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Opinion

Schistosomiasis and Infertility: What Do We Know?

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There is increasing attention on the complex interactions occurring between schistosome parasites and their hosts. However, little is known about the occurrence, epidemiology, and mechanisms of schistosomiasis-associated infertility. In this article, we argue that an in-depth understanding of the interplay between parasites and the host endocrine system may significantly enhance current knowledge of infertility in infected individuals. We discuss the basic hormonal mechanisms that may lead to the discovery of entirely novel anthelmintic interventions against schistosomiasis.

Schistosomiasis and Infertility

Infertility is defined as the incapacity to become pregnant after 12 months of regular and unprotected intercourse. This is a major public health problem that affects about one in six couples (15–20%) worldwide and 12–30% of couples in sub-Saharan Africa [1–3]. It is well recognized as a major sequela of genital tract infection; many women in Africa with this ailment (85–90%) suffer from subsequent infertility, and the cause can be attributed to pelvic infections [4]. Numerous diseases, including febrile diseases, sexually transmitted infections (STDs), and various parasitic infections, such as microfilaria and schistosomiasis, can cause infertility [5].

When considering the diagnosis of infertility there are two main features of this disease: primary infertility, considered when the woman never conceived, and secondary infertility when she had had a previous labor [5]. Most articles addressing infertility-associated schistosomiasis describe only primary infertility, and we found only two reports in the literature describing secondary infertility: one from our group [5] and one from another group [6], both reporting a lack of association between secondary infertility and schistosomiasis.

Epidemiology and Pathogenesis of Genital Manifestations of Schistosomiasis

As stated, schistosomiasis affects millions of people worldwide. About 20 million have severe disease, and the risk of infection affects 600 million others, including travelers from developed countries (Box 1) [7–9]. Both sexes can develop genital tract pathologies, but the prevalence is significantly higher in women [10,11]. The pathogenesis of this disease in the genital tract is thought to be caused by ova deposition and ensuing inflammation causing mechanical blockage, scar tissue, and destruction of anatomical structures [12,13]. Infection of the genital tract is most commonly caused by the *Schistosoma haematobium* species. The eggs are laid by adult worms residing in vasculature and they migrate to the bladder, and it is in this organ that the main pathology occurs. However, *S. haematobium* eggs can be deposited along the genitourinary tract such as the cervix and vagina in women, and testes in men, due to the proximity of the genital venous **plexus** (see Glossary), which allows easy parasitic migration. [10,14–18].

Schistosomiasis is not essentially a thromboembolic disease (i.e., defined as embolic events within the vasculature), but its eggs may lead to occlusion of the terminal veins and impairment of the blood supply [19]. It is widely described as a granulomatous disease, with eggs becoming lodged in tissue which then leads to inflammatory reactions and fibrosis. It is believed that infertility could be related to this tissue scarring, ensuing inflammation, and granulomatous reactions, due to the release of proteolytic enzymes by the ova, causing mechanical blockage, scar tissue, and destruction of anatomic structures [12,20,21]. As mentioned, women's infected ovaries can become scarred and fibrous, and Fallopian tubes may show nodular lesions. Therefore, this fibrosis of the ovaries and/or tubal occlusion, caused by granulomas, is thought to lead to infertility [22–24]. This fibrosis could be explained by the egg granuloma composition of eosinophils, mononuclear phagocytes, fibroblasts, lymphocytes, neutrophils, plasma cells, and mast cells. The systemic

Highlights

In spite of a plethora of epidemiological evidence supporting a key role for schistosome infection for infertility, little is known about the mechanisms of their association.

To date, one of the few well characterized mechanisms by which schistosomes interact with their hosts is the estrogenic imbalance and downregulation of the estrogen receptor.

Remarkably, our understanding of this mechanism has already been successfully studied in cancer-associated schistosomiasis.

