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Impact of Helminth Infections on Female Reproductive Health and Associated Diseases

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A growing body of knowledge exists on the influence of helminth infections on allergies and unrelated infections in the lung and gastrointestinal (GI) mucosa. However, the bystander effects of helminth infections on the female genital mucosa and reproductive health is understudied but important considering the high prevalence of helminth exposure and sexually transmitted infections in low- and middle-income countries (LMICs). In this review, we explore current knowledge about the direct and systemic effects of helminth infections on unrelated diseases. We summarize host disease-controlling immunity of important sexually transmitted infections and introduce the limited knowledge of how helminths infections directly cause pathology to female reproductive tract (FRT), alter susceptibility to sexually transmitted infections and reproduction. We also review work by others on type 2 immunity in the FRT and hypothesize how these insights may guide future work to help understand how helminths alter FRT health.

Keywords: Helminths, female reproductive tract, sexually transmitted infections, fertility, Systemic immunity

BURDEN OF DISEASE

Helminth infections are widespread and are characterized by sophisticated host immune modulation and evasion. Helminth infections are a global health concern, with more than 1.7 billion affected worldwide, particularly in tropical and subtropical regions (1). A feature of helminth infections are the parasites' ability to alter immunity and susceptibility to unrelated diseases (2–7). Of particular interest is the potential impact of helminth immune-regulation on susceptibility to sexually transmitted infections (STIs), given their high incidence in developing regions and detrimental impact on public health (8). For example, Ivan et al. (9) studied a cohort of 328 Rwandan pregnant women on anti-retroviral therapy, 38% of whom were stool positive for helminth infections (9). Mkhize-Kwitshana et al. (10) reported 66% of HIV+ study participants from an helminth endemic region of South Africa, were helminth egg positive and/or helminth-specific IgE seropositive (10). Likewise, Abossie and Petros (11) reported 68% of study participants in Ethiopia were co-infected with helminths and HIV, 35% were women (11). In this review we

address how the geographical overlap between helminth exposure and STIs can result in parasite-induced changes to female reproductive health (12–14).

HELMINTH IMMUNITY

Host immunity to helminths has been studied in depth using mouse models reflective of human infection and immunity (15–18). Typically, helminths induce a type 2-skewed immune response, associated with the production of the canonical cytokines interleukin (IL)-4, IL-5, and IL-13 (19–26). These cytokines amplify alternatively activated macrophages (AAMs; M2) (27–29), eosinophilia (30–32), smooth muscle contraction and goblet cell hyperplasia; cellular and physiological responses that underlie the 'weep and sweep' worm expulsion from the intestine (21, 23, 24, 26, 33, 34). Consistent with *in vivo* studies, epidemiological studies also report type 2-biased immune responses in humans infected with roundworm *Ascaris lumbricoides* (35–37), whipworm *Trichuris trichiura* (36–38), and hookworm *Necator americanus* (39). Furthermore, experimental infections of participants with hookworm has been shown to result in strong mucosal and systemic type 2 cytokine responses (40). Helminth infections also elicit regulatory immune responses, characterized by transforming growth factor-β (TGF-β), IL-10 and expansion of FoxP3-expressing regulatory T cells, involved in immune polarization and controlling inflammation (2, 41–48).

Antagonism between type 1 and type 2 immunity is central to our understanding of the T helper (Th) 1 cells (Th1)- T helper 2 cells (Th2) immune paradigm: Mosmann et al., first described Th1 and Th2 $CD4^+$ T cell differentiation and cytokine responses (49, 50), and Fernandez-Botran et al. (51) first demonstrated Th subtype regulation of each other (51). Furthermore, Reese et al. (52) demonstrated that IL-4 and STAT6 signaling can competitively inhibit interferon (IFN)-γ production (52). This paradigm has been expanded beyond T cell responses, as what is known as type 1 and type 2 immunity and regulation. For example, AAMs are a key feature of helminth infection induced by IL-4, -13 and -10. AAMs synthesize high levels of the enzyme arginase-1, which inhibits nitric oxide (NO) production (53). In addition, AAMs downregulate inflammatory Th1 immune responses mediated by TGF-β (54), which induce the development of regulatory T cells (41). Considering the opposing responses of type 1 and type 2 immunity, it is hypothesized that canonical type 2 immunity induced by helminths, can influence Th1- and Th17-mediated immune protection against STIs in the female reproductive tract (FRT).

