

Helminth infection during pregnancy: insights from evolutionary ecology

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Abstract: Helminths are parasitic nematodes and trematodes, grouped together because of morphological similarities and commonalities in the effects infections have on hosts. These include complications such as anemia and biasing of immune responses, which can alter susceptibility for other diseases. For pregnant women, these complications might have implications for pregnancy outcomes or neonatal health. Here, I review studies of helminth infections during pregnancy, and ask the following questions: Do helminths affect maternal health or pregnancy outcomes? Are there consequences of maternal infection for infants? What are the effects of antihelminth treatment during pregnancy? The evidence suggests that the answers to these questions depend on the particular helminth species in question, maternal nutritional status, and the presence or absence of comorbid infection with other species, such as malaria. Moreover, there may also be unexpected consequences of treatment, as maternal infections can affect the priming of infant immune systems, with potential effects on infants later in life. These complex interactions suggest that a consideration of the evolutionary history of human–helminth interactions, as well as the ecological context of infections, can help to clarify an understanding of these host–parasite interactions and provide direction for future investigations.

Keywords: review, helminths, pregnancy, filariasis, schistosomiasis

Introduction

Helminths are various species of nematode and trematode worms that infect more than a billion people worldwide.¹ Though quite diverse (Box 1), helminths share common features, such as life cycles that require life stages outside of the primary host and complex effects on host immunity.² Helminths can be asymptomatic or can cause disease in their hosts, including anemia, nutritional deficiencies, changes in immunity, and more serious complications, such as elephantiasis and organ blockages.^{3–12} Since these complications might have consequences for pregnant women or developing fetuses, the World Health Organization has recommended that pregnant women be treated for helminth infections.³ However, these recommendations were made largely in the absence of adequate clinical trials, and more recent studies have begun to recognize that helminth infection and helminth treatment can have complex effects on mothers and infants (Tables 1–3). These effects include alterations in immunity, with implications for the development of allergy and autoimmune disease, as well as resistance to other infections.

In this review, I first discuss the effects of helminths on mothers and infants during pregnancy, as well as the results of trials examining the effects of helminth treatment. I then discuss these findings in the context of evolutionary ecology and the history of human–helminth interactions.

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Box 1 Three kinds of helminths

The term helminth is a non-taxonomical term used to refer to several species of infectious trematodes and nematodes. For the purposes of this review, I discuss three broad groups of helminths that infect humans.

Soil-transmitted nematodes are transmitted to humans via a life stage occurring in soil. Soil-transmitted helminths reside in the intestine, where they produce eggs that are excreted in the feces. Hookworm is a common name referring to two distinct species, *Necator americanus* and *Ancylostoma duodenale*. These two species of hookworms cannot be distinguished by standard fecal egg counts, and so are frequently referred to simply as hookworms. Hookworm larvae infect their hosts by penetrating through the skin, generally through the feet.⁷ *Ascaris lumbricoides* or roundworm is the largest of the infectious nematodes. *A. lumbricoides* is transmitted by ingestion of eggs.⁸ After infection, both hookworm and roundworm larvae migrate into the vasculature, to the heart, and then into the lungs. From the lungs, they are coughed up and swallowed, entering the gastrointestinal tract where they develop into adults.^{7,8} Other soil-transmitted nematodes such as *Strongyloides stercoralis* (threadworm) have complex life cycles that involve free-living stages and less directed tissue migration,⁹ while some nematodes, such as *Trichuris trichiura* (whipworm), infect the gastrointestinal tract directly, without tissue migration, when eggs are ingested.¹⁰

Filarial nematodes are smaller than soil-transmitted nematodes. Larvae called microfilariae are transmitted by biting insects from host to host. *Wuchereria bancrofti* is transmitted by mosquitos and infects the lymphatic system. Complications can include elephantiasis. *Onchocerca volvulus* is transmitted by black flies and infects subcutaneous tissue. *Onchocerciasis* (river blindness) is caused when microfilariae migrate into the eye. *Mansonella perstans* is transmitted by midges and infects serous body cavities, usually producing only mild symptoms.¹¹

Schistosomes, also referred to as blood flukes, are trematodes that infect either the mesenteric veins around the intestine or the venous plexus around the bladder. Schistosomes secrete eggs into the intestine or bladder, which are excreted into water. Eggs hatch, and larvae infect snails which serve as intermediary hosts. Motile larvae called cercariae leave the snails to seek out human hosts which they infect through the skin when humans come into contact with infected water.¹² The most serious complications of schistosome infections occur when the host immune system forms granulomas around eggs, which can lead to obstructions in the intestine, liver, kidney, or other areas. The most common species are *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*.

