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Female Genital Schistosomiasis (FGS) in a Nonendemic Setting: Retrospective Case-Notes Review of *Schistosoma haematobium*–Positive FGS Cases at the Hospital for Tropical Diseases, London, With a Pragmatic Clinical Pathway for Nonendemic Settings

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Background. Female genital schistosomiasis (FGS), the genital manifestation of *S. haematobium* infection in women, results in protean gynecological symptoms and longer-term complications. FGS affects an estimated 75% of women with *S. haematobium*, totaling 56 million women, mainly in Sub-Saharan Africa. With increasing migration, FGS will be encountered more frequently in nonendemic settings. Despite this, evaluation of FGS diagnosis and management and guidelines for these settings are lacking.

Methods. A retrospective case-notes review was undertaken of patients presenting to the Hospital for Tropical Diseases, London, from 1998 to 2018 with *S. haematobium* ova in terminal urine or on biopsy. Descriptive and outcome variables were collected. Specific FGS variables included documented gynecological symptoms and referrals to sexual health and gynecology specialists. Results informed a clinical pathway aiding diagnosis and management of FGS.

Results. Overall, 186 patients with *S. haematobium* ova in terminal urine or biopsy were included, 62 (33.3%) of whom were women. Four women had documented gynecological symptoms (4/62, 6.5%). Two symptomatic women were referred to gynecology (2/4, 50%), and 2 were lost to follow-up (2/4, 50%). Gynecological symptoms were not documented for many women, despite proven *S. haematobium* infection.

Conclusions. Given that 75% of women with *S. haematobium* infection may have FGS, there is a gap in diagnosis in this nonendemic setting. We developed a clinical pathway to improve diagnosis and management of FGS, including inquiry about gynecological symptoms, followed by targeted referrals to gynecology, sexual health, and urological imaging. By formalizing a pathway, we aim to improve FGS care in this nonendemic setting.

Keywords. clinical pathway; female genital schistosomiasis; nonendemic; imported infection; *Schistosoma haematobium*.

Female genital schistosomiasis (FGS) is a gynecological disease, mainly caused by infection with *Schistosoma haematobium* flukes [1]. *S. haematobium* pairs reside in the urogenital plexus, which drains both the bladder and the genital organs, so eggs produced here can migrate through both urological and genital tissue, causing inflammation and disease. The resulting genital inflammation can cause symptoms that mimic sexually transmitted infections with bleeding, pain, itching, and localized lesions reported [2, 3]. In addition, FGS has been linked to long-term sequelae, including obstetric complications and subfertility [2–6], increased risk of HIV acquisition [7], and possibly cervical dysplasia, although further evidence is required [8, 9]. Up to 75% of women with schistosomiasis may have FGS [10], equating to ~56 million women, mainly in Sub-Saharan Africa, but despite this vast number and increasing list of associated complications, FGS remains neglected, with ongoing research and guideline gaps [1, 11].

FGS has been reported in nonendemic settings in both migrants and travelers [5, 12–14]. A prospective cross-sectional study in Barcelona of female migrants from *Schistosoma*-endemic regions

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found a *Schistosoma* seroprevalence of 58.8%. Over 96% of seropositive women reported gynecological symptoms, compared with two-thirds of seronegative women, a highly significant difference [13]. A second cross-sectional study of migrants in Spain found that migrant women with positive *Schistosoma* serology or urine microscopy were more likely to report various specific genital symptoms compared with those who had negative *Schistosoma* diagnostics [14].

Given increasing migration from schistosomiasis-endemic regions, cases of imported FGS are likely to rise. However, there remains a lack of knowledge and guidelines for the investigation, diagnosis, and follow-up of FGS patients. A recent study assessed clinician knowledge of FGS across Europe and found that 56.3% of 581 doctors and 88% of 341 nurses surveyed were not aware of FGS, with higher numbers reporting no or very little knowledge about FGS, highlighting the need for education and clear guidelines [15]. The World Health Organization (WHO) FGS Atlas is the mainstay guideline for endemic settings, suggesting diagnosis of women at risk using colposcopy to assess for characteristic signs including rubbery papules, homogeneous and grainy sandy patches, and abnormal blood vessels [16]. A single dose of praziquantel 40 mg/kg is the suggested treatment. Until 2023, there were no available guidelines for nonendemic settings. In 2023, Italian consensus guidelines were published for the screening, diagnosis, and management of schistosomiasis [17]. This includes recommendations for FGS; specifically, colposcopy is recommended for women with suspected FGS. Here we present a retrospective case-notes review of *S. haematobium*–confirmed cases of FGS at the Hospital for Tropical Disease (HTD) in London from 1998 to 2018, with a pragmatic investigation, diagnosis, and follow-up pathway for management of FGS in nonendemic settings.

