Intersecting Infections and Socioeconomic Determinants in Adverse Pregnancy Outcomes: An Integrative Review

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Abstract

Pregnancy-related co-infections, particularly in resource-limited settings, pose significant challenges to maternal and fetal health outcomes. This review explores the complex interactions among HIV, malaria, helminths, and arboviruses during pregnancy and how socioeconomic determinants, such as poverty, education, and healthcare access, amplify infection risks and adverse outcomes. Immunological shifts during pregnancy, characterized by a Th2-biased response, increase susceptibility to intracellular pathogens, while helminth infections further exacerbate this vulnerability. Placental malperfusion, driven by dysregulated angiogenic factors and structural abnormalities, is a key mechanism underlying adverse outcomes in HIV-malaria co-infected pregnancies. Arboviral infections, particularly Zika virus, pose teratogenic risks, while Dengue and Chikungunya viruses contribute to maternal and fetal morbidity. Malnutrition, exemplified by deficiencies in iron, folate, and vitamins A and D, compromises maternal immunity and creates a vicious cycle of infection and adverse outcomes. Emerging diagnostic technologies such as CRISPR-based tools and AI-driven platforms offer promising solutions for the rapid and accurate detection of co-infections. Novel therapeutic strategies, including combination antimalarial and antiretroviral regimens, vaccines, and anthelmintic interventions, have the potential to mitigate the impact of co-infections. However, evidence gaps persist, particularly regarding long-term maternal and child outcomes and the impact of climate change on infectious disease dynamics. Integrated care models that address multiple infections, improve nutrition, and ensure comprehensive healthcare access are crucial for reducing the burden of coinfections during pregnancy. Strengthening healthcare infrastructure, expanding educational programs, and investing in climate adaptation strategies are key policy recommendations for protecting vulnerable populations and improving maternal and fetal health outcomes in high-burden areas.

Keywords: Immunological Modulation , Vertical Transmission , Placental Dysfunction , Diagnostic Innovation , Public Health Equity

Introduction

Pregnancy is a unique immunological state characterized by significant adaptations in the maternal immune system, which are essential for supporting fetal growth while maintaining defense against pathogens[1]. The immune response during pregnancy undergoes a fundamental shift toward tolerance of the semi-allogeneic fetus, creating a crucial adjustment necessary for successful gestation [2]. However, this delicate immunological rebalancing paradoxically

increases susceptibility to infection, particularly in resource-limited regions such as sub-Saharan Africa and Southeast Asia, where multiple infectious pathogens overlap geographically and temporally.

Socioeconomic factors fundamentally shape the landscape of maternal health and infectious disease vulnerability during pregnancy, creating a complex web of interconnected challenges that dramatically amplify the risk of co-infection and adverse pregnancy outcomes[3]. Poverty is a primary driver of maternal health disparities, with women in the poorest households experiencing significantly reduced access to antenatal care, skilled birth attendants, and high-quality healthcare facilities. This economic disadvantage creates a cascading effect of health risks, as impoverished women are substantially more likely to experience malnutrition, live in unsanitary conditions, and have limited resources for preventive healthcare[4] [5]. The temporal overlap between hunger seasons and peak malaria transmission in many endemic areas exemplifies how socioeconomic factors amplify infection risks, as nutritional deficiencies during pregnancy weaken immune function and increase susceptibility to infections such as malaria.

Educational attainment emerges as another critical determinant, with women with lower levels of education facing substantially higher risks of severe maternal outcomes, including a 2-fold increased risk of maternal mortality and morbidity compared to their educated counterparts[6]. Each additional year of maternal education corresponds to a 7-9% decline in under-5 mortality, demonstrating the profound protective effects of education on health outcomes. Education influences health-seeking behaviors, contraceptive use, birth spacing, and the ability to recognize and respond to complications during pregnancy. In developing countries, where female school enrollment remains low, this educational gap directly correlates with higher rates of obstetric complications and maternal mortality.[7] [8]

Geographic location compounds these vulnerabilities, with rural women experiencing disproportionately higher rates of maternal morbidity and mortality than urban women. Rural areas face critical deficits in health care infrastructure, including hospital closures, obstetric service reductions, and severe shortages of health care workers. Transportation barriers, limited access to emergency obstetric care, and geographic isolation create additional risk factors that can prove fatal in the event of pregnancy complications. Healthcare access barriers further exacerbate these challenges, with women from disadvantaged backgrounds facing economic constraints that limit their ability to afford healthcare services, transportation to facilities, and essential medication. These barriers are particularly pronounced in resource-limited settings, where healthcare infrastructure is inadequate, and out-of-pocket expenses can be catastrophic for poor families.[9] [10]