Review methodology

Articles pertaining to infection with helminths during pregnancy were searched for on Google Scholar and Web of Science using the terms (“pregnancy” OR “birth”) AND (“helminth” OR the name of one of the helminth species mentioned in Box 1, eg, “*Ascaris lumbricoides*”). Google Scholar was also used to identify relevant articles citing the articles identified by the initial search. Additional articles cited within the articles found in the search were also included, as were articles previously known to the author through past research, for example, the articles cited in my past study.⁴ Other authors have conducted recent meta-analyses of helminth treatment

during pregnancy,^{5,6} while for topics other than treatment, the identified articles reflected substantial heterogeneity in research context and methods, or were very few in number. Thus, in order to provide as broad an overview as possible, formal inclusion and exclusion criteria were not applied to the located articles, and instead, all articles with relevant and interpretable findings are discussed.

Intersections between pregnancy and helminth infection

Helminths and developing fetuses can both be thought of as foreign, immunologically distinct organisms living in a

Table 1 Effects of soil-transmitted nematodes during pregnancy

Species (common name)	Adult worm infection site	Direct effects on host	Effects on coinfection risk	Effects on infant
<i>Necator americanus</i> / <i>Ancylostoma duodenale</i> (hookworm)	Small intestine	Anemia ^{34–38,63,67,111} Lower IFN- γ response to tuberculosis lysate ⁷⁶ Reduced maternal fertility ⁴	Higher malaria parasitemia ³⁶ or prevalence ^{40,49} Higher HIV viral load ¹¹⁶ Reduced giardia prevalence ¹¹⁷	Higher IFN- γ response to tuberculosis lysate ⁷⁶ Lower rate of eczema ⁸¹ Lower odds of low birth weight with infection ⁶⁶ Poorer motor skills and lower cognitive ability ¹¹⁸ Increased risk of childhood malaria ¹¹⁹
<i>Ascaris lumbricoides</i> (roundworm)	Small intestine	Often asymptomatic Occasional anemia ³⁹ Increase in geophagy ¹²⁰ Higher maternal fertility ⁴	Increased odds of <i>Plasmodium falciparum</i> ⁵⁰ Higher malaria prevalence ⁴⁹	Possibility of limited maternal–infant transmission ⁷¹
<i>Trichuris trichiura</i> (whipworm)	Large intestine	Often asymptomatic, but may cause abdominal pain and anemia	Increased odds of <i>P. falciparum</i> ⁵⁰ Higher HIV viral load ¹¹⁶	Increase in low weight for gestational age, but only in undernourished mothers ⁶⁴

Abbreviations: IFN- γ , interferon- γ ; HIV, human immunodeficiency virus.

Table 2 Effects of filarial nematodes during pregnancy

Species	Adult worm infection site	Direct effects on host	Effects on coinfection	Effects on infant
<i>Wuchereria bancrofti</i>	Lymphatic system	Elephantiasis in hyperresponsive individuals	Little effect on HIV ¹²¹ Unclear or mixed effects on malaria ⁴⁸	Reduced odds of low birth weight with infection ⁶⁶ Increased maternal/infant HIV transmission ⁶⁰ Helminth-specific T-cell immunity and lower IFN- γ response to tuberculosis ^{73,79} Lower response to <i>W. bancrofti</i> antigen 17–19 years later ⁸⁵ Increased infection in tolerant, but not sensitized children ⁷⁴ Increased infection in children of infected mothers ^{80,84}
<i>Onchocerca volvulus</i>	Subcutaneous tissue	Onchocerciasis (river blindness)		Children of infected mothers are also more likely to be infected ^{78,83} Children of infected mothers have higher T _H 2 cytokines and lower T _H 1 cytokines ⁷⁸ Possible in utero transmission ⁷²
<i>Mansonella perstans</i>	Serous body cavities	Generally mild or asymptomatic, but occasional symptoms may occur ¹²²	Higher malaria parasitemia ³⁶ and prevalence ⁴⁷	Maternal infection associated with higher IL-10 to BCG and tetanus immunogens ⁷⁵

