-α (Nagamatsu and Schust, 2010). Macrophages that differentiate in an environment that is dominated by Th2-biased cytokines, such as IL-4, IL-10, or IL-13, or high glucocorticoid concentrations, develop an anti-inflammatory phenotype (referred to as M2 macrophages), which is characterized by arginase activity, scavenger receptor expression, and secretion of IL-1 receptor antagonist (Nagamatsu and Schust, 2010). In women with healthy, full-term pregnancies, there is increased M2 polarization of decidual macrophages as compared with women with preterm pregnancies (Nagamatsu and Schust, 2010).

The immunological shift away from inflammatory responses is necessary for a successful, full-term pregnancy. If the anti-inflammatory bias during pregnancy is altered, by infection for example, this can result in preterm labor or abortion in humans as well as mice (Hill et al., 1995; Krishnan et al., 1996b; Marzi et al., 1996). Elevated Th2 responses also correlate with increased antibody responses during pregnancy (Wegmann et al., 1993). Elevated concentrations of anti-inflammatory factors, such as IL-10, can prevent spontaneous abortions, at least in mice (Chaouat et al., 1995). Concurrent with the increase in Th2 responses during normal pregnancy is an increase in the activity of regulatory T cells at the maternal-fetal interface in mice (Kallikourdis and Betz, 2007). In women, migration of regulatory T cells to the pregnant uterus is mediated by human chorionic gonadotropin, which is a chemoattractant protein secreted by the blastocyst after fertilization (Schumacher et al., 2009). Regulatory T cells are hypothesized to orchestrate immune tolerance of the fetus during pregnancy in mammals.

Pregnancy-associated hormones alter immune function

Pregnancy is associated with changes in concentrations of several hormones, including estradiol (E2), estriol (E3), P4, corticosteroids, and prolactin. These hormonal changes contribute to the immunological shifts during pregnancy (Figure 1). Importantly, the effects of pregnancy-associated hormones on immune function extend beyond what has been examined in the context of pregnancy and may inform future studies. Altered activity of innate immune cells contributes to the differential induction of cell-mediated and humoral responses during pregnancy. Consideration of the diverse effects of sex steroids, in particular, on the functioning of the immune system may provide insight into why the pathogenesis of infectious and autoimmune diseases changes dramatically during pregnancy.

Estradiol

Estradiol (E2) occurs in high concentrations in non-pregnant as well as pregnant females and is responsible for a majority of the `classic' estrogenic effects in reproductive and non-reproductive tissues. Estrogen receptors (ERs) are expressed in various lymphoid tissue cells as well as in lymphocytes, macrophages, and dendritic cells (DCs) (Kovats et al., 2010). There are two subtypes of the receptor for estrogens, ERα and ERβ, that exhibit differential expression in subsets of immune cells, with ERα being highly expressed in T cells and ERβ being upregulated in B cells (Phiel et al., 2005). The differential effects of estrogens on parameters of immune function may reflect not only the concentration of estrogen (i.e., whether physiological or pregnancy doses are used), but the density, distribution, and type of ERs in immune cells.

Estradiol affects several aspects of innate immunity, including the functional activity of innate immune cells that influence downstream adaptive immune responses. Exposure to E2 in vitro enhances NK cytotoxicity and production of IFN-γ (Nakaya et al., 2006; Sorachi et al., 1993), but can also downregulate the expression of NK cell surface activation markers and secretion of granzyme B and FasL (Hao et al., 2007). Estradiol enhances the expression of pattern recognition receptors, like toll-like receptor (TLR) 4, on the surface of peritoneal

macrophages as well as production of TNF-α (Rettew et al., 2009). Estradiol can have bipotential effects on monocytes and macrophages, with low doses enhancing proinflammatory cytokine production (e.g., IL-1, IL-6, and TNF-α) and high concentrations reducing production of these cytokines (Bouman et al., 2005). In vitro exposure to E2 facilitates differentiation of bone marrow precursor cells into functional $CD11c^+$ DCs (Paharkova-Vatchkova et al., 2004) and increases the synthesis of chemokines, including CXCL8 and CCL2, by immature DCs (Bengtsson et al., 2004), but downregulates antiviral responses, including production of IFN-α and CXCL10, following viral infection (Escribese et al., 2008). Treatment of ovariectomized mice with physiological doses of E2 increases production of IFN-γ by $CD11c^+$ DCs and synthesis of proinflammatory cytokines, including IL-1, IL-6, and TNF-α (Miller and Hunt, 1996; Siracusa et al., 2008). Estradiol acts primarily though ERα, not ERβ, to regulate differentiation of DCs (Carreras et al., 2008; Douin-Echinard et al., 2008; Paharkova-Vatchkova et al., 2004).