HELMINTH-INDUCED IMMUNE MODULATION

Co-evolution of parasitic worms with the host is thought to have resulted in their ability to evade host's immunity through highly sophisticated responses. Helminths actively promote the expansion of regulatory T cell populations, promoting helminth persistence as well as host survival following infection (41, 44, 45, 55, 56). This can be achieved by the helminths release of excretory/secretory products, which effectively target and inhibit specific components of anti-parasite immune mechanisms or induce favorable immune regulation (43). For example, *Heligmosomoides polygyrus* excretory/secretory products (HES) contain a TGF-β mimic, the importance of this is supported by blockade of HES TGF-β mimic *in vivo* resulting in parasite expulsion in susceptible C57BL/6 mice (41). Bancroft et al. (57) recently identified the immunomodulatory molecule p43, a major secreted protein by murine whipworm *T. muris*, which binds to and inhibits IL-13 activity (57). Helminth-induced immune modulation benefits parasite survival by supporting asymptomatic or chronic infections. This has been demonstrated by individuals with asymptomatic lymphatic filariasis who display regulatory T and B cell responses (58), as well as skewed Th2 and regulatory T cell cytokine profiles i.e. favorable IL-4 and TGF-β, over IFN-γ and IL-17 production (46, 59–61). Alternatively, symptomatic patients had dominant pro-inflammatory responses, i.e. Th1, Th17 inflammatory responses and uncontrolled Th2 responses, resulting in immune-mediated damage of colonized tissue leading to severe symptoms like dermatitis in hyperreactive onchocerciasis or elephantiasis in lymphatic filariasis (62, 63).

Importantly, helminth-induced immune modulation has bystander effects on unrelated conditions such as allergies, autoimmune and inflammatory disorders, and unrelated infections. McSorley et al. (2) reported the suppression of type 2 allergic lung inflammation from treatment with HES (2), associated with TGF-β-like activity (41). Furthermore, Johnston et al. (42) demonstrated the suppression of skin allograft rejection by treatment with a TGF-β mimic isolated from HES (42). In support, Li et al. (64) demonstrated suppression of allograft rejection with *H. polygyrus*-induced Th2 and regulatory T cell bystander immunity (64). Recombinant hookworm anti-inflammatory proteins have been shown to reduce inflammation during experimental colitis (65) and asthma (66), associated with the induction of regulatory T cells. Layland et al. (67) demonstrated the suppression of allergic airway inflammation mediated by *S. mansoni*-induced regulatory T cells *in vivo* (67). Furthermore, Straubinger et al. (68) showed reduced susceptibility to ovalbumin (OVA)-induced allergic airway inflammation in mice born to mothers infected with *S. mansoni* during pregnancy. Osbourn et al. (69) described the ability of *H. polygyrus* Alarmin Release Inhibitor (HpARI) secreted protein to bind to and suppress IL-33 activity, reducing ILC2 and eosinophil responses, and promoting parasite survival (69). Interestingly, Zaiss et al. (70) demonstrated that infection with GI *H. polygyrus* resulted in changes to host intestinal microbiota and increased microbial-derived short chain fatty acids, which contributed to helminth-induced suppression of allergic lung inflammation (70). Conversely, Pinelli et al. (71) reported exacerbated ova-induced

allergic airway inflammation in mice infected with *Toxocara canis* (71). In humans, Jõgi et al. (5) reported increased risk of allergy manifestations in Norwegian children with anti-*T. canis* IgG4 seropositivity (5).

In addition to modulation of allergies and autoimmunity, Darby et al. (72) recently demonstrated how pre-conception maternal helminth exposure influences offspring immunity to helminth infection. Prior murine hookworm, *Nippostrongylus brasiliensis* infection imprinted Th2 immunity in female mice, which was transferred *via* breast milk and conferred protection against the parasite in their offspring. Protection was associated with maternally-derived Th2 primed $CD4^+$ T cells (72). Helminth-induced bystander immunity has also been implicated in altered vaccine responses (73–77) and immunity to unrelated infections. This highlights the potential significance of a transgenerational axis of influence on immunity by helminth infections.

