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Effect of Maternal HIV Infection on Infant Development and Outcomes

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Early life represents a period of profound immunological development and heightened susceptibility to infectious disease. The developmental trajectory over this period is influenced by a number of factors, including gestational age, mode of delivery, mode of feeding, microbiome development, and environmental exposures. There are also several maternal factors that have been shown to have a negative effect on both immune development and clinical outcomes, including maternal infection and inflammation. Studies have associated maternal HIV infections with an increase in infectious morbidity and mortality and decreased growth measures among their HIV-exposed uninfected (HEU) offspring. Among HEU infants, socioeconomic factors, maternal nutrition, maternal viral load, and maternal inflammation have also all been associated with impaired infant immune status and clinical outcomes. However, the mechanisms underlying these observations have not been elucidated and, apart from measures of disease severity, few studies thus far have undertaken in-depth assessments of maternal health status or immune function during gestation and how these influence developmental outcomes in their infants. The lack of a mechanistic understanding of how these gestational influences affect infant outcomes inhibits the ability to design and implement effective interventions. This review describes the current state of research into these mechanisms and highlights areas for future study include; how HIV infection causes the inflammatory trajectory to deviate from normal gestation, the mechanism(s) by which *in utero* exposure to maternal inflammation influences infant immune development and clinical outcomes, the role of socioeconomic factors as an inducer of maternal stress and inflammation, and maternal nutrition during gestation.

Keywords: maternal HIV, maternal inflammation, HIV-exposed uninfected (HEU), infant development, pregnancy and maternal infection

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INTRODUCTION

Although there is evidence that the underlying trajectory of immune development is fairly resilient (1, 2), studies have also shown that immune development is influenced by a range of factors including gestational age, mode of delivery, mode of feeding, microbiome, and environmental exposure (3–9). Many of these factors have also been associated with impaired clinical outcomes in infants (10–14), including susceptibility to infectious diseases.

Maternal characteristics during gestation can also have a notable effect on infant immune development and clinical outcomes. These include maternal nutrition and microbiome, as well as maternal infection and inflammation (7, 15–18). Maternal HIV in particular has been widely shown to be associated with increased infectious morbidity and mortality, reduced growth parameters, and higher risk of pre-term birth in their HIV-exposed-but-uninfected (HEU) infants (19–22).

There are numerous hypotheses regarding the mechanism(s) underlying the poor outcomes of HEU infants. A definitive consensus remains elusive, and the evidence thus far suggests that the cause is likely multifactorial. Antiretroviral exposure, mode of feeding, a more infectious environment, reduced maternal care, and socioeconomic factors have all been proposed (23). Patterns of altered immune development have also been detected among HEU infants, which may contribute to their increased susceptibility (24). As with the clinical picture, it remains unclear by what mechanism(s) these immune alterations are induced, with *in utero* HIV exposure, ARV exposure, and the influence of maternal nutrition and microbiome all potential candidates to influence the developing immune system (25, 26). Numerous studies have reported that worse maternal health status, as assessed by viral load or CD4 count, also appears to be associated with poor infant outcomes (27–30). Again, the underlying mechanism(s) are not yet clear. Apart from measures of disease severity, a limited number of studies have undertaken in-depth assessments of maternal health status or immune function and attempted to determine how these influence immune development and infectious outcomes in their infants.

POTENTIAL MECHANISMS OF MATERNAL INFLUENCE ON HEU INFANT OUTCOMES

Many mechanisms have been proposed to explain the disparity in clinical outcomes between HEU and HUU infants. Potential factors such as mode of feeding and delivery, while important, are beyond the focus of this review and will be mentioned only briefly here. Several maternal factors have been proposed that may play a role in infant outcomes but have been less well studied. The remainder of this review will focus on these areas.

MATERNAL HIV INFECTION

The placenta protects the developing fetus from maternal infections; however, certain viruses possess mechanisms that allow them to evade this protection (31). HIV has been detected in fetal tissues (32–34), confirming that the virus is able to cross the placenta. While this has obvious implications for mother-to-child-transmission (MTCT), *in utero* HIV exposure presents other potential risks to the developing fetus, including pre-term birth and impaired fetal growth compared to infants born to HIV-negative women (35, 36). Studies have shown that *in utero* HIV exposure may also have long term effects on the development and function of the infant immune system (24), although the relative contribution of maternal factors has not been elucidated.