In socioeconomically disadvantaged environments, co-infections, including malaria, HIV, helminths, and arboviruses such as Zika, Dengue, and Chikungunya, significantly contribute to adverse pregnancy outcomes. Malaria and HIV co-infection affects 0.7%-47.5% of pregnant women in sub-Saharan Africa[11] [12] [13], with HIV-infected women experiencing 1.58 times higher risk of peripheral malaria and 1.66 times higher risk of placental malaria. Arbovirus infections, including acute Zika (3.8%), dengue (9.9%), and chikungunya (11.8%), during pregnancy are associated with significantly abnormal birth outcomes. Helminth infections,

particularly hookworms, affect approximately 44 million pregnant women annually and are associated with maternal anemia and adverse birth outcomes.[14] [15]

These co-infections create dangerous synergistic effects, with outcomes including preterm birth, intrauterine growth restriction, anemia, and maternal-fetal transmission of the infection. The combined effects of these co-infections present a serious public health challenge, often with one infection exacerbating the effects of the others, whereas underlying socioeconomic factors create conditions for these infections to flourish and interact synergistically. Pregnancy-related infections are among the leading causes of maternal mortality worldwide, with the burden disproportionately affecting low-income and middle-income countries.

This review aimed to explore the complex interactions among different pathogens during pregnancy, demonstrate the influence of socioeconomic factors on infection dynamics, assess emerging diagnostic and treatment strategies, and identify knowledge gaps that hinder progress in managing co-infections during pregnancy. By addressing these aspects comprehensively, we aim to contribute to the improvement of maternal and fetal health outcomes in resource-limited settings, with a particular emphasis on understanding how socioeconomic determinants create vulnerability to co-infections and how targeted interventions can address these challenges.

1 Pathogen Interactions and Mechanisms of Adverse Pregnancy Outcomes

1. HIV-Malaria-Helminth Co-infections

Co-infection with HIV, malaria, and helminths during pregnancy presents a particularly challenging clinical scenario because of synergistic immunological disruptions that occur in the maternal immune system. During normal pregnancy, the maternal immune system undergoes a well-characterized shift toward a type 2 (Th2) immune response[16], which is essential for fetal tolerance but creates vulnerability to intracellular pathogens[17]. This pregnancy-induced immunological adaptation involves the upregulation of key regulatory molecules, including human chorionic gonadotropin (hCG) and heme oxygenase-1 (HO-1), which promote Th2 cytokine production and establish the immunological environment necessary for successful fetal acceptance[18]. Th2 bias during pregnancy is characterized by increased production of IL-4, IL-5, IL-13, and IL-10 while simultaneously suppressing Th1-mediated responses that are crucial for clearing intracellular pathogens such as Plasmodium falciparum and HIV[19] Figure 1