Estradiol can enhance both cell-mediated and humoral immune responses (Straub, 2007). Generally, low E2 concentrations promote Th1 responses and cell-mediated immunity and high concentrations of E2 augment Th2 responses and humoral immunity (Straub, 2007). The binding of E2 to the ER increases *Ifnγ* transcription by interacting with estrogen response elements in the promoter region of the *Ifnγ* gene (Fox et al., 1991). Low dose E2 also upregulates mitogen activated protein kinase (MAPK), T-bet, and select microRNAs to increase production of IFN-γ by T cells, which can be reversed by treatment of cells with the ER antagonist ICI 182,780 (Dai et al., 2008; Karpuzoglu et al., 2007; Suzuki et al., 2008). Estradiol regulates proinflammatory responses that are transcriptionally mediated by NF-κB (Dai et al., 2007).

Estradiol enhances the expansion of $CD4^+CD25^+$ T cells (regulatory T cells) in mice (Polanczyk et al., 2004). The number of regulatory T cells increases during proestrus and estrus in mice and during the follicular stage of the menstrual cycle in women (i.e., when E2 concentrations are highest) (Arruvito et al., 2007; Kallikourdis and Betz, 2007). Treatment of mice with high doses of E2 also decreases production of IL-17 by Th17 cells (Wang et al., 2009). Estradiol at physiological concentrations can stimulate antibody production by B cells (Lu et al., 2002). Levels of immunoglobulin (Ig) and numbers of Ig-secreting cells are highest prior to ovulation in females (Franklin and Kutteh, 1999; Lu et al., 2002).

Estriol

Estriol (E3) is produced in high concentrations by the fetoplacental unit during pregnancy and accounts for almost 90% of all estrogens produced during pregnancy (Soldan et al., 2003; Tulchinsky et al., 1972). Estriol is not present in non-pregnant females. The immunological effects of E3 have not been well characterized and it is assumed that the effects of E3 are broadly the same as E2 because both estrogens signal through the same ERs (Voskuhl, 2011). Much of the research on the immunological effects of E3 has been based on studies of multiple sclerosis (MS) in patients and animal models of MS, such as experimental autoimmune encephalomyelitis (EAE). Treatment of female MS patients or male EAE mice with doses of E3 that produce pregnancy levels in circulation significantly lowers proinflammatory cytokine production (e.g., TNF-α and IFN-γ), increases anti-inflammatory cytokines (e.g., IL-5), reduces numbers of $CD4^+$ and $CD8^+$ T cells, increases autoantibody responses, and increases proportions of $CD19^+$ B cells in circulation (Kim et al., 1999; Liu et al., 2003; Palaszynski et al., 2004b; Sicotte et al., 2002; Soldan et al., 2003). In female mice, induction of EAE causes DCs from E3-treated mice to develop a tolerogenic phenotype, in which there is upregulation of activation and costimulatory surface markers, including inhibitory PD-L1, reduction of proinflammatory transcripts (i.e., IL-12 and IL-6 mRNA), and increased expression of anti-inflammatory transcripts (i.e., TGF-β and IL-10 mRNA) (Papenfuss et al., 2011). Adoptive transfer of DCs from E3-treated females prior to

induction of EAE provides protection against development of disease by causing Th2-biased immune responses (Papenfuss et al., 2011). Stimulation of T cells from E3-treated EAE mice with myelin basic protein induces elevated production of the anti-inflammatory cytokine, IL-10 (Kim et al., 1999). The effects of E3 on T cell function are mediated by reduced degradation of IκB leading to inhibition of NF-κB activity and reduced concentrations of proinflammatory cytokines (Zang et al., 2002). Estriol treatment also reduces concentrations of matrix metalloproteinase 9 in EAE mice, which likely contributes to reduced infiltration of monocytes and inflammatory T cells into the central nervous system (CNS) (Gold et al., 2009). Estriol, like E2, stimulates antibody production against innocuous antigens (Ding and Zhu, 2008), which is likely one factor contributing to heightened humoral immunity during pregnancy.