The relentless advancement in molecular studies, together with the discovery of novel biomarkers, provide unprecedented opportunities to investigate schistosomiasis and exploit parasite–host relationships for the development of novel strategies of disease control.

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Box 1. Global Schistosomiasis Status

The **neglected tropical diseases** (NTDs) are a group of chronic, disabling, and disfiguring conditions that occur most commonly in the setting of extreme poverty, especially among the rural poor and some disadvantaged urban populations [52]. One of these NTDs, schistosomiasis, is sometimes referred to as bilharzias, bilharziasis, or snail fever. Schistosomiasis was discovered by Theodore Bilharz, a German surgeon, and is considered a parasitic helminthic NTD. Like many tropical diseases, it is endemic in areas where poor living conditions and poverty are prevalent. Because these parasites are water-borne species, populations that primarily rely on agriculture and fishing for their livelihood are at the highest risk of contamination [32,40,53]. Schistosomiasis remains a major public health problem. It is endemic in 75 countries, and most cases of schistosomiasis occur in Africa, making this condition one of the most common NTDs in the region [14,15,54].

The World Health Organization (WHO) estimates that schistosomiasis affects at least 220.8 million people worldwide. This disease can cause chronic anemia and inflammation associated with a severe **disability burden** among children, adolescents, and young adults and has an incidence of 200 000 deaths yearly [55,56]. Trapped ova induce a chronic granulomatous response that causes local and systemic pathological effects ranging from anemia, growth stunting, impaired cognition, and decreased physical fitness, with largely unknown effects on endocrinological hormones and their receptors, to organ-specific effects such as severe hepatosplenism and portal fibrosis with portal hypertension [16,32,56].

immune response is triggered by cercariae, adult worms, and eggs, and their antigens are transported to lymphoid organs, where they are captured, processed, and presented to antigen-specific T cells which leads to T cell activation and lymphokine secretion. Thus, systemic activation of immune responses ensues, in this way, triggering of chronic fibrosis, tubal adhesions, and possibly infertility. Anything which leads to an inflammatory response, such as an infection in the pelvis, pelvic inflammatory disease, or even a ruptured appendix, can trigger adhesion formation. Adhesions, also called scar tissue, can block or distort the Fallopian tubes [22,23,25]. This could also explain infertility associated with *Schistosoma mansoni*, which characteristically lays its eggs on the **mesenterium** plexus, and is therefore not able to cause infertility by a direct or mechanical cause. In fact, our group has demonstrated that mice infected with *S. mansoni* have impaired reproduction in terms of diminishing gestational length, number of pups, and histopathological alterations in reproductive organs [26].

In men, the symptoms include epididymitis (an inflammation of the epididymis at the back of the testicle) which can simulate tuberculosis and associated **funiculitis**, indolence, and possible formation of a **fistula**, **hematospermia**, pain during urination, prostatitis, and other effects. In men, reproduction is affected by schistosomiasis by the predisposition to secondary infection of the prostate and seminal vesicles. Sometimes it directly affects the testicles. As this is a solid organ, the trapped eggs induce a granulomatous reaction which leads to fibrosis in the case of *S. haematobium* infection [10,11] and metaplasia and necrosis in the case of *S. mansoni* infection [26].

Genital schistosomiasis is also linked to horizontal transmission of HIV and AIDS. The presence of eggs in the lower genital tract, which includes the cervix, vulva, and vagina, gives rise to a wide array of symptoms in affected women, and these lesions, if located in the vagina or vulva, might lead to hypertrophy, and can grow for months or years. Consequently, the capacity of the epithelium to act as a physical barrier to viral transmission is probably reduced, leading to the possibility of transmission and propagation of HIV. This happens because vaginal and cervical lesions tend to bleed easily, so that the HIV present in semen would have direct access to the blood circulation and, through ulcerative lesions, to the regional lymph nodes [27,28].