METHODS

As described in a contemporaneous manuscript [18], a retrospective case-notes review was performed of all patients with confirmed *S. haematobium* infection presenting to the Hospital for Tropical Diseases, London, from February 1998 to August 2018. Confirmed *S. haematobium* infection was defined as terminal urine containing viable or nonviable ova or *S. haematobium* ova seen in histopathological examination of biopsy samples.

Paper and electronic notes were reviewed, and variables were collected for each patient. These included multiple demographic, clinical, and outcome measures as described in a contemporaneous manuscript [18]. FGS-specific variables included any reported gynecological symptoms, along with referral to gynecology or sexual health specialties. Subfertility was included as a gynecological symptom and defined as failure to achieve conception after 12 months of unprotected vaginal sexual intercourse, as per the Royal College of Obstetricians and Gynaecologists definition. As a clinical audit, formal consent was not required from patients. If any egregious errors were found on retrospective reviewing of the clinical notes, patients could be recalled to the clinic if required.

Analysis was performed using STATA, version 13, and Microsoft Excel.

Table 1. Demographic Characteristics of Women With Confirmed *Schistosoma haematobium* Infection Between 1998 and 2018 at the Hospital for Tropical Diseases, London, Including Women With Reported Gynecological Symptoms

	All Women (n = 62)	Women With Gynecological Symptoms (n = 4)
Median age (IQR), y	24 (22–28)	26 (25–27)
Reason for travel, No. (%)		
Tourism	39 (62.9)	2 (50.0)
Visiting friends and relatives	2 (3.2)	0 (0.0)
Business	12 (19.4)	1 (25.0)
Migrant	9 (14.5)	1 (25.0)
Duration of time spent in endemic country, No. (%)		
<6 mo	26 (41.9[a])	2 (50.0)
6–12 mo	19 (30.6[a])	1 (25.0)
>12 mo	16 (25.8[a])	1 (25.0)
Symptoms, No. (%)		
Asymptomatic	16 (25.8)	0 (0.0)
Hematuria	27 (43.5)	3 (75.0)
Lethargy	16 (25.8)	1 (25.0)
Abdominal pain	12 (19.4)	2 (50.0)
Diarrhea	6 (9.7)	1 (25.0)
Fevers	4 (6.5)	1 (25.0)
Gynecological symptoms[b]	4 (6.5)	4 (100)
Median duration of symptoms before presentation, mo	5*	6**

[a]n = 61, excluding missing data for 1 woman, *excluding asymptomatic and missing data n = 59, **n = 3.

[b]Symptoms included subfertility (n = 1), postcoital bleeding (n = 1), pelvic pain (n = 1), genital lesions (n = 1).

