Immune Reconstitution Syndrome and Exacerbation of Infections after Pregnancy

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Pregnancy is a state of subtle immunosuppression characterized by physiologic suppression of proinflammatory host responses that are meant to promote embryonic implantation. Rapid reversal of these changes and a rebound of inflammatory responses during the postpartum period can result in quiescent or latent infection manifesting as symptomatic disease. Infections due to several microbial pathogens and noninfectious diseases with an autoimmune basis have been shown to worsen or begin during the postpartum period. Awareness that symptoms resulting from immune reconstitution can occur in any host with a rapidly changing immunologic repertoire, including women in the postpartum phase, is a critical first step in fully understanding this phenomenon. Future studies to discern the precise pathophysiologic basis of immune reconstitution, to identify pregnant women at risk, and to determine markers that may be diagnostically helpful have significant implications for optimizing treatment of these patients.

The expression and clinical outcomes of infectious diseases have typically been understood to be associated with microbial damage inflicted by the pathogen. However, the host immune response is increasingly considered to play a critical role in microbial pathogenesis [1, 2]. The tenets of “damage response framework of microbial pathogenesis,” a conceptual paradigm that integrates the host and pathogen interactions, dictate that, although host immunity is critical in facilitating the eradication of infection, a strong or overly robust immune response may, in fact, be detrimental to the host [1]. Restoration of host immunity, particularly if abrupt and rapid, may have adverse sequelae, and when a threshold amount is reached, the host can become gravely ill with symptomatic disease resulting from immune reconstitution [1].

The biologic principle yields valuable insights into the basis of infectious complications [3, 4]. Pregnancy is a state of relative immunosuppression characterized by antiinflammatory cellular responses that promote tolerance to fetal antigens [5–7]. Reversal of these changes during the postpartum period may result in overt clinical manifestations of otherwise quiescent or latent infections. The concept of immune reconstitution as a contributor to exacerbation of infection during the postpartum period, however, remains poorly appreciated in the clinical context. Previously, we attempted to define immune reconstitution syndrome (IRS) as it relates to HIV infection and solid-organ transplantation [8], but any clinical condition associated with a rapid change in immune status is conducive to the appearance of IRS. We review pregnancy-associated changes in the immune system, the implications of these changes for infections that may worsen during the postpartum period, and the clinical characteristics of such infections.

UNIQUE IMMUNOLOGIC CHANGES DURING PREGNANCY AND THE POSTPARTUM PERIOD

An immunosuppressive status, characterized by antiinflammatory responses, is critical for the maintenance of pregnancy [5, 9, 10]. During pregnancy, Th2 (e.g., IL-10) and Th3 responses (e.g., transforming growth factor β), which support pregnancy, are enhanced,
whereas Th1 cytokines (i.e., IL-12 and IFN-γ), which are potentially detrimental to the foreign fetus, are suppressed (table 1) [9–15]. Maternal hormones, including progesterone, cortisone, norepinephrine, and 1,25-dihydroxyvitamin, play a major role in modulating immune responses during pregnancy [7, 15–18]. In addition, local immunoreactivity at the maternal-fetal interface also shifts towards Th2 [7]. In murine pregnancy models, most IL-10 and transforming growth factor β2 were derived from γδ T cells, which infiltrated the placental decidua as early as day 8 of gestation to down regulate immune response for acceptance of the fetus [9]. The shift in the maternal immunological repertoire towards Th1 during the postpartum period may be associated with a physiologic or even enhanced proinflammatory response [15]. Reversal in the cytokine pattern was documented 3–6 weeks after delivery in 1 study [15].

A Th2 response also facilitates the establishment of infection caused by a number of pathogens, including fungi and Mycobacteria species [19–21]. Although ultimately beneficial for the eradication of infection, reversal of Th2 to Th1 response because of resolution of immunosuppression may be associated with inflammatory responses that mimic worsening disease expression or relapse [22].