Progesterone

Progesterone is produced by the corpus lutea in the ovaries in non-pregnant females and by the placenta during pregnancy, playing a critical role in reproduction and immune function. Progesterone is typically regarded as anti-inflammatory. Progesterone receptors (PRs) have been identified in epithelial cells as well as in mast cells, eosinophils, macrophages, DCs, and lymphocytes (Kovats et al., 2010). There are sex differences in PR expression. For example, the expression of PRs is higher in DCs from females, which may explain why P4 is better able to suppress the activity (e.g., secretion of TNF-α) of DCs from female than male rats (Butts et al., 2008). Progesterone can bind to glucocorticoid receptors (GRs), which are more abundant in the immune system than are PRs, and may represent an alternative mechanism for progesterone-induced changes in immune function (Jones et al., 2010). Progesterone inhibits TLR-induced cytokine production as well as surface receptor expression via PRs and GRs in DCs (Jones et al., 2010).

Progesterone suppresses innate immune responses, including macrophage and NK cell activity as well as NF-κB signal transduction (Baley and Schacter, 1985; Furukawa et al., 1984; McKay and Cidlowski, 1999; Miller and Hunt, 1996; Savita and Rai, 1998; Toder et al., 1984). Progesterone can inhibit nitrite and nitric oxide production as well as *Tnfα* mRNA expression by murine macrophages (Miller et al., 1996; Miller and Hunt, 1998; Savita and Rai, 1998). Elevated concentrations of progesterone during pregnancy inhibit the development of Th1 immune responses and promote production of Th2 immune responses, including IL-4 and IL-5 production (Piccinni et al., 1995; Piccinni et al., 2000). In humans, elevated concentrations of progesterone during the second trimester of pregnancy is correlated with reduced activity of regulatory T cells (Mjosberg et al., 2009). In contrast, in mice, the activity of regulatory T cells is increased at the maternal-fetal interface and in lymphoid tissues in pregnant females and in non-pregnant females exposed to P4 (Kallikourdis and Betz, 2007; Mao et al., 2010). Progesterone also suppresses antibody production (Lu et al., 2002).

Pregnancy and pregnancy-associated hormones affect disease pathogenesis

The hormonal and immunological changes that occur during pregnancy affect susceptibly to and the outcome of autoimmune and infectious diseases (Figure 2). Generally, the severity of diseases that are exacerbated by inflammatory immune responses, like MS, rheumatoid arthritis, and psoriasis, is reduced during pregnancy (Confavreux et al., 1998; Ostensen and Villiger, 2002; Raychaudhuri et al., 2003). In contrast, the severity of many infectious diseases, which require inflammatory responses for the initial control and clearance of pathogens, is increased during pregnancy (Jamieson et al., 2009; Krishnan et al., 1996a; Luft and Remington, 1982; Menendez, 1995). Hormones contribute significantly to the outcome

of immune-related diseases during pregnancy by altering the functioning of immune cells. Hormones can have additional effects on the outcome of infection during pregnancy. For example, hormonal changes, including increased concentrations of P4, are hypothesized to alter not only local immune responses, but also genital tract mucosa, to increase the risk of HIV infection during pregnancy (Gray et al., 2005). For this review, the diseases selected are intended to provide examples of how pregnancy, pregnancy-associated hormones, or both affect the pathogenesis of disease, primarily by altering immune function.

Multiple sclerosis

Multiple sclerosis is caused by inflammatory immune responses, including Th1 and Th17 responses, that target the myelin sheath of axons within the CNS to promote axon demyelination, axonal damage, and neurological dysfunction. Clinically, MS is characterized by two courses of disease including relapsing-remitting MS (RRMS), the more prevalent form of the disease defined by an acute phase of CNS inflammation and neurological dysfunction, and the chronic secondary progressive (SPMS) phase associated with more severe neurological damage (Tsui and Lee, 2011; Voskuhl, 2011). Although MS occurs more frequently in females than males, the frequency of MS relapses is reduced during pregnancy (Confavreux et al., 1998; Whitacre et al., 1999; Whitaker, 1998). A study of female MS patients monitored before, during, and post-pregnancy revealed that compared with pre-pregnancy relapse rates, pregnant MS patients suffer fewer relapses, an effect most pronounced during the third trimester, during which pregnancy-associated hormones reach their highest level (Confavreux et al., 1998). During the post-partum period, when pregnancy-associated hormones rapidly decline, relapse rates return to comparable levels observed prior to pregnancy (Confavreux et al., 1998).