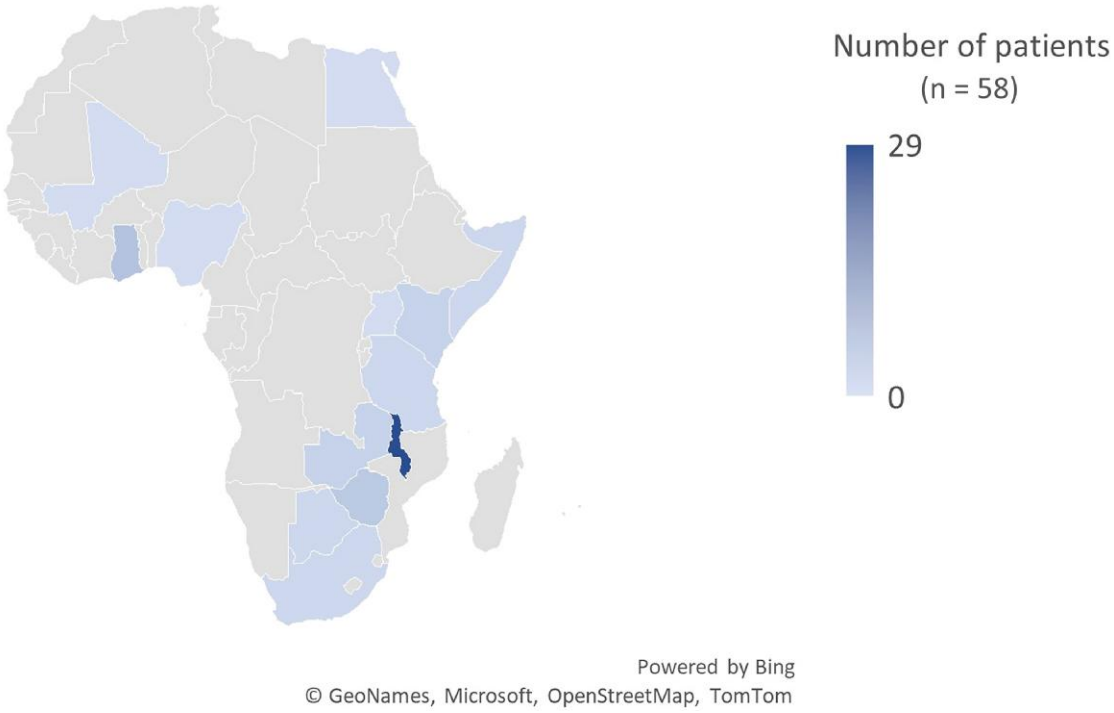

Figure 1. Map showing schistosomiasis-endemic countries that women with confirmed *Schistosoma haematobium* infection presenting to the Hospital for Tropical Diseases had visited.

RESULTS

Overall, 182 patients with *S. haematobium* ova in terminal urine or on biopsy were included in the retrospective case-notes analysis. Of these patients, 33.3% (62/182) were women. The median age of the women (interquartile range [IQR]) was 24 (22–28) years. Two women were known to be pregnant (2/62, 3.23%). The majority of women were tourists (39/62, 62.9%), rather than migrants (9/62, 14.5%), traveling for business (12/62, 19.4%), or visiting friends or relatives (2/62, 3.2%) (Table 1). More women had spent ≤6 months in an endemic area (26/62, 41.9%), compared with 6–12 months (19/62, 30.6%) or >12 months (16/62, 25.8). Of those recorded, Malawi was the most common country visited (29/58, 50%); all countries can be seen on the map in Figure 1.

All bar 1 woman had *S. haematobium* ova detected in terminal urine at presentation (61/62, 98.4%). The woman without ova in terminal urine at presentation was subsequently found to have ova in terminal urine at follow-up. Nine women also had *S. haematobium* ova seen on histopathology (9/62, 14.5%): 7 from bladder biopsies, 2 from rectal biopsies, none from the genital tract.

Over a quarter of women were asymptomatic (16/62, 25.8%) (Table 1). The most common symptom was hematuria, reported by 43.5% of women (27/62), followed by lethargy (16/62, 25.8%) and abdominal pain (12/62, 19.4%). The median duration of symptoms before presentation (IQR) was 5 (3–9.5) months.

Very few of the clinical notes included any details about the presence or absence of gynecological symptoms. Four of the 62 women included had documented gynecological symptoms (4/62, 6.5%), all of which were reported to have started after potential schistosome exposure. Gynecological symptoms reported included postcoital bleeding, pelvic pain, subfertility, and genital lesions. The median age of women with gynecological symptoms (IQR) was 26 (25–27) years. Two women were tourists (2/4, 50%), 1 traveled for business (1/4, 25%), and 1 was a migrant (1/4, 25%) (Table 1). Three of the women with gynecological symptoms also reported hematuria (3/4, 75%), and 2 reported abdominal pain (2/4, 50%). Gynecological symptoms had been present for a median time (IQR) of 6 (5–11.5) months before presentation. Two of these 4 women were referred for specialist gynecological review (2/4, 50%); however, only 1 was seen by the gynecology team. None of the women were referred to a sexual health clinic, although 1 woman had previously attended a clinic and had a negative sexual health screen. Two of the 4 women with gynecological symptoms were lost to follow-up (2/4, 50%).

DISCUSSION

Overall, 62 women with *S. haematobium* ova in their terminal urine and/or on biopsy were seen at HTD over a 21-year period between 1998 and 2018. Only 4 of the 62 women included had