### AUTOIMMUNE DISEASES AND OTHER NONINFECTIOUS ENTITIES

It has been shown that autoimmune disorders that are exacerbated by a Th1 response, such as rheumatoid arthritis and multiple sclerosis, undergo remission during pregnancy but “flare up” during the postpartum period [15]. For example, pregnant women are 70% less likely than other women to develop symptomatic rheumatoid arthritis [23]. On the other hand, the risk of developing rheumatoid arthritis during the postpartum period, particularly during the first 3 months, is markedly increased [23]. In women with multiple sclerosis, the rate of relapse decreases during pregnancy and increases during the first 3 months of the postpartum period before returning to the prepregnancy rate [24]. Other autoimmune disorders (e.g., Graves disease and Hashimoto thyroiditis) also ameliorate spontaneously during pregnancy and then aggravate during the postpartum period [25, 26]. A population-based survey in New York City documented that 45% of the women who developed Graves disease during their lifetime first received a diagnosis during the postpartum period [26]. In another study, 70% of the mothers who had positive results of a screening test for thyroid stimulating antibody developed transient or persistent postpartum Graves disease 3–6 months after delivery [25]. Case reports have also documented postpartum development of hemolytic uremic syndrome, idiopathic polymyositis, autoimmune myocarditis, antiphospholipid antibody syndrome, and sarcoidosis [25, 27–29].

IRS after the initiation of HAART in HIV-infected patients may present as Guillain-Barré syndrome [30]. Severe Guillain-Barré syndrome was reported in 2 pregnant women, 1 of whom required prolonged mechanical ventilation [31]. Treatment of both patients with intravenous immunoglobulin and of 1 of the patients with corticosteroids proved to be ineffective; however, rapid recovery was experienced by both women after delivery. Thus, a primed immune system during the postpartum period may have ultimately facilitated the resolution of an otherwise refractory condition. IRS in HIV-infected patients may

### Table 1. Cellular and humoral immune responses during pregnancy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular immunity</strong></td>
<td></td>
</tr>
<tr>
<td>Innate</td>
<td></td>
</tr>
<tr>
<td>Monocytes and granulocytes</td>
<td>Increased levels, enhanced phagocytosis and respiratory burst activity, and surface expression of CD14</td>
</tr>
<tr>
<td>NK cells</td>
<td>Down regulation of cytotoxic activity by progesterone-induced blocking factor and IL-10; decreased IFN-γ production</td>
</tr>
<tr>
<td>Adaptive</td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>Enhanced Th2 (e.g., IL-4 and IL-10) and Th3 (transforming growth factor-β) and suppressed Th1 (IFN-γ and IL-12) responses</td>
</tr>
<tr>
<td>B cells</td>
<td>Increased Th2-induced B cell activity</td>
</tr>
<tr>
<td><strong>Humoral immunity</strong></td>
<td></td>
</tr>
<tr>
<td>Innate</td>
<td></td>
</tr>
<tr>
<td>Complement</td>
<td>Increased C3, C4, C1q levels and high levels of complement regulatory protein, such as membrane cofactor protein (CD46), decay accelerating factor (CD55), and CD59</td>
</tr>
<tr>
<td>Acute phase reactants</td>
<td>Increase in acute phase reactants, such as fibrinogen and ceruloplasmin</td>
</tr>
<tr>
<td>Adaptive</td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>Increased T cell-dependent immunoglobulin production</td>
</tr>
</tbody>
</table>

**NOTE.** Data were compiled from [6, 7, 11–14]. NK, natural killer.
manifest as cutaneous reactions to injectable agents [32]. Liver extract injections were associated with postpartum erythema nodosum, which resolved after prednisone therapy [33].

A large interindividual variation in the effect of pregnancy on IL-12 production has been noted, suggesting that some women may have a propensity for enhanced Th1 rebound during the postpartum period [15]. These data may explain why exacerbation of infection during the postpartum period is observed in some pregnant women and suggest a role for genetic predisposition or other host factors in the susceptibility to IRS, as has been shown for other patient populations [34, 35].

**INFECTIOUS ETIOLOGIES**

**Bacteria**

*Mycobacterium tuberculosis.* Case series and reports dating as far back as the 1920s have described new onset or acute worsening of preexistent tuberculosis during the postpartum period [36–44]. Pregnant women have been shown to experience progressive impairment of lymphocyte reactivity to purified protein antigen, indicating pregnancy-associated depression of cell-mediated immunity [45]. Lymphocyte reactivity was shown to return to normal as early as 24 h after delivery and to recover completely by 4 weeks after delivery [45]. These data suggest that exacerbation of latent tuberculosis during the postpartum period may be related to rapid reconstitution of pathogen-specific cellular immune responses.

A review of 29 cases that was published in 2003 documented that tuberculosis developed a median of 10 days (range, 1–30 days) after delivery, with 76% of the patients experiencing symptoms within 10 days after delivery [40]. Tuberculosis during pregnancy was associated with extrapulmonary infection in 5%–10% of the patients, and this proportion is comparable to the incidence of extrapulmonary tuberculosis among nonpregnant women of the same age and ethnicity [46]. However, 93% of the patients with tuberculosis during the postpartum period had tuberculosis with extrapulmonary involvement, and of these patients, 69% had CNS infection [40]. The overall mortality rate associated with tuberculosis during the postpartum period was 38% [40]. An additional 14% of the patients experienced severe sequelae related to the infection, such as hemiparesis [40].