Hybrid schistosomes are particularly worrying. Experimental studies have revealed that interspecific hybridization might enhance infectivity and virulence. Also, hybrids can have wider host spectrums, potentially expanding their epidemiologic consequences [29]. At present, there is no report addressing hybrids associated with infertility, but given the fact that these hybrids give rise to

Glossary

Angiogenesis: the formation and development of new blood vessels.

Catechol-estrogen: a steroidal estrogen that contains catechol (1,2-dihydroxybenzene) within its structure. The catechol estrogens are endogenous metabolites of estradiol.

Disability burden: a concept to describe the impact of a condition on the affected population, that is comprised of a disability (YLD) and a mortality (YLL) component. Estimates of disability burden are used to compare and rank the impact of different conditions.

Dyspareunia: painful or difficult sexual intercourse, especially in women.

Dysuria: the experience or condition of experiencing pain while discharging urine.

Fistula: an abnormal connection or passageway between organs or vessels that normally do not connect.

Funiculitis: inflammation of a funiculus, especially of the spermatic cord.

Hematospermia: the presence of blood in the semen.

Hematuria: the presence of blood in the urine.

Mass spectrometry: an analytical technique by which chemical substances are identified by the sorting of ions in electric and magnetic fields according to their mass-to-charge ratios.

Mesenterium: a contiguous set of tissues that attaches the intestines to the posterior abdominal wall.

Metabolite: a chemical substance that is a product of metabolic action or that is involved in a metabolic process.

Neglected tropical diseases (NTDs): a diverse group of 20 communicable diseases recognized by the World Health Organization (WHO) as being underfunded relative to other conditions of equal prevalence; NTDs affect predominantly the world's poorest populations, and many have a chronic course, are physically disabling, and/or are associated with stigmatization.

Pampiniform plexus: a network of many small veins found in the human male spermatic cord.

Plexus: a branching network of the vessels or nerves.

characteristically ectopic egg locations it might increase the association of *S. mansoni* infertility both in females and males.

Mechanisms Underlying Female and Male Infertility-Associated Schistosomiasis
Female
Schistosomiasis hematobia remains a significant risk factor because several cases of infertility in schistosomiasis-endemic areas have been attributed to female genital schistosomiasis (FGS) [30,31]. FGS is defined as the existence of schistosome eggs in the female reproductive system. The eggs cause chronic inflammation in the surrounding genital tissue, comprised of granulomas, fibrosis, and **angiogenesis**. Together with this, girls and women can experience **hematuria**, **dysuria**, urinary frequency, and an increased risk of bladder cancer [12]. 'Classic' lesions of FGS, which consist of eggs and granulomas associated with increased angiogenesis and inflammation, are described as 'sandy patches'. Sandy patches usually bleed on contact and can cause genital itching and pain, stress incontinence, **dyspareunia**, and possibly infertility [14].

FGS can be associated with endometritis, and is likely to cause female infertility. Urogenital schistosomiasis, in individuals of reproductive age, remains highly prevalent and underdiagnosed [15,32]. Lesions in the upper genital tract, which includes the uterus, Fallopian tubes, and ovaries, are less discernible by routine clinical examination [27]. Fibrosis of the ovaries or tubal occlusion caused by granulomas, due to ovarian, tubal, and uterine schistosomiasis, are thought to lead to infertility (Table 1) [27,28]. *S. mansoni* is also likely to cause infertility in women, although there are very few reports in the literature. In fact there are only two reports describing an ectopic location of *S. mansoni* eggs in the endocervix [32] and in the endometrium and ovary [33], and another two reports describing hormonal imbalance in female mice infected with *S. mansoni* [34,35]. Hormonal disturbances may also explain female infertility and subfecundity associated with *S. mansoni* infection (Table 1) [2,5,26].