recorded gynecological symptoms (6.5%). Given that up to 75% of women with an *S. haematobium* infection may have FGS, there is likely a gap in diagnosis [10]. This gap in diagnosis could be explained in several ways and likely is due to a combination of factors. First, this study only included women who had *S. haematobium* ova seen in terminal urine or in bladder or rectal biopsy samples; women with positive *Schistosoma* serology and no ova detected were excluded from this study. It has been found that up to 60% of women with FGS do not excrete ova in the urine [19], so we are likely excluding many women with FGS who do not excrete ova. In addition, others may excrete ova only intermittently, which could have been missed if only 1 sample was taken at 1 time point. Second, the population of women included in this study were most commonly tourists whose exposure in an endemic country was frequently <6 months. Therefore, these women may have had lower burdens of infection and been at lower risk of FGS complications. The final explanation is that gynecological complications were not identified, or if identified not documented during the consultation. Women may not report gynecological symptoms during an infection consultation for many reasons, including due to stigma, or they may not realize the symptoms are pertinent to the consultation. Clinicians who are not working within gynecology or sexual health often do not ask about reproductive tract health. This is compounded by a lack of teaching about FGS as a disease entity for many clinicians. Indeed, in a recent publication investigating FGS symptoms in Sub-Saharan African migrants in Spain, significantly more genital symptoms were reported using a direct questionnaire compared with during a routine clinical review [14]. It would therefore be important for the clinician to enquire specifically about symptoms that may be related to FGS. FGS only became a recognized disease entity in the mid-1990s and has been increasingly recognized over the past 10 years. The WHO atlas of FGS was published only in 2015, near the end of this case-notes review [16]. In accordance with this, it was found in this study that the presence or absence of gynecological symptoms was rarely recorded in clinical notes, suggesting that clinicians were not specifically enquiring. We also found that if gynecological symptoms were reported, women were not reliably referred for an opinion from gynecology or sexual health specialists. We also demonstrated a 50% loss to follow-up rate for the women with gynecological symptoms. This was based on a low number of women and may not have been replicated in a larger group but nonetheless highlights an important challenge to be addressed. Given the variability in practice observed, we felt that a clinical pathway for the diagnosis, investigation, and management of FGS would be an important step to improve the care of women returning from endemic areas.

There were several considerations while creating an FGS pathway. First and foremost, we wanted to ensure that clinicians specifically ask women with schistosomiasis about gynecological symptoms. Without this intervention, further women with FGS are likely to go unrecognized. We then wanted to create a clear referral framework to ensure that women were investigated for FGS, along with other important differential diagnoses. This would include a referral to gynecology for colposcopy for the diagnosis of FGS, as per the WHO Atlas [16] and the Italian consensus guidelines [17], along with investigation of other gynecological differential diagnoses. Women would also require referrals to sexual health services, given that sexually transmitted infections are one of the main differential diagnoses, and referral for urological ultrasound so as not to neglect the urological aspects of this urogenital disease. The clinical pathway therefore involves multispecialty collaboration and consensus. Finally, we wanted to ensure consistent follow-up for women diagnosed with FGS to ensure that they have been adequately treated and that referrals have been followed up. Given the high loss to follow-up rate of women with gynecological symptoms identified in this case-notes review, we needed to balance need for multiple specialty reviews with need to streamline the pathway and minimize the number of appointments to attend.

The pathway we have developed can be seen in full in Figure 2. Patients are referred to HTD via their general practitioner, urologist, or through self-referral if they have traveled abroad in the past 12 months. We are also encouraging referrals from sexual health and gynecology specialists for women presenting with symptoms compatible with FGS who have traveled to an endemic area. All women who have traveled to an endemic area will have the available *Schistosoma* diagnostics: *Schistosoma* serology, terminal urine for ova, and stool for ova, cysts, and parasites. We suggest completing these investigations at least 3 months after return from an endemic area to ensure that any schistosomes present have developed into adults and are producing eggs, avoiding the likelihood of false-negative results. We advocate that all women with any positive *Schistosoma* diagnostic be treated and then specifically asked about a list of gynecological symptoms. If the woman has any of these symptoms, they enter the pathway and are referred to the sexual health clinic for a full sexual health screen, gynecology for colposcopy for the diagnosis of FGS and investigation of other differentials, and referral for ultrasound imaging of the urinary tract. Following these referrals, we suggest that women be followed up at 3 months for repeat terminal urine microscopy if previously positive, as well as a review of symptoms. Further follow-up may then be required, depending on outcomes of investigations and referrals. For diagnosed FGS, follow-up will likely depend on the degree of symptoms and extent of lesions seen during colposcopy. Although there is evidence that FGS symptoms may improve following treatment, the FGS lesions are not thought to resolve [20–22]. This is an important consideration during ongoing follow-up, and women should be made aware. Women should also be asked if they