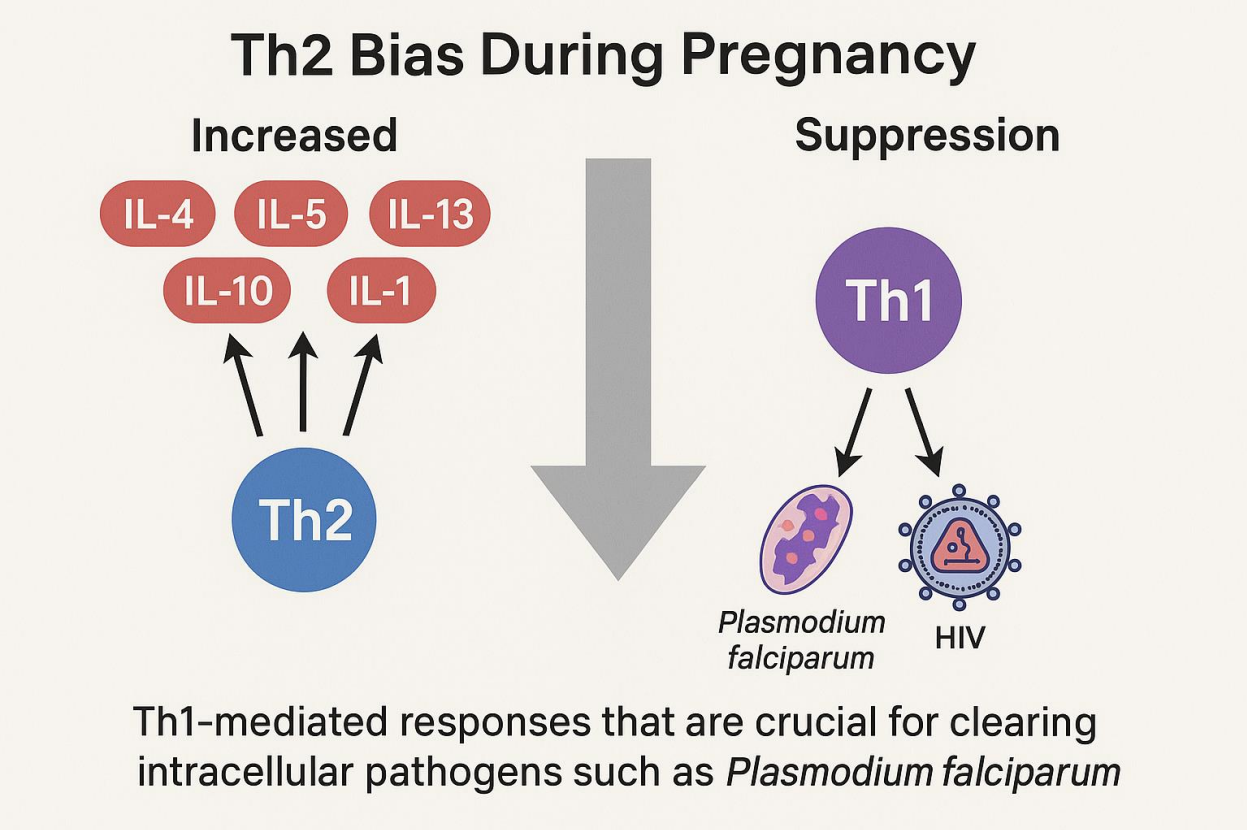

Figure 1. *Th2 immune bias during pregnancy and its consequences for pathogen susceptibility. The figure depicts increased Th2 cytokines (IL-4, IL-5, IL-10, IL-13) and suppression of Th1 responses, which are critical for clearing intracellular pathogens like Plasmodium falciparum and HIV, thereby increasing infection risk during pregnancy.*

While protecting the fetus, this immunological shift renders pregnant women significantly more susceptible to infections that would otherwise be effectively controlled by robust Th1 responses. Helminth infections intensify this vulnerability by independently inducing Th2 immune polarization[20]. Helminth parasites, such as hookworms (Necator americanus and Ancylostoma duodenale) and Trichuris trichiura, activate host immune responses via STAT-6/GATA3 and c-Maf transcriptional pathways, leading to sustained IL-4 production and Th2 cell differentiation[21]. Meta-analysis data from sub-Saharan Africa showed that 20% of pregnant women experienced malaria-helminth co-infection, with hookworms being the most common helminth (48%), followed by Ascaris lumbricoides (37%), and Trichuris trichiura (15%)[22] [23]. The convergence of pregnancy-induced and helminth-mediated Th2 polarization creates a compounded immunological environment, greatly increasing the susceptibility of pregnant women to co-infection. Studies have demonstrated that helminth co-infection significantly worsens HIV disease progression, with increased HIV viral loads and reduced CD4+ T-cell counts during pregnancy. Longitudinal research involving 980 HIV-infected pregnant women showed that antihelminthic therapy with albendazole resulted in positive changes in viral load suppression and CD4+ count recovery[24] [25], providing evidence for the mechanistic link between helminth-induced immunosuppression and HIV progression. Consequently, these immunological interactions between pathogens have important clinical implications in the progression of HIV disease during pregnancy. A cross-sectional analysis of 1,812 HIV-positive patients showed that CD4+ counts below 200 cells/μL were associated with significantly higher rates of opportunistic infections and adverse clinical outcomes[23]. During pregnancy, this

immunological threshold becomes even more critical, as additional immunosuppression caused by pregnancy can accelerate disease progression in women with weakened immune systems. HIV-malaria co-infection rates vary significantly depending on HIV status, with studies indicating co-infection rates between 31-61% in HIV-positive pregnant women compared to 10-36% in HIV-negative pregnant women[26]. This difference underscores the role of HIV-related immunosuppression in increasing the risk of developing malaria during pregnancy. These two infections create a cycle of immune dysfunction in which HIV impairs the immune responses needed to control malaria, and malaria-related inflammation accelerates HIV replication and disease progression.

2.Placental Pathophysiology and Vascular Compromise

Placental malperfusion is a key mechanism underlying adverse pregnancy outcomes in HIV-malaria coinfection [27]. Histomorphometric analysis of placentae from women with HIV-malaria co-infection showed a 2.1-fold increased risk of developing partial maternal vascular malperfusion compared with uninfected controls[28]. This pathological process involves altered placental angiogenesis, characterized by disrupted expression of critical angiogenic factors including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and hypoxia-inducible factor-1α (HIF-1α) (Figure 2).