Abbreviations: IFN- γ , interferon- γ ; IL-10, interleukin-10; BCG, bacillus Calmette–Guérin; HIV, human immunodeficiency virus.

maternal body. Both helminths and pregnancy are associated with changes in maternal immunity and physiology. Normal pregnancy is associated with shifts in immunity toward the production of type 2 (T_H2) responses, which may increase tolerance of an immunologically distinct fetus.^{13,14} Helminths cause similar biases in immunity toward T_H2 responses,^{2,15} and also affect regulatory T-cells, modulating both T_H1 and T_H2 responses.^{16,17} Whether these changes reflect adaptive host responses, parasite manipulation, or some combination remains unclear,² particularly since for helminths, the most adaptive host response may be to develop tolerance rather than mount an excessive immune attack.^{18,19} However, the similarity between the immune responses to helminths and

those induced in pregnancy suggests that similar mechanisms of tolerance may be invoked, and that helminths may have evolved to utilize similar mechanisms for avoiding maternal immune responses that are used by a human fetus.

Some evidence in animals suggests that pregnant individuals might be at a greater risk for helminth infections than nonpregnant individuals.^{20,21} However, in humans, there is little evidence that pregnancy alters transmission risks for helminths,^{4,22} though a few results are suggestive of this possibility.²³ Despite this, helminths and pregnancy might have synergistic effects on other health outcomes. Helminths and pregnancy both require nutritional and energetic resources such as iron, glucose, lipids, and other molecules critical for

Table 3 Effects of *Schistosoma* during pregnancy

Species	Adult worm infection site	Direct effects on host	Effects on coinfection risk	Effects on infant
<i>Schistosoma mansoni</i>	Mesenteric veins	Intestinal schistosomiasis Anemia and undernutrition ^{110,123} Lower serum cholesterol ¹²⁴	No effect on malaria ⁴⁷ No effect on HIV viral load ¹¹⁶ Increased odds of coinfection with <i>Schistosoma haematobium</i> or hookworm ¹²⁵	Increase in total IgE and tuberculosis-specific IgG transfer from mothers. Lower IFN- γ response to tuberculosis lysate, but no change in IL-4 response ⁷⁷
<i>Schistosoma haematobium</i>	Venous plexus around the bladder	Urinary schistosomiasis Anemia ¹¹⁰	Increased odds of coinfection with <i>Schistosoma mansoni</i> or hookworm ¹²⁵	Reduced odds of low birth weight with infection ⁶⁶ Increase in preterm deliveries and lower birth weight in preterm deliveries ¹²⁶
<i>Schistosoma japonicum</i>	Mesenteric veins	Intestinal schistosomiasis Anemia ¹¹⁰		Possible lower birth weight ¹²⁷

Abbreviations: IgE, immunoglobulin E; IgG, immunoglobulin G; IFN- γ , interferon- γ ; IL-4, interleukin-4; HIV, human immunodeficiency virus.

fetal growth and development. Organisms face trade-offs in allocating resources between competing demands, such as survival, reproduction, and somatic maintenance,^{24,25} and these trade-offs may be especially exacerbated by the dual demands of simultaneous helminth infection and pregnancy. Moreover, helminth infections often occur in the context of coinfection with other parasites and pathogens, such as HIV, malaria, and giardia,²⁶ and are most prevalent in areas where resources are scarce and nutrition may be limited.^{1,27}