There are several mechanisms by which pregnancy-associated hormones are hypothesized to alter MS disease pathogenesis, including modulation of the immune response. Elevated concentrations of E3 can reduce MS disease pathogenesis by significantly reducing CNS lesion size, circulating inflammatory cytokines (e.g., IFN-γ), and delayed type hypersensitivity responses (Sicotte et al., 2002). PBMCs isolated from female MS patients treated with pregnancy-level E3 show decreased numbers of $CD4^+$ and $CD8^+$ T cells and increased B cells in both RRMS and SPMS patients (Soldan et al., 2003). PBMC stimulation ex vivo with mitogens and autoantigens also display increased production of IL-5 from $CD4^+$ and $CD8^+$ T cells, IL-10 from $CD64^+$ monocytes and macrophages, and decreased TNF-α production from $CD8^+$ T cells (Soldan et al., 2003). One mechanism by which pregnancy-associated hormones modulate immune function is through inflammatory gene regulation (Soldan et al., 2003). Genome-wide microarray analysis of PBMC mRNA isolated from healthy age-matched females and MS patients before, during, and after pregnancy reveals a distinct pattern of several differentially expressed inflammation-related genes, including TNF-α induced protein 3 (*Tnfaip3*), suppressor of cytokine signaling 2 (*Socs2*), nuclear receptor subfamily-4 member 2 (*Nr4a2*), and CXC chemokine receptor-4 (*Cxcr4*) in MS patients prior to pregnancy; by the third trimester of pregnancy, however, these genes are expressed at levels that are similar to healthy females an effect that is lost post-partum (Gilli et al., 2010). Estrogens regulate several of the immune-related genes characterized in this study and may partially account for the distinct expression patterns observed during pregnancy and the rapid deregulation that occurs post-partum (Gilli et al., 2010).

In the EAE mouse model of MS, disease induced by autoantigen immunization during mid to late gestation is less severe than disease induced in virgin aged-matched females or following parturition (Langer-Gould et al., 2002; McClain et al., 2007). Despite reduced disease severity and decreased production of proinflammatory cytokines (e.g., TNF-α and IL-17) in pregnant EAE mice, cellular infiltrates in the CNS are not reduced in pregnant

compared with non-pregnant females (Langer-Gould et al., 2002; McClain et al., 2007). Estriol or ERα agonist treatment prior to EAE induction in non-pregnant female mice reduces disease severity and TNF-α, IFN-γ, IL-2, and IL-6 production by splenocytes stimulated ex vivo with recall autoantigen (Palaszynski et al., 2004a; Tiwari-Woodruff et al., 2007; Tiwari-Woodruff and Voskuhl, 2009). Estriol treatment during the effector phase of EAE also mitigates the disease severity and increases circulating autoantigen-specific IgG1 and production of IL-10 from antigen-specific $CD4^+$ T cells (Kim et al., 1999). Progesterone-treated EAE mice also have reduced disease severity and inflammatory cytokine concentrations (e.g., IL-2 and IL-17) and increased numbers of B cells and anti-inflammatory cytokine concentrations (e.g., IL-10) (Yates et al., 2010). Progesterone treatment also reduced the expression or several chemokines and related receptors, including chemokine (C-C motif) ligand 3 (CCL3), chemokine (C-C motif) receptor 2 (CCR2), and CCR7 in the CNS during EAE induction, which may influence cellular infiltration into the CNS (Yates et al., 2010). Additionally, P4 promotes axon remyelination and repair through oligodendrocyte progenitor cell activation, maturation, and recruitment to foci of damaged myelin sheaths (Garay et al., 2009; Hussain et al., 2011).