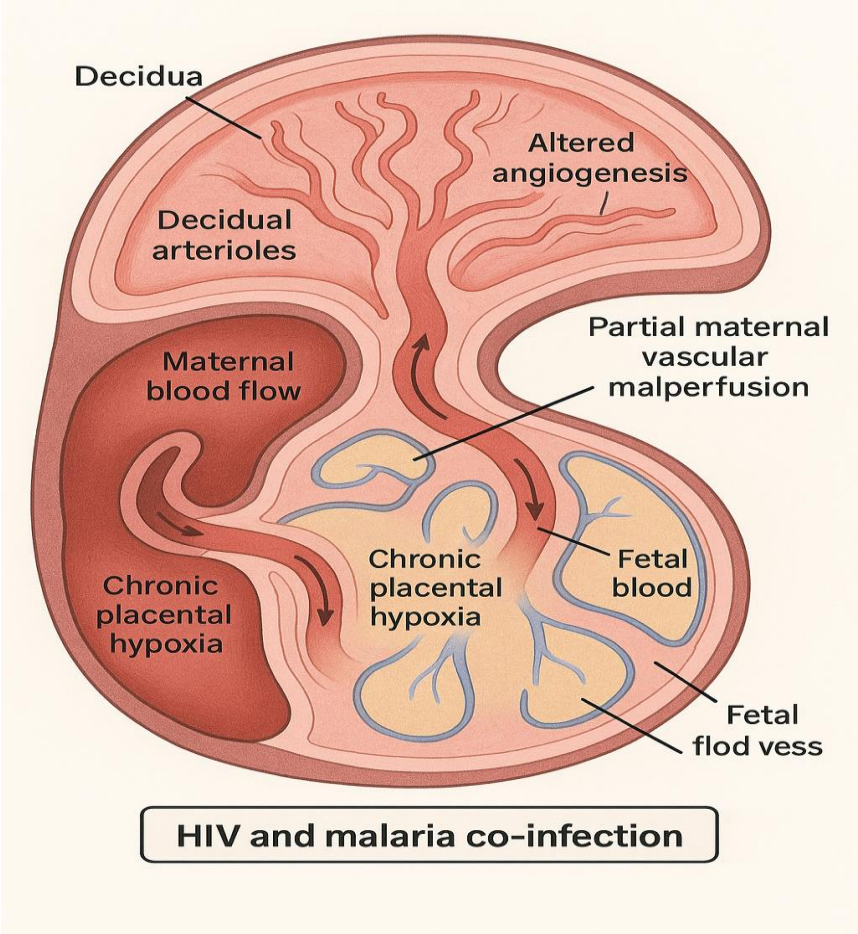

Figure 2. *Schematic representation of placental vascular complications in HIV and malaria co-infection during pregnancy. The diagram illustrates altered angiogenesis, partial maternal vascular malperfusion, and chronic placental hypoxia, highlighting the disruption of maternal and fetal blood flow and the resulting adverse effects on placental function.*

The molecular mechanisms underlying placental dysfunction involve HIF-1α-mediated responses to chronic hypoxic conditions within the placental microenvironment (Fig. 3).