In persons previously infected with *M. tuberculosis*, reactivation at the sites of the initial and lymphohematogenous metastatic foci is effectively inhibited by CD4+ T cell responses, for which IFN-γ and TNF-α are critical [47, 48]. Depression of these responses during pregnancy may lead to reactivation of endogenous foci, which remain quiescent or subclinical until after pregnancy, when abrupt onset of a proinflammatory response may lead to overt clinical manifestations at the sites of these lesions. Granulomatous lesions associated with tuberculosis during the postpartum period demonstrate abundant inflammatory cells with few bacteria [42], signifying attempts on the part of the host to contain infection. However, these responses may not be wholly protective, given the poor outcomes associated with tuberculosis during the postpartum period.

*Mycobacterium leprae.* Disease expression in the context of leprosy is characterized by a paucibacillary tuberculoid form, which develops when cellular immunity is high and the bacterial load is low, or the lepromatous form, which is associated with poor cellular responses and high bacillary load. Tissue specimens of tuberculoid leprosy have been shown to have high levels of mRNA encoding for proinflammatory cytokines, IFN-γ, and IL-12 but a low level of IL-10 [49, 50]. In contrast, lepromatous leprosy tissue specimens show a predominantly Th2 cytokine profile [49, 50]. In addition, an abrupt increase in inflammation may occur within previously quiescent skin lesions and new lesions, or neuritis may develop in the tuberculoid form after initiation of therapy [3]. These clinical manifestations, known as reversal reactions, are associated with a Th1 profile and demonstrate CD4+ T cells with increased levels of IFN-γ and IL-12 [51].

Women infected with *M. leprae* may develop overt leprosy during the postpartum period. In addition, in up to 6% of the cases of leprosy in pregnant women, disease onset has occurred during lactation [3]. Cured patients with tuberculoid leprosy are at risk for relapse, with the development of lepromatous leprosy during pregnancy and reversion to the tuberculoid form during lactation [3, 52]. Likewise, pregnant women receiving treatment for leprosy have a 50% risk of disease conversion to the lepromatous form [3]. Reversal reactions during the postpartum period may be associated with inflammation and loss of function of the large peripheral nerves that had been silently harboring the bacteria. Indeed, it has been recommended that women with cured leprosy should be observed for the development of reversal reactions or evidence of nerve damage; treatment with high dose corticosteroids should be considered if these reactions develop [3, 52].

**Fungi**

*Cryptococcus neoformans.* In patients with cryptococcosis, a Th2 response facilitates the establishment of infection [21, 53–55]. On the other hand, a Th1 profile confers protection and is characterized by inflammatory lesions, which are a hallmark of cryptococcal-related IRS observed in diverse immunocompromised hosts, such as HIV-infected individuals and transplant recipients [22, 56]. Case reports document a similar phenomenon in pregnant women, in whom quiescent cryptococcal infection acutely worsened during the postpartum period; although rare, cryptococcal infection has been reported to be transmitted from mother to child [57]. A review of cryptococcosis during pregnancy reported that 45% of the cases occurred during the third trimester or the postpartum period.
Prior to the advent of specific therapy, neurologic symptoms in a woman who had lived with chronic cryptococcal meningitis for ~16 years worsened after her second pregnancy, and she died [4]. Another report documented onset of C. neoformans var. gattii meningitis during the postpartum period, with markedly elevated intracranial pressure, in an Australian aboriginal woman in whom receipt of antifungal therapy was ultimately shown to revert Th2 to Th1 response [59]. Lesions of cryptococcal osteomyelitis worsened abruptly after delivery in a woman in whom antifungal therapy was deferred initially because of minimally symptomatic disease that had been present since the first trimester [60]. In another instructive case report, a patient became symptomatic several weeks after delivery, with signs of pneumonia [61]. A biopsy specimen of the pulmonary infiltrate revealed necrotizing granulomas with cryptococcus, but the culture result was not reported. The patient received only 2 weeks of fluconazole therapy, and at a follow-up visit a few months later, the infiltrate had improved [2]. It is likely that infection occurred during pregnancy, and because IRS was established and the immune system was activated during the postpartum period, minimal antifungal therapy was needed.