Anemia during pregnancy

Anemia is defined as low iron in the blood, typically measured in terms of hemoglobin concentration. Pregnancy is characterized by a decline in hemoglobin due primarily to hemodilution; as the total blood plasma volume increases, the number of erythrocytes per unit of blood declines.²⁸ Hemoglobin varies across pregnancy, declining during the first and second trimesters, and improving or leveling off during the third trimester as the mother compensates for the added plasma volume.²⁹ Guidelines for what constitutes anemia reflect this pattern, as anemia for pregnant women is defined by the World Health Organization as a hemoglobin concentration of 11 g/dL versus 12 g/dL for nonpregnant women.³⁰ These normal changes in hemoglobin are not associated with adverse outcomes. In fact, women who do not experience pregnancy-related declines in hemoglobin or who have elevated hemoglobin have a higher risk of adverse outcomes, possibly due to a failure of plasma expansion.^{31,32}

Anemia is one of the most common side effects of infection with geohelminths or schistosomes (Table 3), due to blood loss in the intestine or urinary tract. Hookworm, in particular, has been associated with moderate reductions in hemoglobin during pregnancy.^{33–38} Other geohelminths and schistosomes are associated with mild iron deficiency, but generally only when parasite burdens are high.^{33,34,36,39} However, there is little evidence to suggest a synergistic effect between infection and pregnancy; effects resemble those observed in nonpregnant women. Moreover, helminth infections alone are rarely associated with severe anemia in the absence of other confounding factors, such as nutritional deficiencies or coinfection with malaria or HIV. When nutritional deficiencies are present, helminths, and in particular hookworm, may exacerbate iron deficiency.^{36,37} Malaria coinfection is also associated with an increased risk of anemia and other negative outcomes during pregnancy,^{39,40} while the effects of helminths alone are often less clear.⁴⁰

Unfortunately, there is a paucity of data examining whether helminth-induced anemia affects birth outcomes or infant health. Studies typically examine associations between

helminths and anemia or anemia and birth outcomes, but have not examined whether birth outcomes differ with different causes of anemia. Severe anemia during pregnancy is associated with a number of adverse outcomes, including increased maternal mortality,⁴¹ increased risk of preterm birth or low birth weight,^{29,42,43} and increased risk of neonatal anemia.^{29,44} However, mild anemia is generally associated with limited risks during pregnancy.^{41,45} These results suggest that anemia due to helminths may only be of concern when worm burdens are high or when other factors contribute to anemia.

Coinfection during pregnancy

In addition to direct effects on mothers, helminths may affect coinfection risk or disease progression by biasing immunity or through other processes. To date, studies in pregnant women have primarily examined malaria and HIV, as these frequently co-occur in the populations in which helminth infections have been most frequently studied. In the case of malaria, interactions vary considerably by helminth species, parasite burden, and other factors.⁴⁶ The fly-borne *Mansonella perstans* is associated with higher malaria parasitemia³⁶ and prevalence.⁴⁷ Mosquito-borne *Wuchereria bancrofti* has a more complex association with malaria, in part because the same mosquitos transmit both the helminth and *Plasmodium falciparum* parasites and high worm burdens can impact mosquitos, affecting the spread of malaria.⁴⁸ A number of studies have found positive associations between geohelminths and malaria, suggesting that helminths may increase susceptibility,^{36,49,50} with the strongest evidence for an association with hookworm.⁴⁰ Yet, some studies have also found that some species, such as *A. lumbricoides*, may be associated with reduced risk of malaria,⁵¹ and others have reported that infection with *Schistosoma haematobium* can limit parasitemia.^{46,52} In a randomized trial, treatment of helminths led to a short-term increase in malaria parasitemia, but with no long-term effects on malaria symptoms or prevalence.⁵³ Thus, the actual effects of helminths on malaria coinfection remain somewhat unclear, as do any possible interactions with pregnancy.