Male
Male infertility due to schistosomiasis hematobia, unlike female infertility, is poorly reported and can develop through different mechanisms: (i) testicular, in which there is direct damage of testicular tissue by bilharzial inflammation and granuloma formation; (ii) post-testicular, due to obstruction of excurrent genital ductal system at any region between the rete testis and ejaculatory ducts, and/or affection of the accessory sex organs (prostate, seminal vesicles) by bilharzial inflammation and granuloma formation, resulting in severe oligozoospermia (partial obstruction), azoospermia (complete obstruction), or subfertile semen parameters [36–39].

Worms can reach the veins of the spermatic cord, epididymis, and testis through several routes: (i) connection between the superior mesenteric and right spermatic veins, or along those between the inferior mesenteric and left spermatic veins; (ii) connection between the deferential vein and pelvic veins; (iii) connection between the **pampiniform plexus** in the scrotum and pelvic veins that cross near the external inguinal ring; (iv) direct spread from the epididymis to the testis (possible but remote); (v) systemic arterial spread, as observed in cases of ectopic bilharzial lesions (possible but remote) [8].

The trapped *Schistosoma* eggs, in men, lead to occlusion of the spermatic venous plexus and subsequent granuloma formation that may result in testicular infarction; these trapped eggs may also lead to intense granulomatous epididymitis and inhibition of spermatogenesis, causing male infertility [38,40]. **Seminal vesiculitis** can cause hematospermia, painful ejaculation, burning micturition, and low backache (Table 1) [38–40]. Once the disease has progressed to the granuloma stage, the damage is irreversible [38]. Comparable with female *S. mansoni* infection, there are very few documented cases of *S. mansoni* infection causing infertility in men. We found two reports describing ectopic testicular *S. mansoni* eggs [39,40] and two reports describing male sex hormone imbalance [41,42]. In male animals infected with *S. mansoni,* again, only two reports describe hormonal imbalance: the work of Lansoud-Soukate *et al.* [43] corroborated recently by our own work [35] (Table 1).

Quinones: oxidized derivatives of reactive aromatic compounds with electron-donating substituents such as catechols.
Seminal vesiculitis: an uncommon entity characterized by inflammation of the seminal vesicles. It is most commonly infective in etiology and often associated with concurrent infection elsewhere in the male genital tract.

Table 1. Effects of *Schistosomiasis* in Female and Male Reproductive Organs

	Organs affected	Effects	Study model	
			Schistosoma haematobium	*Schistosoma mansoni*
Female	Ovaries	Hypogonadism, retarded puberty Infertility (primary/secondary)	Human [5,11–13,19,27,28,42]	Mouse [26,35] Human [33]
	Tubes	Ectopic/tubal pregnancy Tubal abortion Hemoperitoneum	Human [3,11,17,19,23,24,27,28,30,31,54]	Mouse [26]
	Uterus	Anemia due to chronic blood loss Metaplasia Miscarriage, preterm delivery	Human [22,27,28]	Human [33] Mouse [34]
	Cervix	Anemia due to chronic blood loss Carcinoma Risk for sexually transmitted disease	Human [7,11,18,23,24,27,28,37]	Human [28,32]
	Vagina/vulva	Destruction of hymen and/or clitoris Vesico-vaginal fistula Risk for sexually transmitted disease	Mouse [16] Human [18,23,24,27,28,37]	
Male	Testicles	Hypogonadism, retarded puberty Infertility (primary/secondary)	Human [9,42]	Human [20,39–42] Mouse [26,35,43]
	Epididymis	Pain, funiculitis, fistulization, hemospermia, azoospermia	Human [9,38]	Human [39]
	Prostate	Pain during urination	Human [10]	

Estrogen Receptors (ERs) and Estrogen Metabolism in Schistosomiasis

Estrogens exert several biological effects in humans, such as in the cardiovascular, musculoskeletal, immune, and central nervous systems, and they play an important role in the development and maintenance of normal sexual and reproductive function [44]. Estrogen signaling is primarily mediated through ERs, which incorporate the classical receptors ERα and ERβ and the newly found membrane receptor G protein-coupled estrogen receptor 30 (GPER30) [45]. ERα is mainly expressed in the gonadal organs (uterus, ovary, prostate, testes, and breast), liver, and adipose tissue. ERβ is found mostly in the prostate, bladder, ovary, colon, adipose tissue, and immune system. These classical receptors have common physiological roles such as in the development and function of the ovaries, and estrogen-mediated cardioprotective actions [45,46].