Influenza

Pregnancy is a risk factor for severe disease outcome during both seasonal epidemics and pandemics of influenza viruses, with pregnant women experiencing greater complications than either non-pregnant women of the same age or the general population (Harris, 1919; Jamieson et al., 2009; Klein et al., 2010b; Klein et al., 2010c; Van Kerkhove et al., 2011). During the 1918 H1N1 pandemic, for example, a study of 1350 cases of influenza virus infection in pregnant women revealed that half of the pregnant women developed severe complications, including pneumonia, and almost a third of the women died as a result (Harris, 1919). Hospitalization with severe disease and mortality rates for pregnant women are consistently higher when compared with the general population during the 1918 H1N1 pandemic (Harris, 1919; Rothberg and Haessler, 2010), the 1957 H2N2 pandemic (Lapinsky, 2010; Mosby et al., 2011), and the 2009 H1N1 pandemic (Ellington et al., 2011; Jamieson et al., 2009; Klein et al., 2010b; Lapinsky, 2010; Mosby et al., 2011). In addition to increased hospitalization and death rates during pregnancy, severe influenza can affect the outcome of pregnancy, including preterm delivery, low birth weight, and fetal loss (Creanga et al., 2011a; Creanga et al., 2011b; Harris, 1919; Schwandt et al., 2011).

The risk of severe influenza is greatest during the second and third trimester of pregnancy (Harris, 1919; Neuzil et al., 1998; Van Kerkhove et al., 2011). Women in their third trimester of pregnancy account for over half of the deaths from secondary pneumonia during the 1918 H1N1 pandemic (Harris, 1919). Seasonal influenza cases monitored between 1974 and 1993 revealed that pregnant women are 3–4 times more likely to die from influenza-related illness during the third trimester than are non-pregnant women (Neuzil et al., 1998). Pregnancy-associated changes in cardiovascular and pulmonary function are hypothesized to underlie severe influenza (Louie et al., 2009; Mosby et al., 2011). Although physical changes may contribute to influenza severity in some cases, there is no cluster of physiologic changes that is consistently correlated with increased risk of severe outcome from influenza in pregnant women (Dodds et al., 2007). Even in the absence of co-morbid medical conditions, including asthma, diabetes, and cardiovascular disease, pregnant women still have an increased risk of influenza-related hospitalization and death (Neuzil et al., 1998).

Dysregulated cytokine and chemokine production, excessive immune cell influx, and damage to the lungs are hypothesized underlie influenza pathology (Hennet et al., 1992; Kash et al., 2004; Kash et al., 2006; Kobasa et al., 2007; Perrone et al., 2008; Tumpey et al., 2005). There is a paucity of data on immune responses to influenza virus infection during

pregnancy. During the 2009 H1N1 pandemic, compared to post-partum and non-pregnant women, pregnant women had lower circulating levels of IgG2 antibody, which at high levels is hypothesized to protect against secondary bacterial infections following influenza infection (Chan et al., 2011). Reduced IgG2 is associated with severe influenza outcome and dysregulated cytokine production (Chan et al., 2011; Gordon et al., 2010). Small animal models have been instrumental for understanding the pathogenesis of 2009 H1N1 in pregnant females. Pregnant mice exposed to pandemic 2009 H1N1 have greater mortality than non-pregnant age-matched females (Chan et al., 2011; Marcelin et al., 2011). There are some reports that pregnant females have greater virus replication in their lungs than non-pregnant females, but other reports suggest that virus replication is not affected by pregnancy (Chan et al., 2011; Marcelin et al., 2011). The increased mortality in pregnant female mice correlates with greater induction of proinflammatory cytokines and chemokines, including TNF-α, CCL2, CCL3, and CXCL1, in the lungs following infection (Chan et al., 2011; Marcelin et al., 2011). Pregnant female mice also have greater numbers of pulmonary macrophages and regulatory T cells, but similar numbers of $CD8^+$ T cells and levels of neutralizing antibodies, compared with non-pregnant females (Marcelin et al., 2011). The underlying hormonal mechanisms that might contribute to differential immune responses to and outcome of influenza virus infection during pregnancy remain to be elucidated. Elevation of E2 in non-pregnant female mice reduces, rather than increases, the severity of influenza A virus infection (Robinson et al., 2011), suggesting that this is not the hormonal mechanism mediating increased severity of influenza during pregnancy. Whether other estrogens, P4, or even glucocorticoids alter immune responses to influenza virus infection to result in more severe disease in pregnant females requires consideration.