Helminth-induced bystander immunity has also been implicated in altered vaccine responses and immunity to unrelated infections (73–77). For example, mouse infection with *T. spiralis* and *H. polygyrus* can impair immunity to murine norovirus (MNV) in the co-colonized intestine, mediated through impaired type 1 responses by type 2 activation of macrophages (78). Changes to lymphoid lineage function are demonstrated by Rolot et al. (7), who show helminth-mediated expansion of virtual memory $CD8^+$ T cells which enhance control of subsequent murine γ-HV respiratory infection (7). McFarlane et al. (79) showed that infection with murine nematode *H. polygyrus*, altered gut microbiota, which systemically increased proinflammatory type I IFN, and protected against subsequent respiratory viral infection (79). Additionally, *in vivo* infection with *T. spiralis* reduced pathological inflammation of the airways following influenza A virus infection (80). Helminth infection also impacts on control of bacterial infections. *N. brasiliensis* infections have been shown to impair natural and vaccine elicited T cell and B cell responses against *Salmonella typhimurium* infection *in vivo* (4). Protection against bacterial infections has also been reported; with reduced pulmonary mycobacterial burdens during concurrent nematode infection in mice, that required helminth-modified alveolar macrophage responses (3). Human studies have also identified helminth-associated changes to myeloid responses that relate to protection against MTb. For example, a negative association between hookworm infection and latent Mtb infection in Nepalese immigrants to the UK, was associated with elevated eosinophil numbers (6). Coincidence of filarial infection has also been associated with moderate protective immunity during latent Mtb infection (62, 81) and in a recent study, *S. stercoralis* infection in latent tuberculosis patients, was associated with down-regulated chemokine responses (82). Associations between soil-transmitted helminth (STH) infection and higher risk of concurrent bacterial and protozoal infections, and lower risk of concurrent viral infections in children and adults have also been reported (83). Recent studies have also demonstrated that prior nematode infection can confer resistance to subsequent infection by a different nematode species (84, 85). Together this existing body of work shows that helminths infections can have diverse influences on unrelated disease at sites distal to the anatomical location of the helminth in the host.

HELMINTHS, FEMALE REPRODUCTIVE TRACT, AND SUSCEPTIBILITY TO STIS

Immune imprinting on helminth infected hosts is therefore a feature of tissues not colonized by the parasite (86), including the FRT (87). The impact of helminth infection on immunity in the FRT and subsequent immune responses to sexually transmitted infections is not well studied, but it is apparent that significant effects on disease control in the FRT are likely.

Immune Control of STIs

The vaginal mucosa, the entry point for most STIs, is a unique and dynamic mucosal site under the cyclic influence of female sex hormones, and is made up of stratified squamous epithelial, lined by mucous, commensal bacteria and other anti-microbial defenses (88–91). In addition, the vaginal submucosa is surveyed by resident immune cells such as dendritic cells (DCs), which mount the response against invading pathogens (92–95). Host immune control of STIs is strongly correlated with the pattern of cytokine production in the host. Differential activation of Th1 cells, producing IL-2 and IFN-γ, mediate cellular immune responses, whereas Th2-like cells producing IL-4, IL-5, and IL-13, facilitate humoral immunity (96). Persistence of STIs can also be influenced by the production of IL-10 (97) and activation of regulatory T cells (98). While many STIs are initially asymptomatic, lack of treatment can result in an increased risk of acquiring another STI, infertility, organ damage, cancer, or death.

The most common sexually transmitted viral infections (STVIs) of the FRT are Herpes Simplex Virus type II (HSV-2), Human Papillomavirus (HPV) and Human Immunodeficiency Virus (HIV). Control of STVIs is typically associated with type 1 immune responses (99, 100). With the exception of HIV, killing of virally infected cells requires Th1 polarization of $CD4^+$ T cells (101), production of type 1 cytokines such as IFN-gamma (IFN-γ) (102, 103) and cytotoxic T cell responses (104–106) (**Figure 1**). Th1 immunity is also critical for early control of HIV, however, this response is insufficient to resolve infection (110), due to the virus' ability to rapidly mutate and evade $CD8^+$ T cell responses (107). Pre-existing inflammation and increased presence of $CD4^+$ target T cells in the FRT are major risk factors for increased susceptibility to HIV infection (111). Elimination of $CD4^+$ T cells by HIV is a hallmark of acquired immune deficiency syndrome (AIDS), resulting in increased susceptibility to opportunistic infections (112) and viral-associated cancers (113).

Similarly to STVIs, bacterial infections of the FRT require a Th1 and/or Th17 response to clear the infection (114, 115). *Chlamydia trachomatis* is a common bacterial STI worldwide, with women carrying the burden of this disease (116). IFN-γ