GPER30, a member of the G-protein-coupled receptor superfamily, has been recognized as a membrane estrogen receptor which can trigger rapid estrogen nongenomic signaling independent of ERα and ERβ. GPER30 is expressed in many brain regions, including the hippocampus, cortex, hypothalamus, specific nuclei within the midbrain, and the Purkinje layer of the cerebellum, as well as the adrenal medulla, renal pelvis, and ovaries [45,47]. Many studies suggest that there are a number of pathways by which estrogens and their receptors regulate biological processes (Box 2).

While addressing schistosomiasis-induced hypogonadism in male patients infected with *S. haematobium* and *S. mansoni*, Botelho *et al.* [42] observed a noteworthy elevation in serum levels of estradiol (E2), whereas those of luteinizing hormone (LH) and follicle stimulating hormone (FSH) remained normal, and hypothesized that the excess E2 could be external to the host. In fact, we found by **mass spectrometry** that the molecule responsible for the effect was an *S. haematobium*-derived E2-like molecule that is an antagonist of E2 and thus repressed the transcriptional activity of the ER.

Box 2. Pathways by Which Estrogens and Their Receptors Regulate Biological Processes

The classical pathway includes ligand activation and direct binding to estrogen responsive elements (EREs) in target gene promoters, leading to transcriptional changes in estrogen-responsive genes. The binding of the ligand to the receptor can trigger the recruitment of a variety of coregulators which can alter chromatin structure and facilitate the recruitment of the RNA polymerase II transcriptional machinery [44,45,57,58].

However, ERs can also regulate gene expression without directly binding to DNA. This occurs through protein–protein interactions with other DNA-binding transcription factors in the nucleus. In addition, membrane-associated ERs mediate nongenomic actions of estrogens, which can lead to altered functions of proteins in the cytoplasm and also to regulation of gene expression [44,45,57,58]. The ligand-independent pathway includes activation through other signaling pathways, such as growth factor signaling. In that case, growth factors activate protein-kinase cascades, which lead to phosphorylation and activation of nuclear ERs which, in turn, causes them to dimerize, bind DNA, and regulate genes [44,45,57].

A nongenomic mechanism is characterized by rapid effects. In such type of mechanims a receptor is activated by a ligand, possibly associated with the membrane, and the complex formed is associated with the activation of various protein-kinase cascades, leading to indirect changes in gene expression which can alter functions of proteins in the cytoplasm, due to phosphorylation of transcription factors. This rapid effect can cause mobilization of intracellular calcium, generation of cAMP, production of nitric oxide, production and activation of the mitogen-activated protein kinase (MAPK) signaling pathway, activation of the phosphoinositol-3-kinase (PI3K) signaling pathway, and activation of membrane tyrosine kinase receptors [44,45,57–59].

Estrogen also interacts with GPER30, a third ER discovered more recently, and the stimulation of GPER30 activates heterotrimeric G proteins, which, in turn, can activate multiple effectors, resulting in the production of cAMP and the activation of the tyrosine protein kinase Src, and sphingosine kinase. Src, in turn, stimulates matrix metalloproteinases (MMPs) which leads to the release of heparin-binding epidermal growth-factor-like growth factor (HB-EGF) that can transactivate EGF receptors (EGFRs). The activation of MAP kinases and PI3K, results in the activation of EGFR and leads to the expression of transcription factors [47,60]. When classic ERs are absent, or blocked, the effects mediated by GPER30 are maintained [2,61].

Outstanding Questions

How extensively do the effects of schistosomiasis cause infertility in their hosts?