Despite the lack of mechanistic explanation, evidence for the effect of *in utero* HIV exposure on the immune development and function of the infant has been strengthened by numerous studies that have demonstrated a linkage between maternal disease severity, as measured by viral load or CD4 count, and infant outcomes. Reduced maternal CD4 counts have been associated with increased infant mortality (29, 37) and morbidity (27, 28); similarly, high maternal viral load has also been shown to be a significant predictor of infant morbidity and mortality (29). This is not surprising, as where more severe maternal disease will expose the infant to quantitatively higher levels of HIV antigen. There will also be exposure to a maternal immune environment biased towards systemic activation and chronic inflammation. These exposures may, individually or together, influence the development of the infant, resulting in an increased susceptibility to infections in early life.

Infant growth parameters are also influenced by maternal disease severity (38). Low maternal CD4 counts were associated with reduced length-for-age (LAZ) scores over the first two years of life (39). Lower maternal CD4 counts were also associated with reductions in weight-for-age (WAZ) (40, 41), LAZ (41), weight, length, and head circumference measurements (42) as well as increased intrauterine growth restriction (IUGR) (43). Higher maternal cervical HIV RNA (44) and low maternal CD4 counts were associated with increased risk of low birth weight (LBW) (45). A high maternal viral load was significantly associated with infant stunting (46) and lower infant weight (30).

The collective evidence from these studies supports that infants born to mothers with advanced disease are at increased risk of poor outcomes (21, 37, 47–49), although the precise underlying mechanism(s) are not yet known. More severe maternal disease will expose the infant to quantitatively higher levels of viral particles as well as a more activated maternal immune environment biased towards systemic activation and chronic inflammation. These exposures may, individually or combined, exert a deleterious influence on the developing fetus, resulting in poorer infant outcomes.

Maternal Inflammation

Along with hormonal and physiological changes, immunological alterations during pregnancy may increase the risk of adverse infant outcomes (50). In recent years, our knowledge of the maternal immune system during pregnancy has undergone a significant shift. Previously thought to exist primarily in a state of immune suppression to accommodate the semi-allogeneic fetus, our current understanding, while incomplete, now points to a system that is constantly changing according to a predetermined physiological pattern, or 'pregnancy clock' (51). Initially, a proinflammatory state is maintained during the first trimester of pregnancy, which is critical for embryo implantation, placentation, and initial fetal growth, followed by transition to an anti-inflammatory state during the rapid fetal growth of the second trimester, and finally a return to a proinflammatory state prior to labor (52).

Despite the natural tendency towards a pro-inflammatory milieu at certain stages of gestation, it has been hypothesized that chronic exposure to low-grade systemic inflammation in fetal and early postnatal life, of the type that is characteristic of HIV infection (53) may result in stunting (54). Maternal HIV infection has been associated with an increased risk of preterm birth, a complication likely related to inflammation at the materno-fetal interface (55, 56). Prendergast et al. further reported strong associations between maternal and infant inflammatory markers at birth, supporting the hypothesis that an increased maternal inflammatory environment contributes to an increase in inflammation in the infant (54). However, these findings have been contradicted by multiple studies that have found that maternal and infant levels of inflammation do not correlate (31, 57, 58) suggesting that the increased levels of inflammatory mediators that have been described in HEU infants may not be solely the result of direct maternal transfer.

Although HIV infection is associated with increased levels of serum inflammatory mediators, it has not conclusively been shown that these cytokines can cross the placenta, making it difficult to accurately gauge their effect on the developing fetus (59). The presence of inflammation in cohorts with controlled maternal viral load suggests that antigenic exposure *via* placental transfer does not provide an adequate explanation either. Further complicating efforts to determine the impact of maternal inflammation on infant outcomes is the finding reported by multiple studies that maternal HIV infection is associated with lower levels of pro-inflammatory mediators in both mothers and children (60–62), conflicting with studies that have reported increased inflammatory mediators in HEU mothers and infants (58).