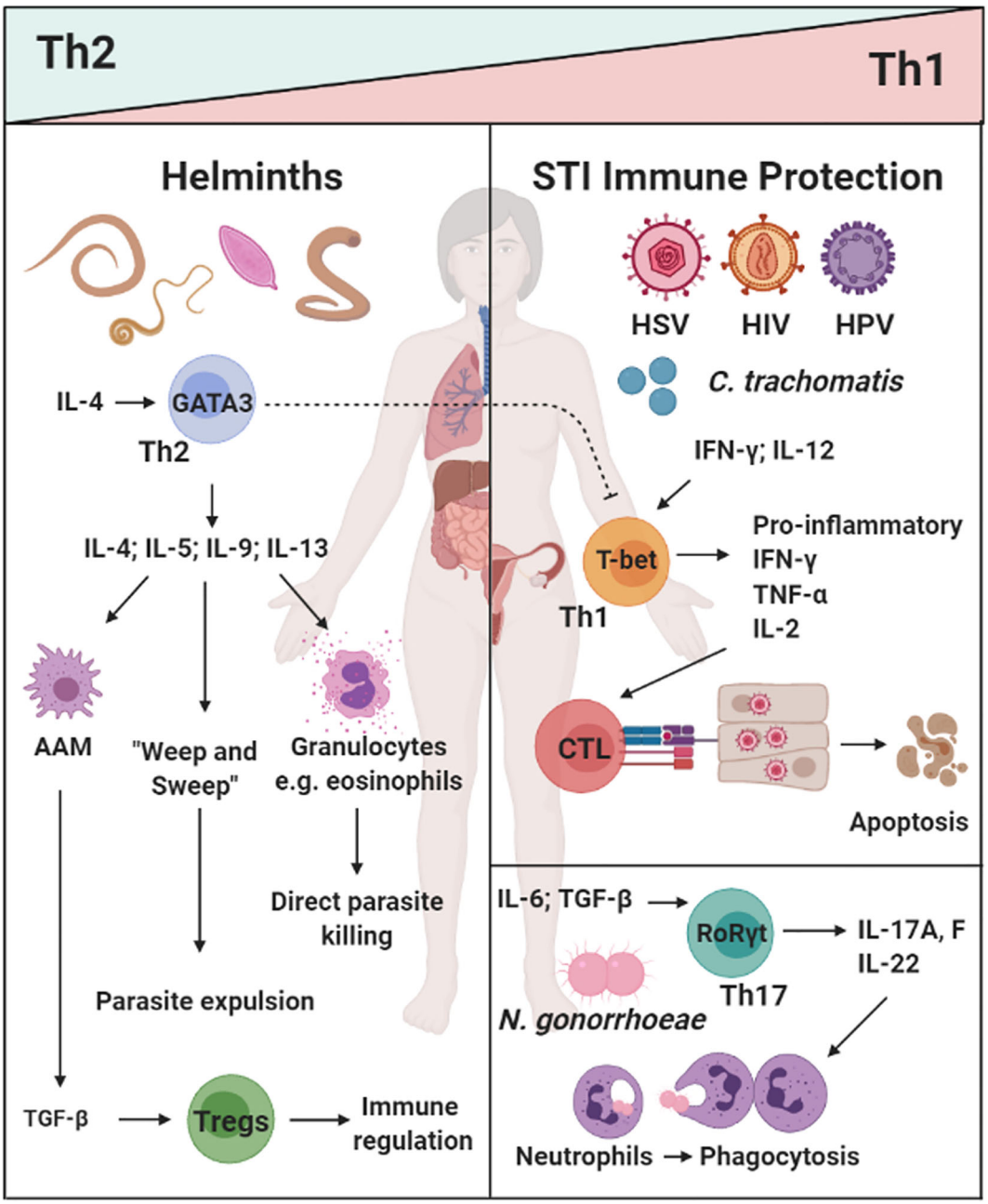

FIGURE 1 | The dichotomy of helminth-induced Th2/type 2 and regulatory immunity, and protective responses against sexually transmitted infections (STIs) in the female reproductive tract (FRT): Helminth infections (e.g. *A lumbricodes, T. trichiura, Schistome eggs*) commonly induce a potent Th2/type 2 immune response characterized by type 2 cytokines IL-4, IL-9, and IL-13, which induce a potent type 2 effector cells and functions (e.g. eosinophils, alternatively activated macrophages(AAMs), "weep and sweep" responses) (20, 21, 35, 36, 38–40). Prevalent viral [Herpes Simplex Virus type II (HSV-2), Human Immunodeficiency Virus (HIV), and Human Papillomavirus (HPV)] and bacterial (*C. tranchomatis and N. gonorrhoeae*) vaginal infection are a serious health concern for women in low- and middle-income countries (LMICs). Protective immunity against these pathogens can be classified a Th1/type 1 and Th17 responses i.e. cytotoxic killing of infected cells or phagocytosis of extracellular pathogens (101–107–109). How helminth exposure and immune modulation may influence susceptibility and control of STIs, is not fully understood. Created with BioRender.com.

production by Th1 $CD4^+$ T cells have been shown to be important for the resolution of *C. trachomatis* infections (117, 118). Cytotoxic T lymphocyte (CTL) responses are not required for clearance of this infection and instead have been shown to promote tissue pathology in the upper genital tract (108, 109). Another common bacterial STI is *Neisseria gonorroeae*, the causative agent of gonorrhea. In a murine model of infection, Th17 immune responses were shown to be favorable for

N. gonorrhoeae clearance (114). Considering the established counterbalance between Th2/Treg immunity and Th1/Th17 responses (50, 52, 119, 120), it is important to understand the consequence of helminth-induced immunity on susceptibility to co-endemic STIs (**Figure 1**).