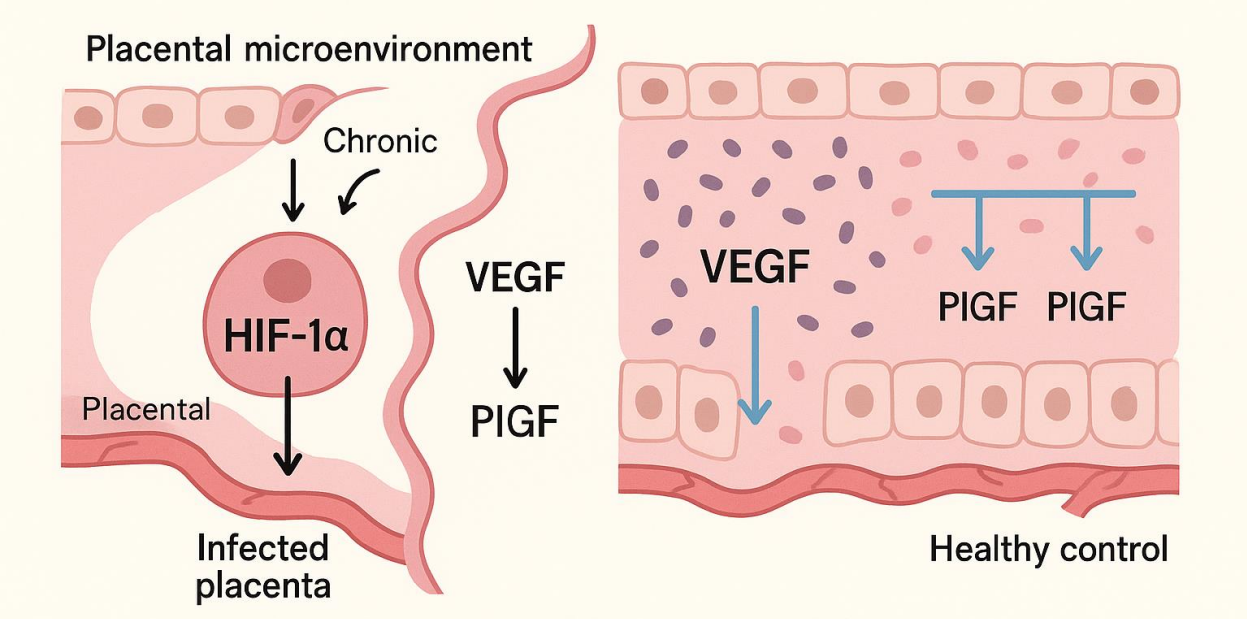

Figure 3. *Molecular mechanisms underlying placental dysfunction in malaria-infected pregnancies. The illustration contrasts the placental microenvironment in infected versus healthy controls, showing HIF-1α-mediated responses to hypoxia and dysregulation of angiogenic factors (VEGF, PlGF) that contribute to placental pathology.*

Research has shown that malaria infection causes significant changes in angiogenic factor expression, with infected placentae exhibiting dysregulated VEGF and PlGF levels compared with healthy controls[29]. These molecular alterations lead to structural placental abnormalities, including reduced placental weight (454 g vs. 488 g in controls), decreased villous perimeter (119 μm vs. 130 μm), and a smaller villous surface area (937 μm² vs. 132 μm²).[30]

Maternal vascular malperfusion disrupts the normal architecture of the intervillous space, impairing the maternal-fetal exchange interface[31], which is critical for nutrient and oxygen delivery. This pathophysiological process leads to placental hypoxia, intrauterine growth restriction (IUGR), and a high risk of preterm birth. A longitudinal cohort study involving 628 pregnant women showed that early malaria infection (before 24 weeks of gestation) increased the risk of preterm birth by 67% (adjusted relative risk 1.67, 95% CI 1.20-2.30), with the mechanism involving dysregulation of angiogenic, metabolic, and inflammatory pathways throughout pregnancy.[32]

The temporal relationship between infection timing and outcomes is especially important, as women with malaria infection before 24 weeks of gestation have a higher risk of preterm birth (28% versus 17% in uninfected controls). This finding indicates that early pregnancy infections have lasting effects on placental development and function, highlighting the need for preventive strategies that begin before conception or during the first trimester.

3.. Arboviral Infections and Pregnancy

The rising global prevalence of arboviruses, such as Zika, Dengue, and Chikungunya, increasingly threatens maternal and fetal health (Figure 4), particularly in regions where these viruses are common. In particular, the Zika virus has garnered substantial attention because of its

teratogenic effects, causing congenital birth defects such as microcephaly[15] [33]. Zika virus tends to infect cortical progenitor cells, which are crucial for proper brain development during the first trimester of pregnancy[34]. Dengue virus infections during pregnancy have been linked to various adverse outcomes, including fetal loss, preterm birth, low birth weight, and maternal bleeding, and can cause significant neurodevelopmental defects that may result in lifelong disabilities in affected individuals[35]. A key factor contributing to dengue severity is antibody-dependent enhancement (ADE), in which antibodies from a previous dengue infection boost the severity of later infections with different serotypes. This process worsens viral replication in both the mother and fetus [36]. Although chikungunya virus (CHIKV) is not as widely known to cause severe pregnancy complications, such as Zika or Dengue, it still presents significant risks during pregnancy. It is associated with vertical transmission during labor[37], which can lead to severe effects in newborns, such as joint deformities and neurological issues. Increased maternal viral load during labor increases the risk of transmission and negative outcomes, underscoring the need for proper management.