Maternal Immunity

Pregnancy involves a tightly regulated immunological trajectory (51) designed to provide adequate immune protection to the mother and fetus while simultaneously maintaining tolerance towards the semi-allogeneic fetus (50). During a healthy pregnancy, the maternal immune system undergoes a series of adaptations in both the adaptive and innate arms (50). Initiated early in pregnancy (63), these adaptations result in a progressive shift from a cell-mediated, pro-inflammatory, Th1-biased profile towards a humoral, anti-inflammatory, Th2-biased profile (64).

Increased maternal immune activation has also been identified as a factor in the association between maternal viral infections and adverse infant outcomes (31). HIV infection and antiretroviral therapy (ART) both impact key immune mechanisms, which may in turn disturb this normal immunological trajectory of pregnancy (65). Maternal HIV infections are commonly associated with increased levels of pro- and anti-inflammatory cytokine levels in cord blood, independent of pathogen transmission (16).

Maternal HIV and ART has been associated with distinct systemic cytokine profiles throughout pregnancy that differ from an HIV- pregnancy profile (65). HIV-exposure has further been shown to affect the maternal/fetal unit, with increased levels of proinflammatory cytokine produced by placenta cells, as well as altered infant immune responses (66). HEU infants have high levels of inflammatory mediators in their cord blood. Further studies are required to address the origin and long-term consequences of prenatal HIV-exposure and subsequent immune activation for infant health.

Maternal Antibodies

Maternal antibodies are a central component of the newborn immunity against pathogens in early life. In healthy pregnancies, antibodies are selectively transferred across the placenta (59), while chronic maternal infections are associated with reduced transfer of IgG across the placenta, presenting a unique 'disruption model' (67–70). In HIV positive pregnancies, factors associated with maternal disease progression are associated with poor placental IgG transfer (29, 67, 71–73). The mechanisms underlying this impaired transfer are not fully defined. One hypothesis that has been proposed is that increased levels of maternal antibodies saturate the placental Fc receptor (24). Martinez et al. showed that placental transfer of maternal IgG is a selective process in which a combination of factors, including IgG FcR binding strength, subclass, and glycan profiles, play a role in the selective and differential transfer of maternal antigen-specific IgG across the placenta (67).

The functional potential of antibodies are determined by their glycosylation profile, which defines the Fc receptors that the antibody can bind to (74). Binding to placental Fcγ receptors can predict the transfer of placental IgG transfer efficiency. Altered antibody glycosylation profiles in the context of maternal HIV infection could also be related to the reduced transfer efficiency observed in HEU infants. The occurrence of inflammation due to maternal HIV infection may also negatively influence the passive immune transfer to the fetus (73).

Maternal Microbiome

Over the course of a normal pregnancy, changes naturally occur to the maternal vaginal and gut microbiota (7). The vaginal microbiome becomes less diverse and develops a higher relative abundance of Lactobacillus species (75). There is some evidence of decreased diversity in the gut microbiome as well as pregnancy progresses, along with a shift towards a greater abundance of pro-inflammatory Proteobacteria (76).

Previous studies have shown that HIV infection also alters the composition of the gut microbiome (77). Reported differences include increased diversity and abundance of Prevotella species (77, 78) as well as increased Proteobacteria and decreased Bacteroidetes (53, 78).

Emerging studies have shown that the maternal microbiome plays a major role in the early microbial colonization of the infant as well as in the development of the infant immune system. Factors that disrupt the maternal transfer of microbiota, such as perinatal antibiotics, mode of delivery, and mode of feeding, have been shown to influence the composition of the infant microbiome and have been associated with adverse outcomes later in life (7). A study in Zimbabwe reported an association between gestational maternal gut microbiota and birthweight and neonatal growth (79). In the context of

maternal HIV infections, a Haitian study reported that the microbiome of HEU infants was altered compared to that of UE infants (80). However, a study comparing the microbiome of HEU infants across different regions demonstrated that these differences are not universal but rather are complicated by population-dependent differences (81).