Toxoplasmosis

Infection with the parasite *Toxoplasma gondii* typically results in mild or asymptomatic disease in adults, but can become severe in pregnant females (Pfaff et al., 2007; Roberts et al., 2001). Congenital transmission is documented in humans and rodent models (Pfaff et al., 2007). There are, however, reports that chronic *T. gondii* infection, in either humans or mice, does not result in transmission of parasites to offspring (Roberts et al., 2001), even if re-infected during pregnancy (Roberts and Alexander, 1992), suggesting that maternal immunity, probably transmission of antibodies, is sufficient to protect offspring. If pregnant females are infected early during pregnancy, prior to the anti-inflammatory skewing of the immune response, then transmission of parasites to offspring is low. Infection during early pregnancy, however, can result in excessive IFN-γ production, apoptosis of placental cells, and fetal resorption (Senegas et al., 2009). If pregnant females are infected during later stages of pregnancy, when inflammatory responses are low, then congenital transmission is likely to occur (Pfaff et al., 2007; Roberts et al., 2001).

Pregnant female mice are more susceptible to infection with *T. gondii* and experience worse disease outcome than non-pregnant females (Luft and Remington, 1982; Shirahata et al., 1992). The activity of NK and T cells as well as production of IL-12, IFN-γ, and TNF-α during the early stages of infection are necessary for induction of adaptive immune responses and clearance of parasites (Roberts et al., 2001). Pregnant females produce significantly less IFN-γ than non-pregnant females during *T. gondii* infection (Luft and Remington, 1982; Shirahata et al., 1992). Administration of recombinant IFN-γ to pregnant female mice improves the outcome of *T. gondii* infection and can reduce congenital transmission of parasites (Abou-Bacar et al., 2004a; Abou-Bacar et al., 2004b; Shirahata et al., 1992) but can also directly harm the developing fetus (Pfaff et al., 2007). There is growing evidence that hormones underlie increased susceptibility of pregnant females to toxoplasmosis. In female mice, E2 exacerbates, whereas gonadectomy reduces, parasite burden and disease pathogenesis (Kittas and Henry, 1979, 1980). High concentrations of P4

also increase susceptibility to *T. gondii* during pregnancy by suppressing production of IL-12 and IFN-γ (Jones et al., 2008).

Malaria

In malaria endemic areas, susceptibility to malarial infections is increased during pregnancy and is higher among primiparous (i.e., females that are in their first pregnancy) than multiparous (i.e., females that have had multiple pregnancies) females. Females are more susceptible to infection during the first pregnancy because they are immunologically naïve to the parasite adhesion proteins (i.e., they do not possess anti-adhesion antibodies) that are expressed in the placenta during pregnancy (Fried et al., 1998; Hviid et al., 2010; Rogerson et al., 2007). Increased susceptibility to infection among pregnant females is attributed to both increased parasites sequestered in the placenta and pregnancy-associated suppression of inflammatory responses caused by hormonal changes during pregnancy (Rogerson et al., 2007). In primiparous women infected with *Plasmodium falciparum* during pregnancy, elevated proinflammatory responses (e.g., IFN-γ and TNF-α) combined with low anti-inflammatory responses (e.g., IL-10) in the placenta are related to low birth weights (Fried et al., 1998). Following stimulation with parasite antigen, NK cells from infected primiparous women produce more IFN-γ that those from infected multiparous women suggesting that these innate immune cells play a role in the immunological profile of infected females during pregnancy (Bouyou-Akotet and Mavoungou, 2009).

Maternal infection is often associated with negative fetal outcomes. For example, offspring of women infected with *P. falciparum*, nonhuman primates infected with *P. coatneyi*, and rodents inoculated with *P. berghei* during pregnancy have lower birth weights and slower growth rates than offspring from uninfected females (Akingbade, 1992; Davison et al., 1998; Menendez, 1995). Although *Plasmodium* parasites sequester in the placenta of humans and rodents, infected females do not transmit parasites to offspring in utero (Rogerson et al., 2007). In rodent malaria models, negative pregnancy outcome, including an inability to maintain a viable pregnancy, is associated with elevated inflammatory responses, including IL-1β and IFN-γ production, both systemically and in the placenta (Poovassery and Moore, 2009; Poovassery et al., 2009).