A number of studies have examined coinfection between HIV and helminths in pregnant women. Both HIV and helminth infections can cause depletions in CD4⁺ T-cells,^{54–58} and treatment of helminths reduces HIV progression and improves CD4 counts, although reductions in viral load may be small.⁵⁹ At least one study has found that helminths are associated with increased mother-to-infant transmission of HIV.⁶⁰

Premature birth and low birth weight

A number of studies have found associations between helminths and lower birth weights; however, the majority of

these studies have involved limited samples with comorbid conditions, and many have not used multivariate statistics to partition the effects of different helminth species or other contributing factors. In a study of HIV-infected women in Tanzania, helminth infections were associated with low birth weight,⁶¹ and another study in Nigeria found that helminth infections were associated with lower birth weight, but without isolating the effects of HIV status.⁶² Yatich et al³⁹ found that in women with anemia, coinfection with helminths and malaria was associated with low birth weight, preterm delivery, and small birth weight for gestational age. Much of this effect appeared to be driven by malaria, as the only significant effect of helminths alone was an increase in the risk of being small for gestational age. A hospital-based study of Nigerian women found that helminth–malaria coinfection was associated with lower birth weight than malaria infection alone, but did not present data or make comparisons with uninfected women.⁶³ A study conducted in Guatemala City found that helminth and protozoa were associated with risk of small birth weight for gestational age, but only in undernourished women, with undernourishment determined based on maternal height.⁶⁴ In contrast to these studies, other studies of helminths alone have found no association between infection and birth weight⁶⁵ or have actually found that women with infections have higher birth weights even in the presence of coinfections.⁶⁶

Perinatal mortality

Few studies have directly measured whether infant mortality is affected by maternal infection during pregnancy. In a non-randomized study in which women were given albendazole, prenatal mortality was lower in the women who received treatment.⁶⁷ A second study in Sri Lanka found that mebendazole was associated with reduced odds of stillbirth or perinatal death.⁶⁸ However, neither study determined infection status either before or after treatment, and both may have been confounded by factors affecting which women received treatment in the first place. In three randomized trials, treatment had no significant effect on perinatal mortality.^{5,65,69,70}

Modulation of infant immune response

In humans, there are scattered case reports suggesting that maternal–fetal transmission of infection may occasionally occur.^{71,72} Yet, these reports are rare, and on the whole, it appears that, for humans, helminths are rarely able to infect a developing fetus. However, several studies have found that helminth antigens are transferred to infants in utero. Evidence

suggests that this occurs across a range of species, including filarial helminths,^{73–75} geohelminths,⁷⁶ and trematodes.⁷⁷ As a consequence, infants whose mothers are infected during pregnancy show a variety of alterations in immunity, frequently characterized by increases in T_H2 responses to helminth antigens and decreases in T_H1 responses to non-helminth antigens.⁷⁸ For example, *W. bancrofti* infection during pregnancy is associated with changes in cytokine production in response to helminth antigens, as well as reductions in interferon (IFN)- γ production in response to tuberculosis antigen.^{73,79,80} There is also evidence that infants with helminth-infected mothers are less likely to develop eczema, suggesting reductions in certain allergic responses.^{81,82} In many cases, these alterations resemble the effects of infection on adult immunity.^{77,78} However, in some cases, effects on infants have been found to be contrary to those in adults; that is, one study found that infants of mothers with hookworm showed increased IFN- γ production to hookworm antigen, whereas their mothers had decreased IFN- γ .⁷⁶ While most studies have grouped all infants and measured average changes in immune function or resistance in children, a study by Malhotra et al⁷⁴ took a different approach, and grouped infants of mothers with *W. bancrofti* based on whether their cord blood mononuclear cells showed a response to helminth antigen. Roughly half of the exposed newborns showed a response and were considered sensitized, while the other half did not respond and were considered tolerant. Tolerant infants were themselves more likely to become infected with *W. bancrofti* and had reduced IFN- γ responses relative to sensitized or unexposed infants.