Maternal Nutrition

Maternal nutritional status has a strong influence on infant growth and development (82). Fetal growth involves a complex interplay of factors including metabolic and endocrine signaling as well as maternal nutritional and immune status (83). Maternal malnutrition can impair the nutrient stores of the developing fetus, which consequently can inhibit fetal immune function and growth (84). Maternal gestational weight gain and body mass index have been positively associated with infant birth weight (82) while low maternal BMI was associated with an increased risk of low birth weight (85–87). Maternal height has been inversely associated with infant mortality, stunting and underweight in survey data from 54 low- to middle-income countries (88).

Pregnancy increases the need for both absolute calories as well as specific nutrients (89). These increased nutritional requirements are necessary to support the physiological changes that take place during gestation as well as fetal growth and development (90).

HIV infection also increases both energy and micronutrient requirements. Infected individuals often have compromised nutritional status (91) and/or are micronutrient deficient (92, 93). Common HIV-related issues, such as diarrhea, appetite loss, and opportunistic infections, all place an increased burden on available energy stores (84). As such, HIV has long been associated with changes in body mass and composition (84, 94).

Although there is not a great deal of previous literature regarding the specific effect of HIV on nutrition in women, certain sex-specific changes have been identified. HIV infection was associated with a reduction in the fat mass index (FMI) in women, while no difference in FMI was observed between men with and without HIV (94). Further, women suffering from AIDS wasting syndrome experience a disproportionately high decrease in body fat relative to lean body mass compared to men (95).

Both pregnancy and HIV infection increase the risk of anemia. The risk of developing anemia during pregnancy is higher for HIV infected women (96, 97). Maternal anemia has been shown to negatively affect infant outcomes, regardless of infection status. In uninfected mothers, maternal anemia is associated with low birth weight (82) while anemia in HIV-infected mothers was associated with increased risk of PTB and LBW (98) and small-for-gestational-age (SGA) (99).

Taken together, it is apparent that the combined nutritional requirements of pregnancy and HIV can leave HIV-infected mothers at greater risk of malnutrition. This has been borne out by studies in which maternal wasting was shown to be more prevalent in HIV-infected mothers compared to uninfected mothers (90). This compromised nutritional status may also affect the growth and health status of their infants. Reductions in the MUAC of HIV-infected mothers during gestation were associated with reductions in infant WAZ and LAZ through to 6 months of age (100). Similarly, greater maternal weight change during pregnancy was associated with higher LAZ of their HEU infants (101), while lower maternal BMI was associated with lower length and weight gain in their 2 wk old HEU infants (102). Indeed, the use of maternal anthropometry as an indicator of infant outcomes appears to be more applicable in the context of maternal HIV infection than in HIV-negative mothers (103).

SOCIOECONOMIC FACTORS

It is well established that a range of maternal factors influence infant outcomes; developing a comprehensive understanding of these forces needs to include consideration of non-biological factors. Studies into non-biological factors have identified several indicators that are associated with determinants of maternal and infant health. The non-biological maternal factors associated with reduced infant anthropometry are not unique to the HEU population but rather are in line with factors that have previously been identified in UE infants, particularly in lower income countries, such as parental education, income, and number of children within the household (104–106).

Lower educational outcomes have been associated with increased risk of HIV infection among women of childbearing age (107, 108). Maternal education has also been linked to infant health and growth outcomes. Lower maternal education is associated with increased infectious morbidity in infants among both HIV-infected and uninfected women (109) and is an independent predictor of infant stunting, wasting, and underweight measures (46, 110). Reduced maternal education was found to be associated with decreased LAZ and WAZ scores over the first two years of life (39), while maternal illiteracy was identified as a risk factor for reduced linear growth (111). The mechanisms underlying this association have not yet been conclusively established. Higher educational attainment may result in increased knowledge related to hygiene, pre-natal care, childcare, and feeding practices (110). As well, lower education has been associated with reduced knowledge about PMTCT (112) and decreased access to testing (113, 114).

It is possible that education is a surrogate for socioeconomic status, and poverty is the real causative factor (109). Poverty is associated with increased risk of HIV infection (108, 114–116); thus it follows that poverty would also have a role in maternal HIV status. Low socioeconomic status has been associated with poor maternal nutrition and gestational anemia (96, 117, 118) factors that have been linked to worse infant outcomes.

TIMING OF ART

Given the observed associations between severity of maternal disease and infant health status, it is not surprising that the use of maternal ART has been shown to improve infant outcomes.