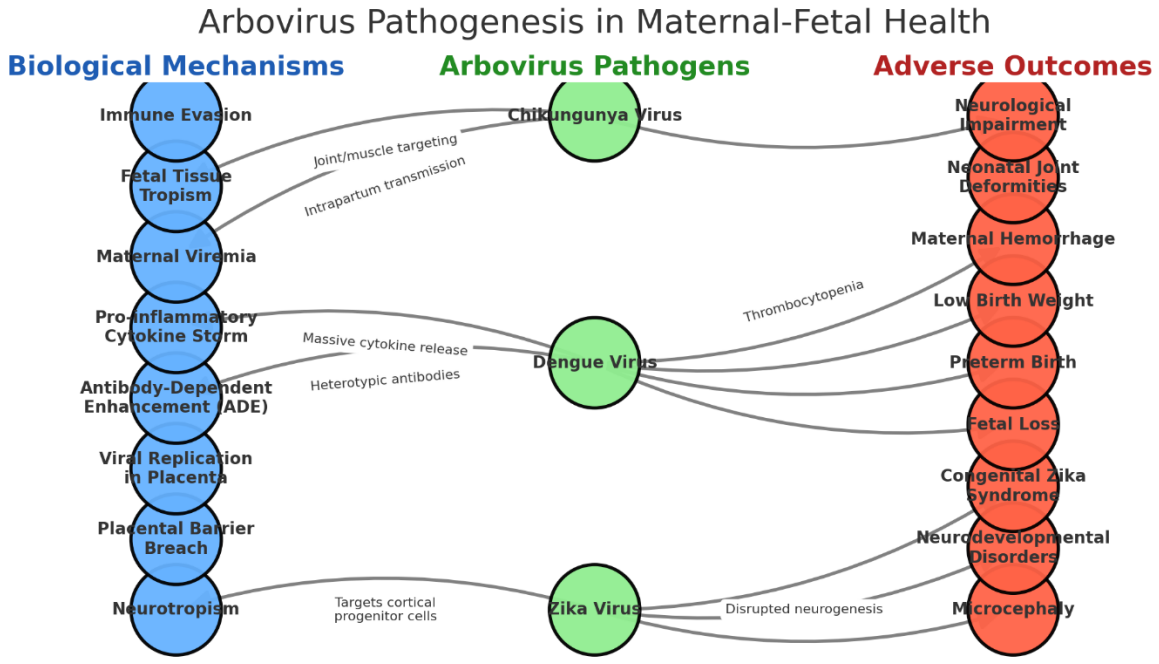

Figure 4. *Biological pathways and adverse outcomes of arbovirus pathogenesis in maternal-fetal health. The diagram maps the mechanisms by which Zika, Dengue, and Chikungunya viruses cause neurological impairment, fetal loss, preterm birth, and other adverse outcomes through immune evasion, cytokine storms, placental barrier breach, and neurotropism.*

Socioeconomic Factors Modulating Co-infection Interactions.

1.Nutrition and Maternal Immunity

Malnutrition significantly contributes to increased susceptibility to infection during pregnancy, with stark regional variations that reflect the underlying socioeconomic disparities (Figure 5). Nutrient deficiencies, particularly iron, folate, and vitamins A and D compromise the maternal immune system, leading to an increased risk of infection. In Nigeria, 20% of maternal deaths and 50% of child deaths under the age of five are directly caused by malnutrition, with anemia prevalence reaching 86.4% during pregnancy[38]. Iron deficiency anemia exemplifies cascading health vulnerabilities - in Papua New Guinea, 66.4% of pregnant women had iron deficiency, with hookworm infection affecting 44 million pregnant women annually and creating a vicious cycle through blood loss and impaired nutrient absorption.[39]

Vitamin A deficiency is another critical intersection of poverty and maternal vulnerability. In Nigeria, 35% of mothers have vitamin A deficiency, with supplementation coverage of only 41%, despite the known 3-12 times increased mortality risk for deficient children[40]. Geographic and economic barriers create additional vulnerability layers; in Ethiopia, over 10 million people face hunger, with 4.4 million pregnant and breastfeeding women needing treatment[41] [42]. As one displaced pregnant woman in Tigray noted, "I have survived my pregnancy on hardly one meal a day. Now, I am concerned about my baby's health".[43]

Barriers to accessing healthcare compounds due to these nutritional vulnerabilities. In rural Tanzania, pregnant women face multiple barriers, including stigma, decision-making constraints, and healthcare worker shortages, with one provider explaining: "Health professionals have not received a salary since July. Many are now discontinuing work." [44] [45] Diagnostic challenges further exacerbate co-infection management - in Cameroon, malaria detection varied dramatically from 5.6% in peripheral blood to 60.5% in placental tissue, highlighting how limited diagnostic capacity masks true infection burden.[46]

The Sierra Leone intervention provides a compelling solution. A randomized trial of 1,489 undernourished pregnant women demonstrated that combining nutritional supplementation with anti-infective therapies significantly improved birth outcomes, with infants showing longer birth lengths, larger weights, and decreased mortality at six months[47]. Evidence from Nigeria, Ethiopia, Tanzania, Kenya, and Sierra Leone demonstrates that socioeconomic factors create conditions for co-infections to flourish synergistically, requiring integrated interventions that address both immediate nutritional needs and structural health care barriers.