Pregnancy-associated changes in cell-mediated immune responses and increased susceptibility to *Plasmodium* infections have been attributed to hormonal changes that occur during pregnancy (Rogerson et al., 2007). Studies of women in malaria endemic regions, as well as mouse models of *P. berghei*, reveal that concentrations of glucocorticoids (i.e., cortisol in human and nonhuman primates and corticosterone in rodents) are higher in pregnant females infected with malaria parasites than in uninfected pregnant females (Bayoumi et al., 2009; Van Zon et al., 1983; Van Zon et al., 1986; Vleugels et al., 1989; Vleugels et al., 1987). Elevated glucocorticoids increase, while adrenalectomy decreases, parasitemia in pregnant female mice which may be caused by glucocorticoid-induced suppression of inflammatory responses (van Zon et al., 1982). Prolactin concentrations are either reported to not change with malaria infection during pregnancy (Bouyou-Akotet et al., 2005) or to be lower in *P. falciparum* infected than uninfected pregnant females (Bayoumi et al., 2009). Malaria infection also reduces E2 concentrations in late pregnancy (Watkinson et al., 1985). The bi-directional interactions between hormones and malaria infection contribute both to female susceptible to infection as well as the outcome of pregnancy.

Conclusions and future directions

The immunological shifts that occur during pregnancy are necessary for reproductive success and, thus, are favored by natural selection. Hormones are the driving factors behind changes in immune function and disease susceptibility during pregnancy. This provides

insight into how to therapeutically manipulate the hormonal milieu in non-pregnant individuals to reduce the pathogenesis of infectious and autoimmune diseases (Klein et al., 2010b; Voskuhl, 2011). The observation that the impact of malaria infection is less detrimental among multiparous than primiparous females should be expanded to other infectious as well as autoimmune diseases as this might provide novel insights into disease pathogenesis among pregnant females. Is the severity of disease, in general, reduced with an increased number of pregnancies? Whether the memory responses mounted are an evolved host-mediated response to infectious diseases during pregnancy requires consideration.

Congenital transmission of pathogens from an infected female to her offspring, although not extensively discussed in this review, is of significant consideration during pregnancy. Several pathogens, ranging from *T. gondii, P. falciparum*, and *L. major* to HIV and influenza can be transmitted from mother to offspring in utero (Andiman, 2002; Pfaff et al., 2007; Rogerson et al., 2007; Yawn et al., 1971). The mechanisms mediating why some pathogens (e.g., *T. gondii* and *P. falciparum*) but not others (e.g., seasonal influenza viruses) harm the fetus when vertically transmitted are diverse (Henriquez et al., 2010; Klein et al., 2010c). The factors that appear to be most significant determinants of the impact of infection on pregnancy outcome include the timing of infection (i.e., whether exposure occurs during early or late pregnancy), the magnitude of the host inflammatory responses mounted, and whether the pathogen is sequestered in the placenta and causes physical damage (Henriquez et al., 2010). Future studies should systematically evaluate the role of endocrine-immune interactions in the context of congenital transmission of pathogens.

Mechanistically, several proteins and pathways emerge as being most consistently altered during pregnancy. The activity of sex steroids signaling through intracellular steroid receptors generally suppresses transcriptional regulation of inflammatory cytokines. Hormonal-suppression of IFN-γ, which has critical anti-viral and anti-parasitic properties, contributes significantly to the worse outcome from infectious diseases and improved outcome of inflammatory autoimmune diseases during pregnancy. Studies of mice in which recombinant IFN-γ is administered to pregnant females and improves outcome of infection (Abou-Bacar et al., 2004a; Abou-Bacar et al., 2004b; Shirahata et al., 1992) should be explored further. Because global increases in IFN-γ can compromise the outcome of pregnancy, greater attention should be paid to designing prophylaxis and therapeutic treatments that boost pathogen-specific immunity or select arms of the immune system. The concurrent upregulation of regulatory T cell activity and anti-inflammatory cytokines also consistently contributes to altered disease outcome among pregnant females and should be explored further.

Host immunity is typically not therapeutically manipulated in pregnant females and this population is often not enrolled in drug or vaccine efficacy trials. Use of animal models and primary cell cultures (e.g., placental cell or umbilical vein cultures) will continue to elucidate the direct effects of hormones on immune cell function and disease pathogenesis and may provide insight into the aspects of immunity that could be safely manipulated in pregnant females. From a public health perspective, knowledge that protective immunity against pathogens is reduced during pregnancy provides grounds for evaluating interventions, like vaccinations, that could improve protection of pregnant females and their fetuses. Because the hormonal and immunological environment of a pregnant females is vastly different from that of non-pregnant females, these females must be considered separately when analyzing the efficacy of treatments for disease (Klein et al., 2010a).