**Coccidioides immitis and other mycoses.** Although pregnancy does not increase the risk of coccidioidomycosis, it has been critically linked with disseminated disease, especially during the third trimester of pregnancy and the postpartum period [62]. In a review of 29 cases of coccidioidomycosis that occurred during the third trimester of pregnancy, the mortality rate was 55%, and among 7 cases that occurred during the postpartum period, the mortality rate was 29% [63]. A study of pregnant women in a region of endemicity documented 10 cases of coccidioidomycosis among 47,120 pregnancies [64]. Only 2 of the 10 pregnant women with coccidioidomycosis developed disseminated disease, and both became ill during the postpartum period, as did a patient in another report [65].

During pregnancy, cell-mediated immunity is progressively depressed in patients with prior coccidioidal immune reactivity [66]. In 1 study, pregnant women who developed acute coccidioidomycosis during pregnancy failed to develop an immune response, and in fact, the suppression of coccidioidal-specific antigen response persisted for >1 year after delivery [66]. T cell immunity through elaboration of cytokines is also critical in the control of coccidioidomycosis. In experimental models of infection, IFN-γ, IL-6, and IL-12 conferred resistance, whereas IL-4 and IL-10 lead to susceptibility to *C. immitis* [67–71]. An exaggerated proinflammatory response, however, has been linked to severe disease manifestations due to *C. immitis* [67, 72]. The extreme difficulty with regard to this infection during pregnancy may also be related to depressed cellular immunity during pregnancy combined with the known alterations in 17β estradiol and progesterone levels, which have been shown to increase the maturation and growth of *C. immitis* [73]. Thus, it appears that the host environment is ideal for coccidioidomycosis during the latter period of pregnancy and shortly after delivery, and immune reconstitution is not consistently successful in decreasing morbidity and in preventing mortality.

Limited data exist with regard to IRS related to other fungi. Some investigators have reported that disseminated infection due to blastomycosis is also more likely to occur during the third trimester of pregnancy [74]. Finally, a case report documented skin lesions due to *Aureobasidium* species; the diagnosis was determined at 19 weeks of gestation. Although the disease remained stable throughout the pregnancy without specific antifungal therapy, the patient presented 3 weeks after delivery with brain abscess and pulmonary mass related to this mycosis [75].

**Viruses**

**Hepatitis virus.** In HIV-infected patients initiating potent antiretroviral regimens, “flare-up” of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and accelerated disease progression as a result of immune reconstitution–mediated liver injury is a well recognized phenomenon [76–79]. Rapid restoration of immunity, for example, because of withdrawal of chemotherapy for malignant lymphomas in HIV-infected patients who were carriers of HCV has also been shown to lead to worsening of hepatitis [80].

Women who are chronic carriers of HBV or HCV may experience an acute exacerbation of hepatitis during the postpartum period. Serum levels of alanine aminotransferase (ALT) and HCV RNA were measured before pregnancy, during the first and third trimester, and 1 and 3 months after delivery in a woman who was a carrier of HCV [81]. ALT levels normalized, and HCV RNA levels decreased significantly during pregnancy, with the lowest viral load having been observed during the third trimester. An abrupt increase in HCV RNA level, paralleling a hepatitis flare, and a >20-fold increase in ALT level was documented 1 month after delivery. HCV RNA level decreased and ALT level normalized 3 months after delivery [81]. In a study involving 55 hepatitis B surface antigen–positive pregnant women, HBV DNA levels increased a mean of 0.4 log during the latter period of pregnancy or shortly after delivery [82]. HBV DNA levels 6 weeks after delivery tended to be higher, compared with levels detected during late pregnancy; 1 year later, they returned to the levels detected during early pregnancy [82]. ALT levels increased after delivery in both hepatitis B early antigen–positive and hepatitis B early antigen–negative mothers; however, hepatitis B early antigen–positive women were more likely to develop an elevated ALT level after delivery than were hepatitis B early antigen–negative women (14 [33%] of 43 women vs. 7 [78%] of 9 women; *P* = .02) [82]. Monitoring liver enzymes during the postpartum period in women who...
Table 2. Manifestations and proposed pathogenic basis of pathogens or clinical conditions exacerbated during the postpartum period.