The benefits of maternal ART use have been well reviewed elsewhere (119–121); this review focuses on the timing with which ART is established relative to pregnancy. There is a conflicting body of literature suggesting that ART initiation can result in HU-equivalent status for the infant if ART was initiated prior to conception or early in pregnancy. Although these findings are still somewhat inconsistent, early studies indicate that this result is at least partly dependent on whether the cohort is located in high-income countries vs low-income countries.

In an Ethiopian study, infants exposed to ART from conception displayed decreased growth compared to those exposed late in pregnancy (122). A Belgian HEU infant cohort reported that initiation of maternal ART before pregnancy reduced the risk of infant infection-related hospitalizations (123). In a Brazilian cohort, although ART use was associated with a high frequency of adverse events in newborns, these were mainly of low severity (124). In contrast, the effect of maternal ART on infant outcomes was not so clear in a South African cohort (125). The mechanisms underlying these distinctions between cohorts are not yet clear and are the basis of ongoing studies. It could be an artifact of differences in study design, or it could be related to population-level differences in health status affecting the study participants.

FUTURE RESEARCH DIRECTIONS AND NEW TECHNOLOGIES

Given the immense influence they have on infant outcomes, maternal factors in the context of HEU infants have been understudied. Gaps in knowledge that should direct future research directions include a more thorough understanding of maternal immunity, particularly the innate arm, and of how immunological markers change across the entire gestational span in both normal and pathological pregnancies (126). Improved standardization of immune measures would also improve the comparability between studies, as well as allowing for a more defined metric to measure the extent of the adverse outcomes in infants. A deeper understanding of the maternal microbiome is also required, and how it affects infant development and outcomes. Further, future studies need to move beyond the observational and begin to attempt to elucidate the underlying mechanisms.

Among the tools that are available to advance these research agendas are the recently developed field of 'omics technologies. To date, these have primarily been used to map the immune profile of the adults and infants; few comprehensive investigations into maternal profiles exist thus far (127, 128). The systems approach harnesses multiple "omics" technologies and applies computational methodologies to analyze large volumes of data about parameters of various interacting biological systems, can help to address some of these gaps. This pooling of efforts results in a comprehensive, high-resolution picture of a system of interest. The application of these systems has begun to elucidate a number of trajectories in pregnancy, including the characterization of the proteomics, transcriptomics, and metabolomics (51, 129–131). In addition, systems serology is shedding new light on the assessment of antibody function and glycosylation (132).

The main advantages of applying the systems biology approach is the ability to acquire novel insight into immune trajectories and to develop well-defined outcome parameters. Pregnancy has a defined trajectory and complex ontogeny. To best understand the complexity of the trajectory, the timeline needs to be considered. Each trimester, month, and week of pregnancy is marked by rapid development and change. It remains a challenge to determine the optimal degree of granularity required to adequately define this trajectory.

Furthermore, well-defined parameters for outcomes of interest are essential but limited primarily to infant outcome and exclude other factors such as maternal health and long-term health outcomes of the infant. The outcomes of a normal versus impaired immune state in the infant and beyond are nuanced. Defined parameters need to be established for systems biology to assess the presence and clinical relevance of optimal ontogeny and deviation of that trajectory.

CONCLUSIONS

Despite the relative lack of attention given to maternal factors, there is sufficient evidence to conclude that maternal HIV infection adversely affects infant outcomes in early life. Among the many reasons for these deleterious outcomes, the focus has largely fallen on feeding practices and ARV exposure. Yet studies have shown that, despite improvements in outcomes in the context of breastfeeding and ARV use, these adverse outcomes persist (133, 134). Further, evidence that the extent of this influence is affected by the severity of maternal disease suggests that the mechanism is at least partly related to *in utero* exposure, although it remains an open question whether the virus itself or the activated maternal environment is most responsible. Understanding the mechanisms by which *in utero* HIV exposure affects infant outcomes is the next step towards understanding how best to design effective interventions to improve infant outcomes.

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CR and KS contributed equally to the conceptualized, writing of original draft, and editing of final draft. All authors edited, reviewed, and approved the manuscript prior to submission.

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