Genital Schistosomiasis

Schistosoma haematobium infections have profound effects on female genital health. *S. haematobium* larvae (cercariae) emerge from aquatic snails and infect the human host through skin penetration. The larvae develop into schistosomula and migrate through the vasculature. Eventually, these mature into adult parasites, pair up and reside for years in the pelvic venous plexus. *S. haematobium* eggs produced here lodge in the urinary bladder wall and FRT, causing urogenital schistosomiasis (121). In chronically infected individuals, vaginal pathology here is acute with reported itching, pain, hematuria and ulceration in *S. haematobium*-infected individuals (122–125). Pathology is driven by eggs traversing host tissue and the formation of calcified granulomas in the female urinary and reproductive tract. The World Health Organization (WHO) International Agency for Research on Cancer (IARC) declared *S. haematobium* a group 1 carcinogen, as the correlation between urogenital schistosomiasis and the occurrence of bladder cancer has been extensively proven (126).

In the mouse model of urinary schistosomiasis, injection of eggs into the urinary bladder results in formation of a granuloma around the eggs made up of neutrophils, eosinophils and macrophages, as well as the onset of fibrosis in the surrounding bladder tissue (127). Furthermore, in this model *S. haematobium* eggs induced a strong type-2 response characterized by eosinophilia and elevated IL-4, IL-13 and IL-5 in the tissue surrounding the eggs. A compromised FRT epithelium is associated with increased HIV risk (128). The bystander tissue damage resulting from *S. haematobium* egg-induced inflammation (129, 130), increased immune activation (131) and lesions in the FRT is reasonably hypothesized to increase host risk of HIV infection, by providing routes for viral entry and increased number of target cells at the site of infection (132) (**Figure 2**). Furthermore, the type 2 response induced during *S. haematobium* infection (127) may dampen type 1 responses required for protection against viral pathogens such as HIV. These hypotheses are supported by clinical findings, where women infected with *S. haematobium* may have up to a 3-fold increased risk of acquiring HIV (133–135).

Following treatment with the anti-helminthic drug, praziquantel, the immune response in treated individuals shifts from a type 2 and regulatory T cell immune response (131, 136, 137) to a pro-inflammatory state, with elevated levels of egg antigen-specific TNF-α, IL-6, IFN-γ, IL-12p70, IL-8 and Th17 cytokines (IL-17, IL-21, and IL-23) post-treatment (138). If this inflammatory state results in reduced susceptibility to HIV infection is yet to be explored.

Filariasis

Filarial-driven immune modulation (i.e. induction of Th2, regulatory immune responses and suppression of inflammatory/Th1 responses) may increase susceptibility to viral and bacterial infections in the FRT, as Th1/inflammatory responses are important for the defense against these pathogens (139, 140). This is supported by identification of an association between infection with the filarial nematode *Wuchereria bancrofti* and increased risk of HIV infection (141). This increased HIV susceptibility may be associated with systemic increase in proportions of $CD4^+$ T cells expressing HLA-DR and HLA-DR/CD38, as well as effector memory $CD4^+$ T cells in lymphatic filariasis patients, i.e. an increase in HIV target cells in these patients (142). This supports *in vitro* findings demonstrating increased HIV infection of PBMC from lymphatic filariasis patients in comparison to uninfected individuals (12). Increased inflammation has also been reported in lymphatic filariasis patients (62, 143), with systemic IL-17 and IFN-γ elevated in response to PBMC stimulation with filarial antigen in these individuals. With chronic filarial infections, a type 2 immune signature, i.e. elevated IL-4 and IL-5, is detected in antigen-stimulated host PBMCs (143, 144). In contrast to schistosomiasis, regulatory T cells were reduced in lymphatic filariasis cases (62, 144) however type 1 responses (IFN-γ production) were suppressed in these patients (144). These studies suggest that chronic filarial infections could alter susceptibility to common FRT pathogens requiring type 1-mediated immune control. Surprisingly, genital manifestations of *W. bancrofti* infection have not been associated with any changes to fertility or pathology in the FRT (145).