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Abbreviations

DC	dendritic cell
E2	estradiol
E3	estriol
IFN	interferon
IL	interleukin
NK	natural killer
PBMCs	peripheral blood mononuclear cells
P4	progesterone
PIBF	progesterone-induced binding factor
Th1	helper T cell type 1
Th2	helper T cell type 2
TNF	tumor necrosis factor

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Highlights

- Inflammatory responses are lower and anti-inflammatory responses are higher during pregnancy
- The immunological shift during pregnancy promotes healthy fetal development
- the severity of diseases that are caused by inflammation is reduced during pregnancy
- the severity of diseases mitigated by inflammatory responses is increased during pregnancy
- sex steroids mediate the immunological shift and altered disease pathogenesis during pregnancy

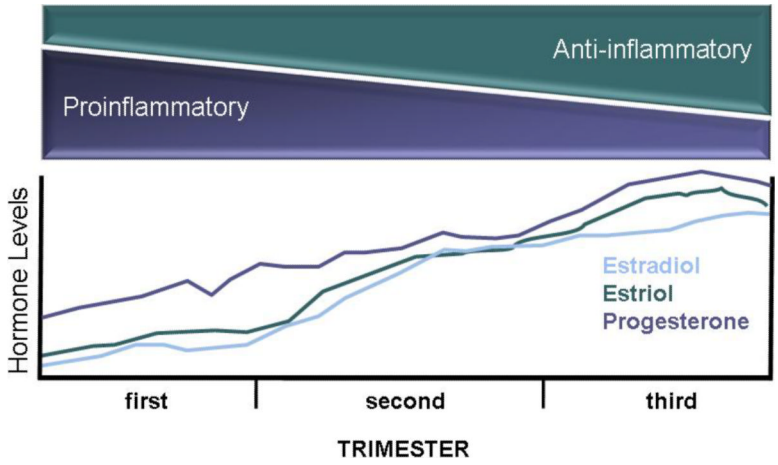

Figure 1.

During the three trimesters of pregnancy, there is a shift in the balance of proinflammatory and anti-inflammatory responses. By the third trimester, anti-inflammatory responses, including the activity of M2 macrophages, Th2 cells, and regulatory T cells, are elevated and inflammatory responses, including the activity of NK cells, M1 macrophages, and Th1 cells, are reduced. Changes in the concentrations of sex steroids, including estradiol, estriol, and progesterone, lead to the immunological shifts during pregnancy.

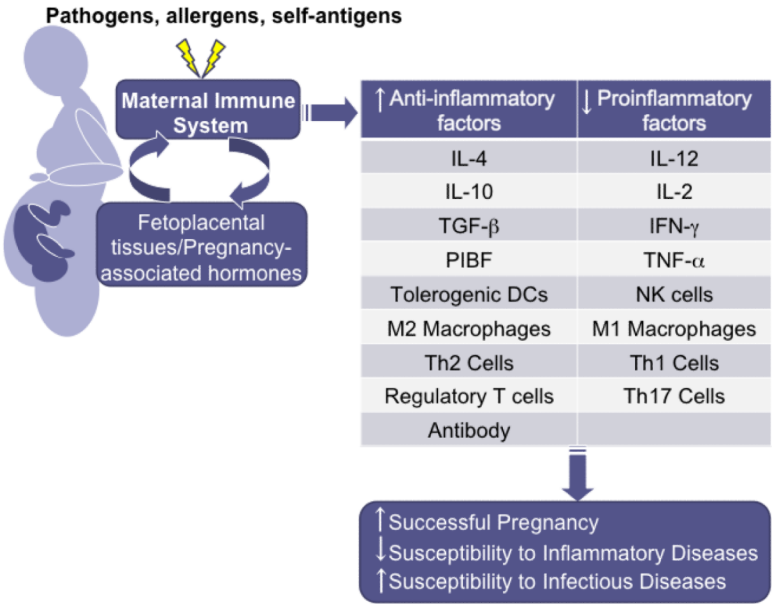

Figure 2.

Hormonal changes and exposure to fetal antigens during pregnancy skew the maternal immune system toward higher anti-inflammatory responses and away from proinflammatory responses, especially during the third trimester. These immunological changes are necessary for successful pregnancy, but also affect the outcome of disease.