The evolutionary context of antigen transmission and tolerance

Most studies have implicitly considered the in utero transfer of antigen to infants to be a negative consequence of infection, with warnings that such transfers can induce tolerance or sensitization in the infant. The idea is that antigens transferred from the mother might be mistaken as self-antigens by the developing fetal immune system, and thus, responses to these antigens might be suppressed. Indeed, some evidence suggests that infants of infected mothers are at higher risk of infection, at least for filarial nematodes, including *W. bancrofti* and *Onchocerca volvulus*.^{78,80,83,84} Some of these changes appear to persist for years, with effects documented as much as 19 years later.⁸⁵

However, immunological tolerance may not always represent a negative outcome, despite the potential for higher prevalences of infection. In many instances, the most serious consequences of infections are caused not by the infections

themselves, but by an overactive immune response to an infection. In the case of *W. bancrofti*, clinical disease such as elephantiasis develops in those with more hyperactive immune responses. Those with tolerant responses are often asymptomatic, despite being infected.^{86,87} Similarly, schistosomiasis is characterized by the formation of granulomas around schistosome eggs in the intestine or urinary tract, which accumulate to form physical blockages. The immunological profiles of those who develop disease differ from those who do not, with those developing disease having stronger responses to egg antigen.⁸⁸

From an evolutionary perspective, immune responses always represent trade-offs between the costs of immunity and the benefits.^{89–91} Immune responses have both energetic and somatic costs from collateral damage. Thus, organisms have evolved to modulate immune responses when possible to avoid excess damage to self. Similarly, immune responses should be moderated when they are ineffective, or when the cost of clearing an infection outweighs the costs imposed by the infection itself. Under these circumstances, tolerance may represent the most adaptive host immunological strategy.^{18,19}

Thus, an alternate hypothesis is that the tolerance induced by the maternal transfer of antigens to her infant represents an adaptive strategy. In support of this, most proteins cannot passively diffuse across the placental membrane, and so must be actively transported.⁹² This includes antibodies and antibody–antigen complexes, which are actively transported across the placental membrane.^{93–95} Moreover, transplacental immunization is not specific to helminths but is rather a much more general phenomenon.^{96–98} Thus, the maternal transfer of antigens is unlikely to be a consequence of manipulation by the parasite and more likely to represent an adaptation for preparing the immune system of the neonate to face pathogens present in the local environment. Infants who receive information from their mothers which conveys immunity, as well as information about the appropriate moderation of immune responses, might be expected to be at an advantage compared to infants born with completely naïve immune systems.

Hypothetical interactions between helminths and pregnancy

Fecundity and early pregnancy loss

There are multiple pathways through which helminth infections might affect fecundity or lead to early loss of pregnancies, including redirection of resources, alteration of the hormonal milieu,²⁰ or immunological biasing.⁴ However, there is little direct evidence. Anemia may affect egg maturation, leading to overall lower fecundity.²⁹ Consistent

with this, one study found that infection with hookworm was associated with both lower hemoglobin and a lower probability of a women becoming pregnant.⁴ The same study found that *A. lumbricoides*, which was not associated with anemia, was associated with an increased risk of becoming pregnant, perhaps due to immunological biasing toward an immunological environment favorable for a fetus.⁴

Gestational diabetes

We know of no studies testing whether helminth infections lead to complications such as gestational diabetes. However, helminth infections affect blood glucose, insulin resistance, and diabetes, leading to improved glucose tolerance and lower blood levels.^{99–104} Thus, helminths might also help modulate blood glucose during pregnancy.²² Helminth-induced anemia may also affect the risk of gestational diabetes, as excess iron during pregnancy is associated with increased risk of gestational diabetes.¹⁰⁵

Preeclampsia

Preeclampsia is a complication of pregnancy characterized by hypertension, systemic inflammation, and increased protein in the urine. The symptoms of preeclampsia resemble tissue rejection of an immunologically distinct fetus.^{106–108} Indeed, a primary cause of preeclampsia is a mismatch between maternal killer immunoglobulin receptors and fetal HLA molecules.¹⁰⁹ Given the immunological effects of helminths on maternal immunity, helminth infections might also affect preeclampsia, by increasing maternal tolerance of the fetus and by moderating inflammatory responses. Unfortunately, data addressing this hypothesis are currently lacking. However, such an effect might be behind the association between *A. lumbricoides* infection and increased fertility that we have previously reported.⁴

