—Short Review—

Role of the Placenta in Adverse Perinatal Outcomes among HIV-1 Seropositive Women

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Abstract

Women seropositive for human immunodeficiency virus type 1 (HIV-1) are at an increased risk for a number of adverse perinatal outcomes. Although efforts to reduce mother-to-child transmission of HIV (MTCT) remain a priority in resource-limited countries, HIV testing and treatment have led to steep declines in MTCT in well-resourced countries. Even so, HIV seropositive pregnant women in the United States continue to deliver a disproportionately high number of preterm and low birth weight infants. In this mini-review, we address the role of the placenta in such HIV-related perinatal sequelae. We posit that adverse perinatal outcomes may result from two mutually non-exclusive routes: (1) HIV infection of the placenta proper, potentially leading to impaired maternal-fetal exchange; and (2) infection of the maternal decidual microenvironment, possibly disrupting normal placental implantation and development. Further research into the relationship between HIV-1 infection and placental pathology may lead to the development of novel strategies to improve birth outcomes among HIV-1 seropositive parturients.
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Key words: human immunodeficiency virus type 1, placenta, placenta diseases, low birth weight, preterm birth

Women of child-bearing age comprise approximately half of the estimated 33.3 million people currently living with human immunodeficiency virus type 1 (HIV-1)[1]. It is well-established that HIV-1 seropositive pregnant women are at increased risk for a number of adverse perinatal outcomes, including spontaneous abortion, stillbirth, intrauterine growth restriction (IUGR), low birth weight (LBW), preterm birth (PTB), infant mortality, and mother-to-child transmission of HIV (MTCT)[2–13]. In well-resourced countries, access to HIV testing, antiretroviral therapy, and other interventions has resulted in precipitous reductions in MTCT rates[14,15]; however, similarly pronounced reductions in the risks of PTB and LBW among HIV seropositive women in the United States have not been realized[16]. Here, we briefly review possible reasons for these observations.

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In normal pregnancy, the placenta facilitates maternal-fetal nutrient and gas exchange, serves as a tolerant immunological barrier, and produces hormones required to maintain pregnancy. Deficiencies in placental function are causally linked to obstetrical complications and adverse birth outcomes[17]. Nevertheless, in the setting of maternal HIV-1 seropositivity, the relationship between placental HIV-1 infection and adverse perinatal outcomes has been difficult to establish[18]. At issue has been whether cells of the placenta are susceptible to HIV infection, and by extension, whether such infections could be sufficient to account for perinatal sequelae. Evidence that viral replication may occur locally within the placenta is supported by phylogenetic studies demonstrating genetic divergence between placental and circulating maternal HIV-1 quasispecies[19–21]. However, efforts to characterize HIV-1 infection within villous placental have proved challenging, resulting in conflicting estimates of the nature and extent of infection depending upon clinical context and the sensitivity and specificity of given means of detection[18,20,22–30]. Most authors have observed that that *ex vivo* cultures of placental villi support HIV-1 infection[18,30–35], yet primary trophoblasts or trophoblast-derived cell lines are generally resistant to infection[36–42]. It is possible that these discordant results indicate that HIV-1 does not preferentially infect trophoblastic cells, but rather, leukocytes present within the villous parenchyma of *ex vivo* cultures[24,36,43]. Collectively, these data suggest that while the villous placenta may be infected by HIV in some instances, the exact nature of viral replication with this "placental compartment" requires clarification.

Assuming that placental HIV infection occurs in an appreciable number clinical cases, it is striking that most histopathological studies have failed to demonstrate specific placental lesions[18,23,44–47], which is in contrast to many other infectious pathogens[47]. Among the non-specific pathologies, villitis has been an inconsistent finding[23,29,44,47,48], and some (but not all) studies have reported alterations in villous maturity[45,48,49]. A fairly consistent finding among these studies has been an increase in the proportion of cases with chorioamnionitis among placentas delivered of seropositive women relative to uninfected controls[23,44,50–52]. Chorioamnionitis is strongly associated with PTB and may also increase the risk for MTCT[53]; as such, HIV-associated chorioamnionitis might contribute to adverse outcomes among seropositive pregnant women.

In addition to chorioamnionitis, Goldenberg et al. observed in a large study that a high proportion of placentas delivered of HIV seropositive women exhibited deciduitis[54]. Moreover, these authors found that marked leukocyte infiltration into the decidua basalis was significantly associated with adverse outcomes, including LBW and PTB. Such observations highlight the clinical importance of the decidual microenvironment, and particularly the decidua basalis, which is the portion of the uterine mucosa into which the placenta implants. Proper implantation is essential for normal placental function and fetal growth, and requires that placental trophoblastic cells interact with cells of the decidua (decidualized fibroblasts, uterine natural killer cells, and maternal macrophages, among others) in a highly orchestrated manner. Studies of feline immunodeficiency virus (FIV) infection showed that experimental inoculation of pregnant cats triggered decidual inflammation, resulting in reproductive failures[55,56]. The high incidence of early spontaneous abortions among HIV-infected women[57] has invited speculation that similar immune dysregulation may occur in HIV-infected human decidua[58]. That HIV can infect maternal immune cells in the decidua is supported by the *ex vivo* experiments of Menu and colleagues, who showed in first trimester decidual histocultures that macrophage-like $CD14^+$ cells could be productively infected with some HIV strains[59]. In addition, HIV has been detected in lymphocytes and macrophages of the decidua and chorion *in situ*[26]. Based on these observations in aggregate, we put forth the hypothesis that HIV infection of decidual macrophages (and possibly lymphocytes) prior to or early in pregnancy might serve to create an inflammatory intrauterine environment that is unfavorable for normal implantation; this may explain a portion of the adverse perinatal outcomes

associated with maternal HIV infection.

In summary, infection of the placenta and/or decidual microenvironment represent two mutually non-exclusive routes through which HIV-1 might result in adverse perinatal outcomes. Further research into the relationship between HIV-1 infection and placental pathology may help to improve birth outcomes among HIV-1 seropositive parturients.

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