Figure 1: Socioeconomic-Biological Interface Model

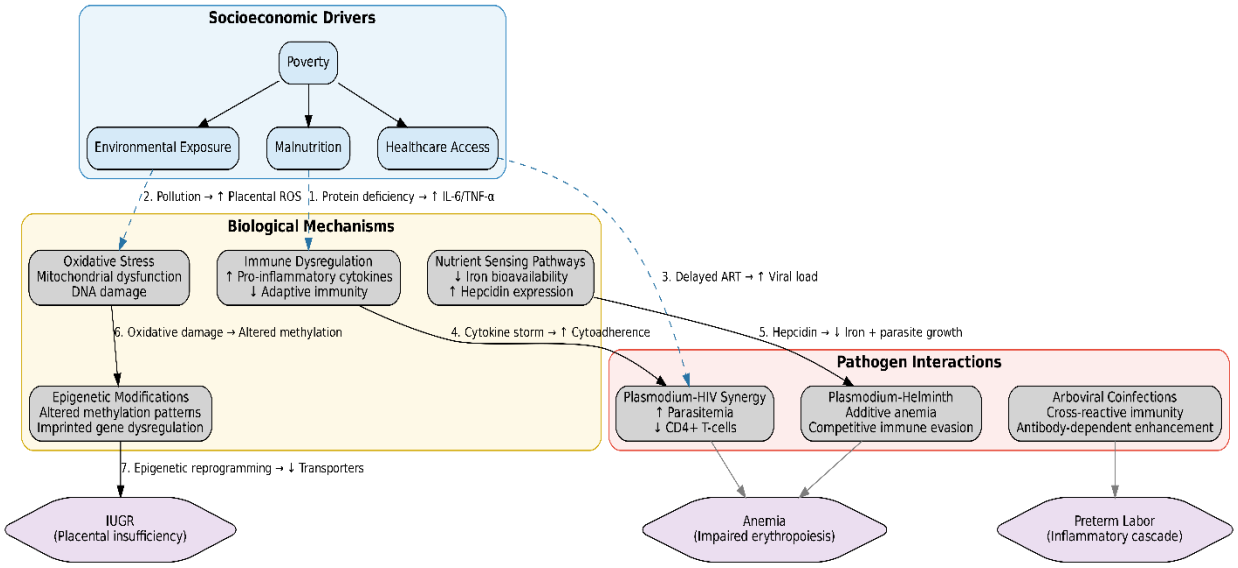

Figure 5. *Socioeconomic-Biological Interface Model illustrating the pathways by which poverty, environmental exposure, malnutrition, and healthcare access drive adverse pregnancy outcomes in high-burden settings. The diagram integrates socioeconomic drivers, biological mechanisms (oxidative stress, immune dysregulation, nutrient sensing), and pathogen interactions (HIV, malaria, helminths, arboviruses), highlighting their combined impact on intrauterine growth restriction, anemia, and preterm labor. This model underscores the need for integrated interventions addressing both structural and biological determinants to improve maternal and fetal health.*

Emerging Diagnostics and Therapeutic Strategies.

Recent advances in diagnostic technology have shown promise in addressing the challenges of coinfection diagnosis, particularly in resource-limited settings. CRISPR-based diagnostics, such as Specific High-Sensitivity Enzymatic Reporter UnLOCKing (SHERLOCK) and DETECTR (DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR), offer rapid, sensitive, and cost-effective solutions for detecting infectious diseases[48] [49]. These tools can detect low concentrations of target pathogens and provide results within 30 minutes of testing. The ability of CRISPR-based systems to perform multiplexing or simultaneous detection of multiple pathogens in a single test is particularly advantageous for the diagnosis of coinfections. In the context of pregnancy, this feature allows for the rapid detection of HIV, malaria, and helminths from a single blood or urine sample, significantly improving the diagnostic capabilities in remote settings where laboratory facilities are scarce[50]. Artificial Intelligence (AI) is another promising technology for improving diagnostic accuracy. AI algorithms, particularly those based on machine learning, can analyze vast datasets from various sources, including clinical records, genomic sequences, and medical imaging, to detect coinfection patterns[51]. AI-driven diagnostic platforms can assist in identifying subtle risk factors and complex interactions between pathogens, thereby enabling healthcare providers to make informed decisions.

Novel Therapeutic Approaches

Table 1 summarizes the key therapeutic strategies for managing co-infections during pregnancy. Combining antimalarial dihydroartemisinin with antiretroviral Co-trimoxazole in HIV-positive pregnant women reduced malaria incidence by 68%, was well tolerated with no increase in adverse maternal or fetal events, and may warrant inclusion in WHO guidelines for high-

transmission settings[52] [53]. These regimens not only improve treatment efficacy, but also mitigate the risk of drug resistance. The PfSPZ vaccine, based on irradiated Plasmodium falciparum sporozoites, provided 55% protection at 21 weeks and 100% protection in a subset at 59 weeks post-immunization, with a favorable safety profile[54]. Administering this single-dose regimen before conception could markedly decrease the malaria burden in pregnant women in endemic regions. Albendazole and mebendazole are the mainstays of antenatal care for helminthic infections. Albendazole effectively reduces worm burden and maternal anemia but carries an FDA pregnancy category C rating—reserved for cases where benefits outweigh risks— whereas mebendazole (category B3) lowers parasitic loads and improves hemoglobin levels when administered after the first trimester, making it a routine second-trimester intervention[55] [56].