Antihelminth treatment during pregnancy

Given the complex interactions helminths can have on maternal and infant immune function, health, and coinfection risks, the question of whether helminths should be treated in pregnant women is far from straightforward. Initial studies established the safety of common helminth treatments, including albendazole, mebendazole, and praziquantel. These studies have generally found that treatment does not result in an increased prevalence of birth defects.^{65,68,110} However, these and additional studies have also found that treatment has limited effects on maternal and infant health. Both a meta-analysis conducted in 2012⁵ and a more recent

Cochrane review⁶ found that antihelminth treatment had no clear overall effect on maternal anemia, low birth weight, or perinatal mortality. The 2012 review found a reduction in very low birth weight, but this was based only on one study with a significant effect and one without.^{5,69}

What these meta-analyses may obscure is heterogeneity between study populations. Given the limited number of studies, it is difficult to ascertain whether antihelminth treatment might have beneficial effects under certain conditions and limited effects under others. For example, one study that found an effect of albendazole on maternal anemia also found that albendazole had far less effect than iron supplementation and had little effect when given alone.¹¹¹ It may be that antihelminth treatment is only beneficial in women with very high parasite burdens, dietary insufficiencies, or both. In most instances when women are adequately nourished and burdens are low or moderate, treatment might have little effect.

Additional studies have examined whether helminth treatment during pregnancy affects infant immune responses. Several have found that treatment is associated with an increased incidence of eczema, suggesting that treatment may affect the development of mechanisms regulating infant immune responses.^{81,82,112} Others have examined whether treatment affects infant immune responses to helminth antigens. In general, infants of mothers who were infected but treated have similar immunological responses as infants of mothers infected but not treated.^{76,81,113} Treatment has also been found to have no significant effect on HIV transmission.¹¹³ However, given the limited scope of these trials, a number of questions remain regarding the effectiveness of treatment, the generalizability across helminth species, and possible effects dependent on the timing of treatment during pregnancy.¹¹⁴

Conclusion: old enemies or old friends?

Hosts and the organisms that live within them are constantly negotiating their relationships, both within individual lifetimes and over evolutionary time spans of many generations. Thus, these relationships are rarely settled, and the same organisms can impose costs or provide benefits to different individuals or in different contexts. Helminths are relatively long-lived organisms that depend on the survival of their hosts for continuous transmission. In this respect, helminths and their hosts share an interest in keeping the host alive and defending it against other competing pathogens and parasites. Unlike some other pathogens, such as viruses, for which humans develop effective immunity against particular

strains, humans are also constantly reinfected by helminths, and transmission occurs largely within localized geographical areas. Thus, helminths may also benefit from maintaining reasonably healthy hosts that their descendants can continually infect. This history helps explain why the symptoms of helminth infections are often subtle and why human hosts frequently develop tolerant immune responses.

The difficulty of studying parasite interactions in natural settings means that many studies of helminths and pregnancy remain inconclusive. Confounding factors such as multiple comorbidities and small sample sizes make isolating the effects of particular species difficult, let alone elucidating the details on multispecies interactions. Future studies might provide more insight by using more sophisticated multivariate statistical approaches to partition variance and test explicit causal pathways, as opposed to simple associations which might be confounded by other variables.¹¹⁵

Despite these difficulties, some general conclusions can be drawn with regard to helminth infections during pregnancy. While comorbidities make separating effects difficult, there is sufficient evidence to suggest that some helminths are more harmful than others. Hookworm, for example, is found to cause anemia in pregnancy much more frequently than other geohelminths. As with most interactions of this kind, the evidence also suggests that conflicts of interest between host and parasite are most pronounced when resources are scarce. Helminths are more likely to be associated with negative outcomes when they occur with comorbid conditions, such as malaria or nutritional deficits. Yet in these cases, treating the comorbid condition may be more beneficial than treating the helminths.¹¹¹ In the absence of such confounding factors or evidence of confounds, such as severe anemia, treatment may impose more costs than benefits, for example, by increasing the risk of infant eczema. Treatment may also have additional unanticipated effects by altering maternal blood glucose regulation, microbiota, or hormonal environment. Thus, broad efforts to treat all women should be approached with caution until future studies investigate these outcomes and how they play out under different ecological conditions.

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