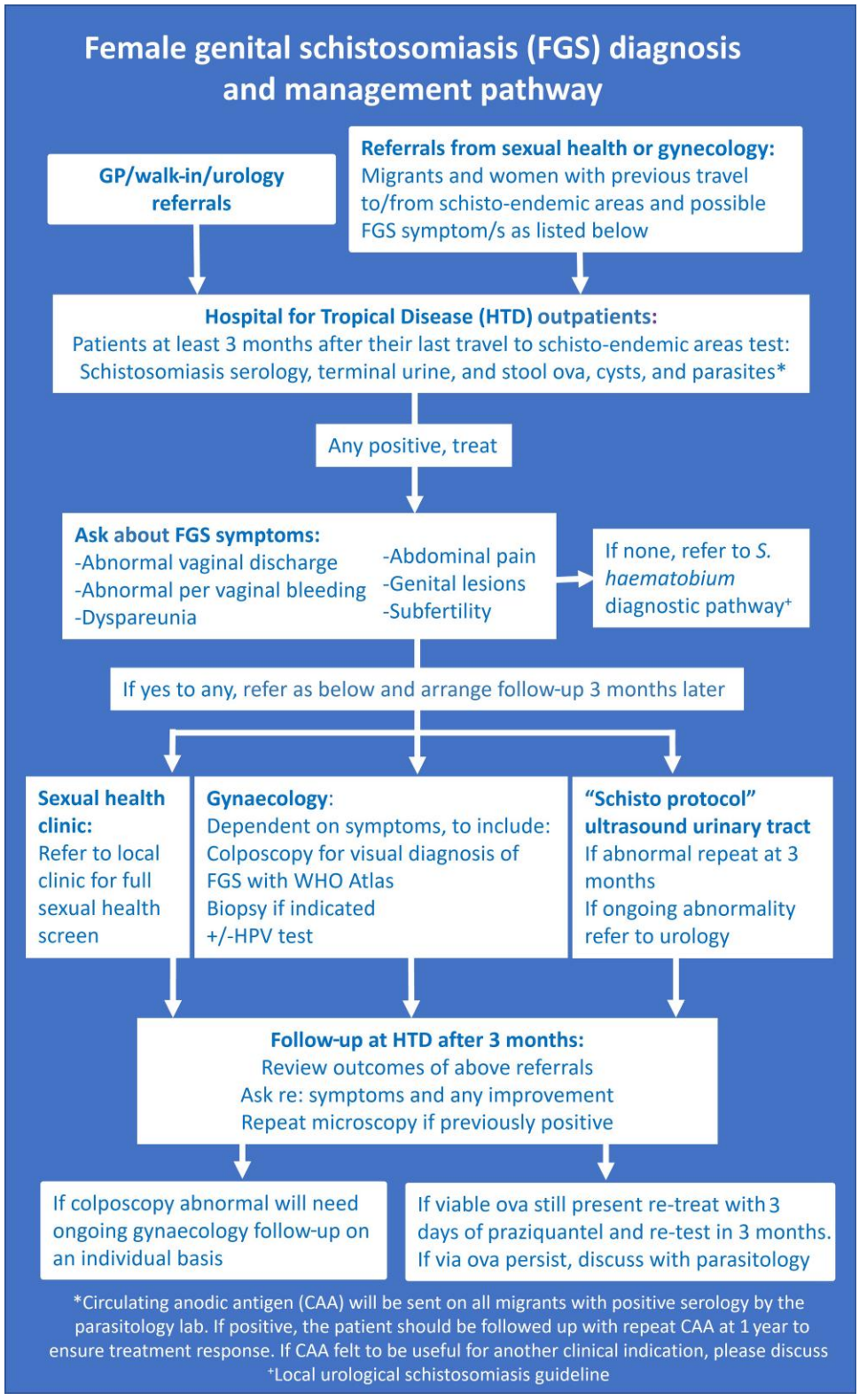

Figure 2. Pragmatic investigation, diagnosis, and follow-up pathway for female genital schistosomiasis in nonendemic settings.

traveled with anyone else to the schistosomiasis-endemic area. Individuals who came into contact with the same water sources should also be screened for schistosomiasis, if women follow our outlined FGS pathway.

Further work will involve assessment of the pathway's performance. To this end, we have developed a prospective database of all FGS cases at HTD, so we can monitor pathway use in real time. We will also be asking for feedback from all included specialties to identify any issues. We then hope to collaborate with other centers to adapt this pathway to facilitate the investigation, diagnosis, and management of women with FGS on a wider scale and further efforts to improve care for women with this traditionally neglected disease.

CONCLUSIONS

Over a 21-year period at the Hospital for Tropical Diseases, London, only a small percentage of women with confirmed *S. haematobium* infection had recorded gynecological symptoms. This suggests that there may be a gap in diagnosis of FGS in this nonendemic setting. To address this, we have created a pragmatic pathway to ensure that all women with a positive investigation for schistosomiasis are being specifically asked about gynecological symptoms. For all symptomatic women, we recommend treatment, then referral to sexual health, gynecology, and for urological imaging to investigate differentials and diagnose FGS by colposcopy. We hope this will improve the clinical management of FGS in this setting and encourage other centers to consider similar guidelines to improve the care for women with FGS.

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