Table 1. *Summary of key therapeutic interventions for managing malaria and helminth co-infections during pregnancy. The table details each intervention's target infection, efficacy, pregnancy safety profile, and relevant clinical notes. Highlighted are combination antimalarial-antiretroviral regimens, preconception malaria vaccination, and anthelmintic therapies, with emphasis on their effectiveness, safety considerations, and recommendations for use in high-burden, resource-limited settings. This overview supports evidence-based decision-making for optimizing maternal and fetal health outcomes in populations at risk.*

Intervention	Target Infection	Efficacy	Pregnancy Safety	Notes
Dihydroartemisinin+ Co-trimoxazole	Malaria in HIV-positive pregnant women	Reduced malaria incidence by 68% when added to daily cotrimoxazole	Well tolerated; no increase in adverse maternal or fetal events	WHO may update guidelines to include this combination in high-transmission areas
PfSPZvaccine(irradiated P. falciparum)	Preconception prevention of malaria	55% of vaccinees protected at 21 weeks; 100% of a subset protected at 59 weeks post-immunization	Favorable safety profile in adults; intended for administration prior to conception	Single-dose regimen shows promise for long-term protection
Albendazole	Soil-transmitted helminths (e.g., hookworm)	Effectively reduces worm burden and maternal anemia	FDA pregnancy category C; animal teratogenicity observed; use only if benefits outweigh risks	Recommended during antenatal care only when no safer alternatives exist
Mebendazole	Soil-transmitted helminths (e.g., pinworm)	Effective anthelmintic; lowers parasitic load and improves hemoglobin levels	Pregnancy category B3; no controlled human data but cohort studies show no increase in malformations when used after first trimester	Avoid during the first trimester; routinely administered in second trimester

Evidence Gaps and Future Research Directions

Despite significant progress in understanding the impact of coinfections during pregnancy, substantial evidence gaps remain, particularly regarding long-term maternal and child outcomes. Longitudinal studies are needed to explore the neurodevelopmental effects of in utero exposure to co-infections and the delayed consequences of these exposures, which often manifest years after birth. Additional research is needed to understand the impact of co-infections on maternal health post-pregnancy. The effects of chronic conditions such as HIV or malaria, which are exacerbated during pregnancy, can persist long after delivery, affecting women's overall health and quality of life. Understanding these long-term health trajectories is critical for providing adequate care for women who experience co-infections during pregnancy. Another emerging area of concern is the impact of climate change on infectious disease dynamics. The changing climate alters the distribution of vector-borne diseases such as malaria and dengue, extending their range to previously unaffected areas. This shift in disease epidemiology poses new challenges to maternal health, particularly in regions where healthcare systems are already under strain.

Conclusion and Recommendations

The burden of coinfections during pregnancy represents a complex and multifaceted challenge that requires integrated solutions that address both biological and socioeconomic factors that contribute to adverse pregnancy outcomes. The interplay between multiple infections, combined with inadequate healthcare access and poor nutritional status, exacerbates the risk to maternal and fetal health. To reduce the burden of co-infections, healthcare systems in high-burden regions must be strengthened by focusing on improving diagnostic capabilities, ensuring the availability of essential medications, and expanding access to antenatal care. Additionally, emerging technologies such as CRISPR-based diagnostics and AI-driven platforms offer significant potential for improving the speed and accuracy of diagnosis, particularly in resource-limited settings. Morover, integrated care models addressing women's overall health should also incorporate affordable, non-invasive treatments such as transcutaneous electrical nerve stimulation (TENS), which has shown effectiveness in managing common neurological disorders like migraine, significantly improving quality of life among postmenopausal women [57], Research should continue to focus on understanding the long-term impacts of coinfections on maternal and child health, with an emphasis on tracking neurodevelopmental outcomes in children and chronic health conditions in mothers. Furthermore, as climate change exacerbates the spread of infectious diseases, public health strategies must be adapted to address these emerging risks. Integrated care models that simultaneously address multiple infections, improve nutrition, and ensure comprehensive healthcare access are crucial for mitigating the impact of co-infections during pregnancy. Policy efforts should focus on strengthening the healthcare infrastructure, expanding educational programs, and investing in climate adaptation strategies to protect vulnerable populations.

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