Soil-Transmitted Helminths

Unlike schistosomiasis that causes direct pathology to the FRT, evidence has emerged of the potential systemic effect of helminths at sites that are not colonized by these pathogens. In a STH endemic region of Peru, Gravitt et al. (87) reported an increased prevalence of HPV among older women (30–45 years old) infected with STHs, which included *T. trichiura, A. lumbricoides, Ancylostoma duodenale* and *Strongyloides stercoralis*. Importantly, the life cycle of these helminths does not involve any larval transit through, or egg deposition in the FRT. The type 2 cytokine IL-4 was detected in cervicovaginal lavages of these women and IL-4 levels correlated positively with other cytokines involved in anti-helminth immunity; IL-25, IL-21, IL-5, IL-10, IL-8, and IL-31 (87). The authors hypothesized that the increased HPV prevalence among older women in STH-endemic regions, is mediated by helminth-induced immune regulation which may impair viral control, supported by a *in vivo* studies which demonstrate IL-4-mediated impairment of anti-viral immunity (52, 78, 146) (**Figure 3**). This study therefore suggests a systemic skewing of the immune response towards a type 2 phenotype detectable in the FRT impairing host ability to control HPV *via* type 1-mediated mechanisms. In contrast, murine hookworm *N. brasiliensis* antigen has been shown to inhibit HPV-16 pseudovirion uptake by human cervical cell lines. Furthermore, murine hookworm antigen exposure and *in vivo* infection decreased expression of cell surface vimentin or total vimentin expression in the cell line or the FRT, respectively (152). Cell surface vimentin has previously been described as a restriction factor that mediates internalization of HPV pseudovirion particles (153). This suggests that helminth

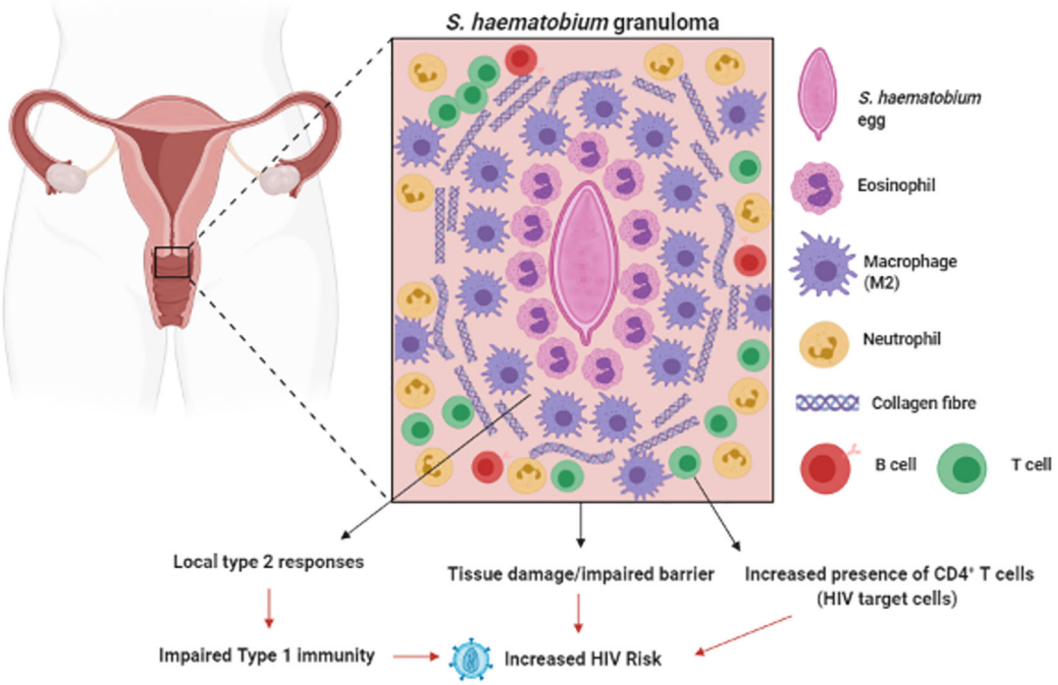

FIGURE 2 | Genital Schistosomiasis: In S. *haematobium infected* women, eggs can become lodged in the cervix, resulting in inflammation around the schistosome eggs (granula) and bystanders tissue damage. Genital schistosomiasis is common and can impair vaginal immunity and increase Human Immunodeficiency Virus (HIV) risk (129–133). Created with BioRender.com.

exposure may alter cervical epithelial susceptibility to HPV infection. Further, *N. brasiliensis* L3 somatic antigen decreased migration of cervical cancer cells in motility assays, suggesting a possible downmodulation of cancer cell metastasis by this helminth. Further studies are required to fully understand the complex consequences of helminth infection on HPV infection and pathogenesis.