<table>
<thead>
<tr>
<th>Pathogen or clinical condition</th>
<th>Usual clinical manifestations</th>
<th>Proposed pathogenic basis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Pulmonary infiltrates, meningitis, CNS lesions, osteoarticular infection</td>
<td>Reactivation of endogenous foci presenting as symptomatic disease triggered by inflammatory responses during the postpartum period</td>
<td>[36–44, 93]</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>Skin lesions and neuritis caused by tuberculoid leprosy</td>
<td>Increased cellular immunity and reversal reactions associated with Th1</td>
<td>[3]</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Meningitis, CNS lesions, pulmonary nodules and/or infiltrates, soft-tissue or osteoarticular infection</td>
<td>Symptomatic disease due to Th2 and Th1 reversal during the postpartum period</td>
<td>[59–61]</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td>Disseminated infection, particularly during the third trimester and postpartum period</td>
<td>Hormonal modulation of cellular immunity, proinflammatory responses during the postpartum period</td>
<td>[62, 63, 65]</td>
</tr>
<tr>
<td><strong>Virus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis virus</td>
<td>Increased levels of aminotransferases and HCV RNA or HBV DNA in chronic carriers of HCV or HBV</td>
<td>Restoration of virus-specific cellular immune responses and paradoxical viral replication</td>
<td>[81, 82]</td>
</tr>
<tr>
<td><strong>Herpes virus</strong></td>
<td>Herpes simplex virus endometritis, higher frequency of cytomegalovirus excretion</td>
<td>Reversal of pregnancy-related suppression of nonspecific mitogenic and virus-specific lymphocyte responses</td>
<td>[88, 91]</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Reactivation of latent infection</td>
<td>Not known</td>
<td>[92]</td>
</tr>
<tr>
<td><strong>Noninfectious disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Autoimmune disorder</strong></td>
<td>Worsening or new onset of Graves disease, Hashimoto thyroiditis, hemolytic uremic syndrome, sarcoidosis, multiple sclerosis, and/or rheumatoid arthritis</td>
<td>Th2 to Th1 shift</td>
<td>[23–29, 31]</td>
</tr>
</tbody>
</table>

**NOTE.** HBV, hepatitis B virus; HCV, hepatitis C virus.

are carriers of HCV or HBV is prudent, as has been suggested for patients with HIV coinfection who are initiating HAART [77, 78, 83]. An increase in viral load that corresponds with immune recovery may seem intuitively paradoxical; however, a similar phenomenon has been reported in HIV-HCV–coinfected patients [83, 84]. Enhanced replication of HCV quasispecies that were suppressed during the immunocompromised state, as well as increased replication of circulating virions in the peripheral blood and mononuclear cells, rather than the lymphocyte compartment, are proposed to account for these findings [83, 84].

**Herpes viruses.** A study involving an ethnically diverse cohort of HIV-infected individuals initiating HAART documented that a vast majority of the IRS events were attributable to either genital herpes (50% of events) or anogenital warts (23% of events) [85]. Case reports have documented endometritis during the postpartum period due to herpes simplex virus infection, with severe sequelae in the mother [86, 87]. In 2 cases, transmission to the neonate resulted in disseminated infection, and both infants died [86]. Cellular responses to herpes simplex virus infection are significantly lower during the second and third trimesters of pregnancy [88]. In addition, prostaglandin E2 synthesis has been shown to cause suppression of nonspecific mitogenic responses and herpes simplex virus type 1– and type 2–specific lymphocyte responses, which may facilitate recurrent symptomatic disease [86, 89]. Similar observations have also been made with regard to cytomegalovirus. Suppression of cytomegalovirus-specific cell-mediated immune responses was most notable during late pregnancy [90]. In total, 20% of pregnant women during the first trimester, 78% during the second trimester, and 100% at the end of the third trimester had suppressed responses; these responses reverted to normal 8 weeks after parturition [90]. The rates of cytomegalovirus excretion in women early during the postpartum period (9.8%) were higher than in gynecologic patients (4.2%) in the same clinic; a decrease to normal rate was achieved after the women experienced the return of menstruation [91]. Reactivation of latent human papilloma virus infection was proposed to account for a progressive increase in the frequency of this infection as gestational age progressed [92]. In 1 study, the overall frequency of human papilloma virus infection increased from 8% during the first trimester to 23% during the third trimester [92].
CONCLUSION

The accumulated evidence summarized in this review reveals that immunologic recovery triggered by rapid resolution of pregnancy-associated immunosuppression may tip the balance in favor of a proinflammatory state and could potentially lead to deleterious consequences through production of disease, and thus, seemingly stable or otherwise smoldering infections in women during the postpartum period may cause clinical symptoms (table 2). Recognition of this phenomenon is a critical first step in fully understanding the pathophysiologic basis of exacerbation of infection during the postpartum period; developing clinical or laboratory criteria for precise diagnosis and determining therapeutic approaches for the management of such infections are essential.

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