What are the complete mechanisms by which infertility is a sequela of schistosomiasis? Is this mechanism different between *S. haematobium* and *S. mansoni* infections? How does this differ across male and female hosts?

Are estrogen metabolites important for infertility-associated schistosomiasis?

Can knowledge of cancer-associated schistosomiasis, particularly estrogen metabolites, provide tools for disease control?

Moreover, new estrogenic molecules were identified in *S. haematobium* total antigen as well as in the serum of infected individuals with this parasitic disease that seem to be produced by this parasite [48]. ER transcriptional activity was suppressed in urothelial cells, and ER expression was also suppressed in the bladders of mice in response to *S. haematobium* [49].

Schistosome eggs produce a **metabolite** derived from estrogen called **catechol-estrogen**. Cytochrome P450 oxygenases metabolize these estrogenic molecules to active **quinones**, that include the formation of the catechol estrogen-3,4-quinone, the major mutagenic derivative of estrogen, that causes alterations in DNA [5,50,51]. This ability to cause alterations in DNA is a strong inducer of carcinogenesis; in addition we [52] and others [53] demonstrated that these molecules are associated with schistosomiasis-associated bladder cancer as well as thyroid and breast cancer.

In further recent studies, the presence of estrogen-like metabolites during FGS was also associated with self-reported infertility [5]. These metabolites downregulate ERα and ERβ in estrogen-responsive cells *in vitro* because they can react with DNA to form depurinating adducts, which may generate DNA apurinic sites that, in turn, initiate mutations [49]. Our group demonstrated that the eggs of *S. haematobium* secrete these novel catechol estrogens, and that estrogens are metabolized to active quinones that modify DNA. Therefore, it is believed that the presence of parasite-derived catechol-estrogens may influence infertility during infection with *Schistosoma* through the blockage of estrogen receptors acting as endocrine disruptors [5,50,51]. More recently, in order to better understand this hormonal imbalance, our group investigated a serum panel of steroid hormones in *Schistosoma mansoni*-infected female and male hamsters [35]. Surprisingly, we found a decrease in the serum levels of E2 in infected females but not in infected

males (as expected from previous results in men), in comparison with controls. These new results shed light on our understanding of the hormonal mechanism involved in schistosomiasis-associated infertility: E2 is augmented in males, explaining hypogonadism and consequent infertility, but in females E2 is below normal levels amplifying infertility observed in infected females.

Concluding Remarks

In spite of substantial evidence that points towards a key role of schistosomiasis in infertility of infected hosts, current knowledge of the fundamental mechanisms by which this phenomenon happens is scarce and fragmented. Nonetheless, the relentless progress in investigating ERs and estrogen metabolism, and their role in bioprocesses (Box 2), provides us with unprecedented opportunities to thoroughly characterize the functions of such ERs in schistosomiasis. At the core lie questions surrounding modes of action of schistosomiasis (*haematobium* and *mansoni*) causing infertility in their hosts, the complete mechanisms by which infertility is a sequela of schistosomiasis, how this sequela affects female and male hosts, the functions that schistosome estrogen catechols play in the host endocrine system, and the effects that disrupting estrogen metabolites may exert on the host, causing cancer and infertility (see Outstanding Questions). In turn, the new knowledge can be expected to provide us with a plethora of opportunities to exploit parasite–host associations to our advantage, for example, by applying cutting-edge novel ER modulators as innovative intervention strategies against schistosomes and the diseases that they cause. Two different complementary pathways probably contribute to estrogen imbalance leading to (i) infertility, and (ii) initiation and promotion of cancer progression. Future studies are necessary to study ERs in the genital organs of animals infected with *Schistosoma*. This should be done to determine, compared with *S. haematobium*, if *S. mansoni* also includes estrogen-related metabolites that can downregulate ERα and ERβ, as well as the more recent estrogen receptor GPER30. Including informative estrogen-responsive cells should allow us to understand the impact of schistosomiasis on fertility.

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