HPV, Cancer, and Type 2 Immunity

Persistent HPV strains evade protective host immune responses, which are the first steps to the development of high-grade cervical lesions and cancer (154–156). Interestingly, type 1/type 2 antagonism can be manipulated by oncogenic HPV, to suppress anti-viral responses, promote persistence and tumor development (157). For example, Lepique et al. (147) described an association between M2-like macrophages and the suppression of anti-tumor responses and tumor progression during HPV-related cancer (147). Here, they identified tumor-associated macrophages (TAMs) as a dominate population in tumors, with high baseline Arginase I and IL-10 expression, and low iNOS activity, when stimulated with LPS/IFN-γ. Additionally, Petrillo et al. (148) reported a correlation between increased ratio of M2:M1 macrophages and poor responses to treatment and survival (148). Regulatory cytokines IL-10, TGF-β and prostaglandin E2 (PGE_2) produced by M2-like TAMs, promote the accumulation of regulatory T cells, which are associated with viral persistence and tumor development (158–160). Production of type 2 cytokines (e.g. IL-4, IL-13) by M2-like TAMs promotes Th2 polarization, reducing Th1 and CTL responses (149, 161–164). Moreover, Xie et al. (150) reported high levels of eosinophils in cervical cancer lesions and demonstrated that thymic stromal lymphopoietin (TSLP)-mediated eosinophil infiltration and activation promoted proliferation of cancer cells *in vitro* (150). Considering the significance of type1/type 2 imbalances during HPV persistence and related cancer progression, we hypothesize that helminth-induced type 2 immunity may impair anti-viral and anti-tumor immune responses, resulting in the promotion of tumor progression in the FRT (**Figure 3**).

Type 2 Immunity in the FRT

The role of type 2 immunity in modulating immune responses in the FRT has been demonstrated by Oh et al. (165), where induction of the type 2-associated 'alarmin' IL-33 in the genital mucosa, increased susceptibility to the HSV-2 pathology *in vivo* (165). The mediator of this effect was vaginal dysbiosis, which promoted IL-33 and impaired recruitment of memory T cells and reduced IFN-γ production in the FRT. These mice also demonstrated marked eosinophil accumulation and elevated IL-5 in the FRT (165). Furthermore, administration of recombinant IL-33 or protease-mediated induction of IL-33 in the vagina resulted in heightened susceptibility to HSV-2 (165). Oh et al. (166) elaborated on this model of IL-33-mediated type 2 immune

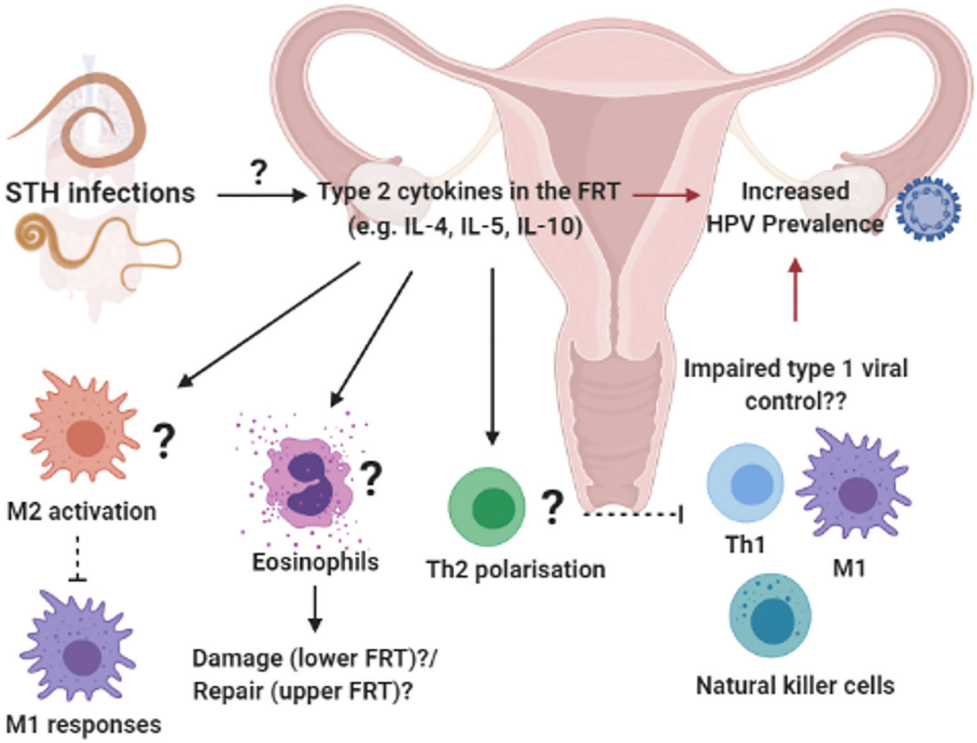

FIGURE 3 | Systemic influences of soil-transmitted helminths on uncolonized female reproductive tract (FRT): Prevalent soil-transmitted helminth (STH) infections, which transit the lung and GIT, can systemically alter host immunity in biological compartments not directly colonized by the parasite. For example, STH exposure was associated with increased HPV risk and a helminth-associated type 2 cytokine profile in vagina fluid of women in a STH endemic region (87). We hypothesize that the induction of type 2 immunity in the FRT e.g. type 2 cytokines activating M2 macrophages, eosinophils an Th2 differentiation of $CD4^+$ T cells, could impair protective type 1 immune responses and increased susceptibility to viral STIs (52, 147–151). Created with BioRender.com.

induction in the FRT, through administration of the serine protease papain. Here, papain-induced IL-33 in the vagina lead to the accumulation of vaginal eosinophils and production of canonical type 2 cytokines IL-4, IL-5, and IL-13 in genital lymph node T cells (166). Furthermore, elevated levels of type 2-associated IgE and IgG1 were detected in vaginal washes of papain-treated mice. Although elevated levels of IL-5 and eosinophils were detected in the FRT, papain induction of type 2 immunity in the FRT was not dependent on eosinophil recruitment, but rather on myeloid differentiation primary response gene 88 (MyD88) signaling and $PDL2^+CD301b^+$ dendritic cells under the control of interferon regulatory factor 4 (IRF4) (166).

Conversely, Vicetti Miguel et al. (151) demonstrated the protective role of type 2 immunity during *in vivo C. trachomatis* infection. *Chlamydia*-induced damage of the upper genital tract was prevented by IL-4 producing eosinophils, which promotes proliferation of endometrial stromal cells and tissue repair (151). Together, these studies demonstrate the significance of type 2 immunity in the FRT during STI infections and highlight potential differences in the role of type 2 responses at different sites in the FRT.

Helminths and Fecundity

The dichotomy of type 1: type 2 immune responses has been studied during the stages of pregnancy and labor, with a type 2 bias contributing to immune tolerance and a successful pregnancy (167). This would suggest that type 2-inducing helminth infections may systemically influence pregnancy in infected mothers in a positive manner. Interestingly, *in vivo* studies have demonstrated that helminth infection can result in pregnancy loss and failure of implantation of fertilized eggs (168), as well as reduced fecundity in parasitized hosts (169). Using a *Schistosoma mansoni* mouse model, Straubinger et al. (68) demonstrated that infected female mice gave birth to pups with lower birth weights during the Th2 phase of the immune response, as opposed to uninfected mice (68). In humans, Kurtis et al. (170) reported an association between maternal schistosomiasis and increased levels of inflammatory cytokines in mothers', placental and cord blood (170). As mother-to-child transmission of the schistosomes has not been reported in humans, the authors hypothesized the inflammatory response is likely due to helminth antigen movement across the placenta (170, 171). Furthermore, McDonald et al. (171) measured increased levels of pro-fibrotic proteins in the cord blood of

neonates born to *S. japonicum*-infected mothers (171). Clinical trials by Ndibazza et al. (172) and Olveda et al. (173) reported that treatment of pregnant women in endemic regions with anti-Schistosome drug praziquantel, did not significantly alter birth outcomes (172–174).

For maternal STH infections, Blackwell et al. (175) reported an association between hookworm infection and delayed age of first pregnancy and lower odds of successive pregnancies after the initial pregnancy. The converse was observed with *Ascaris* infection, which positively associated with conception at a younger age and shortened intervals of subsequent pregnancies after the first, among women younger than 32 years of age living in helminth endemic regions (175). The authors hypothesized that the opposing observations in fecundity between hookworm and *Ascaris* infections, is associated with the differing immune responses to the parasites; *A. lumbricoides* is associated with a polarized Th2 response (37) whereas hookworm infections may induce a mixed Th1/Th2 response (176). Together these studies suggest that helminth infections can have profound effects on female reproductive health, experimental investigation is required to better understanding of these effects.

CONCLUDING REMARKS

In this review, we have outlined the local and potential systemic effects of helminth infections on female reproductive health and susceptibility to STIs. Considering the great geographical overlap between STI and helminth prevalence, as well as the reduced access to health care and poor female health in helminth endemic regions, the study of helminth influences on the FRT should be a priority going forward, with focus on systemic effects of these parasites on uncolonized mucosal sites. Importantly, further comprehension on the systemic effects of GI helminths is needed, to direct health care strategies to mitigate the burden of helminth infections on the female reproductive health in those most at risk.

AUTHOR CONTRIBUTION

All authors contributed to the article and approved the submitted version.

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