Female genital schistosomiasis – Understanding the correlation between clinical and histopathological findings

Student thesis

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ABSTRACT

Schistosomiasis is a tropical disease caused by an intravascular parasitic worm of the *Schistosoma (S.)* family. More than 200 million people are infected, most of them live on the African continent. The human disease relates to tissue reactions in the locations where worms lay their ova. Various *Schistosoma* species have preferred anatomical locations for egg deposition. *S. haematobium* typically settles in pelvic vessels and is clinically most known for egg related lesions in the urinary bladder mucosa. This leads to ulcerations and bleeding, presented as hematuria. Similar egg related lesions can however be seen in other epithelial locations such as the mucosa of the female genital tract, referred to as female genital schistosomiasis (FGS). In recent years, FGS has received more attention due to an association with increased risk of HIV transmission.

Our thesis consists of two parts. The first part relates to a non-systematic search in schistosomiasis literature with focus on FGS. The second part relates to data from fieldwork in a shisto-endemic area in KwaZulu Natal in South Africa. We participated in preparatory work for a hospital-based study on colposcopic and histopathologic correlations in the various FGS lesions.

Better understanding of the correlation between an observed FGS mucosal lesion and the tissue reaction is important in the diagnostics, risk assessment and treatment strategies. A more fact based clinical assessment of FGS lesions is especially important, as African guidelines warn taking biopsies from the cervix and vagina due to increased risk of HIV transmission in biopsy relate ulcers.

ACKNOWLEDGEMENT

We would like to acknowledge our supervisors Dr. Kjetland and Prof. Roald, both heavily engaged and involved in projects regarding FGS. Kjetland has been involved in various projects in sub Saharan Africa related to *Schistosoma* lesions in the female genital tract since 1993. Roald have done histopathology and immunohistochemistry research on biopsy material from Kjetland´s studies. Their support, guidance and expertise are sincerely appreciated.

We are grateful to Dr. Sigve Holmen for his kindness, letting us follow and observe the clinical work at the rural St. Andrews Hospital in KwaZulu-Natal.

Finally, thanks to Lions Club Ekeberg for partly funding our fieldwork.

Abbreviation	
FGS	Female genital schistosomiasis
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
NTD	Neglected tropical disease
STI	Sexual transmitted infection
WHO	World Health Organization

INTRODUCTION

Schistosomiasis, also called Bilharzia, is a parasitic disease caused by *Schistosoma* worms (1). It is classified by the World Health Organization (WHO) as a neglected tropical disease (NTD); a group of protozoan, helminthic and bacterial diseases. NTDs are almost invariably found in poor rural areas in the third world (2, 3), and the diseases have been largely ignored for many years. Only recently, NTDs have got attention from the world and the pharmaceutical companies (4).

Already in 1899, Dr. F. Cole Madden described a case of schistosomiasis in the vagina of a young Egyptian woman (5). Despite this early publication, focus on clinical symptoms and findings of disease in female genital tract generally has been lacking, both publicly and professionally. *Schistosoma* infection in the female genital tract, now usually is referred to as female genital schistosomiasis (FGS). Recently the interest of FGS has increased, especially as an epidemiological overlap (6), and a possible correlation seems to exist between FGS and added risk of HIV infection in women (7-10).

Many studies have documented the clinical findings of FGS and the underlying tissue reaction (11-15). The understanding of the exact correlation between these is however insufficient (11, 16). To increase this knowledge, a hospital based research project is planned: *"Management of Female Gynaecological Bilharzia through better understanding A hospital based study in schistosomiasis endemic KwaZulu-Natal exploring the correlations between optical diagnostic*

tools and histopathology." During our stay in South Africa in January 2016, we did a fieldwork contributing in the preparatory work for this study.

PART 1: LITERATURE SEARCH ON SCHISTOSOMIASIS AND FGS

METHODS

In a non-systematic search in the electronic databases PubMed, UpToDate and Helsebiblioteket.no we used various terms including 'schistosomiasis', '*Schistosoma* lifecycle' 'scistosomiasis AND histopathology', 'female genital schistosomiasis', 'female genital schistomiasis AND symptoms', 'female genital schistomiasis AND treatment', 'female genital schistomiasis AND diagnostics', 'HIV AND *Schistosoma* hematobium' and 'female genital schistomiasis AND urinary schistosomiasis'. We collected relevant information on schistosomiasis and FGS, with special focus on the lifecycle of *Schistosoma* species, the tissue reaction in infected humans and what is known about the correlation between the clinical/colposcopic and histopathological findings in FGS.

HUMAN SCHISTOSOMIASIS

Different types of *Schistosoma*

Five main *Schistosoma* species that infects humans have been reported: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma mekongi, Schistosoma guineesis* and *Schistosoma haematobium*. The species all have a specific snail as their intermediate host. The geographical distribution of *Schistosomas* is thus depending on the habitat of the relevant snail. Table 1 shows an overview of the

various *Schistosoma* species, their preferred anatomic sites and geographical distribution.

	Species	Geographical distribution
Intestinal schistosomiasis	*Schistosoma mansoni*	Africa, the Middle East, the Caribbean, Brazil, Venezuela, Suriname
	Schistosoma japonicum	China, Indonesia, the Philippines
	Schistosoma mekongi	Several districts of Cambodia and the Lao People's Democratic Republic
	Schistosoma guineensis and related *S. intercalatum*	Rain forest areas of central Africa
Urogenital schistosomiasis	*Schistosoma haematobium*	Africa, the Middle East

Table 1. Anatomic site of the different species, and their geographical distribution. http://www.who.int/schistosomiasis/epidemiology/table3/en/

Nomenclature

S. haematobium was previously associated with pathology and symptoms in the urinary bladder, and named urinary schistosomiasis. It is now well acknowledged that *S. haematobium* also can induce its lesions in the female and male genital tract. Recently, WHO recommended that *S. haematobium* lesions should be referred to as urogenital schistosomiasis (17).

Schistosoma lifecycle

Fresh water contact is required for transmission of schistosomiasis. *Schistosoma* ova are released into fresh water from urine and/or feces from infected human as shown in Figure 1. In water, the ova hatch and release miracidia, small amoeboidic bodies. They infect their specific freshwater snails, their necessary intermediate hosts (1, 2). Within the snail, the miracida will in 4-6 weeks

multiply and develop into sporocytic stages, resulting in thousands of small worms called cercariae (1).

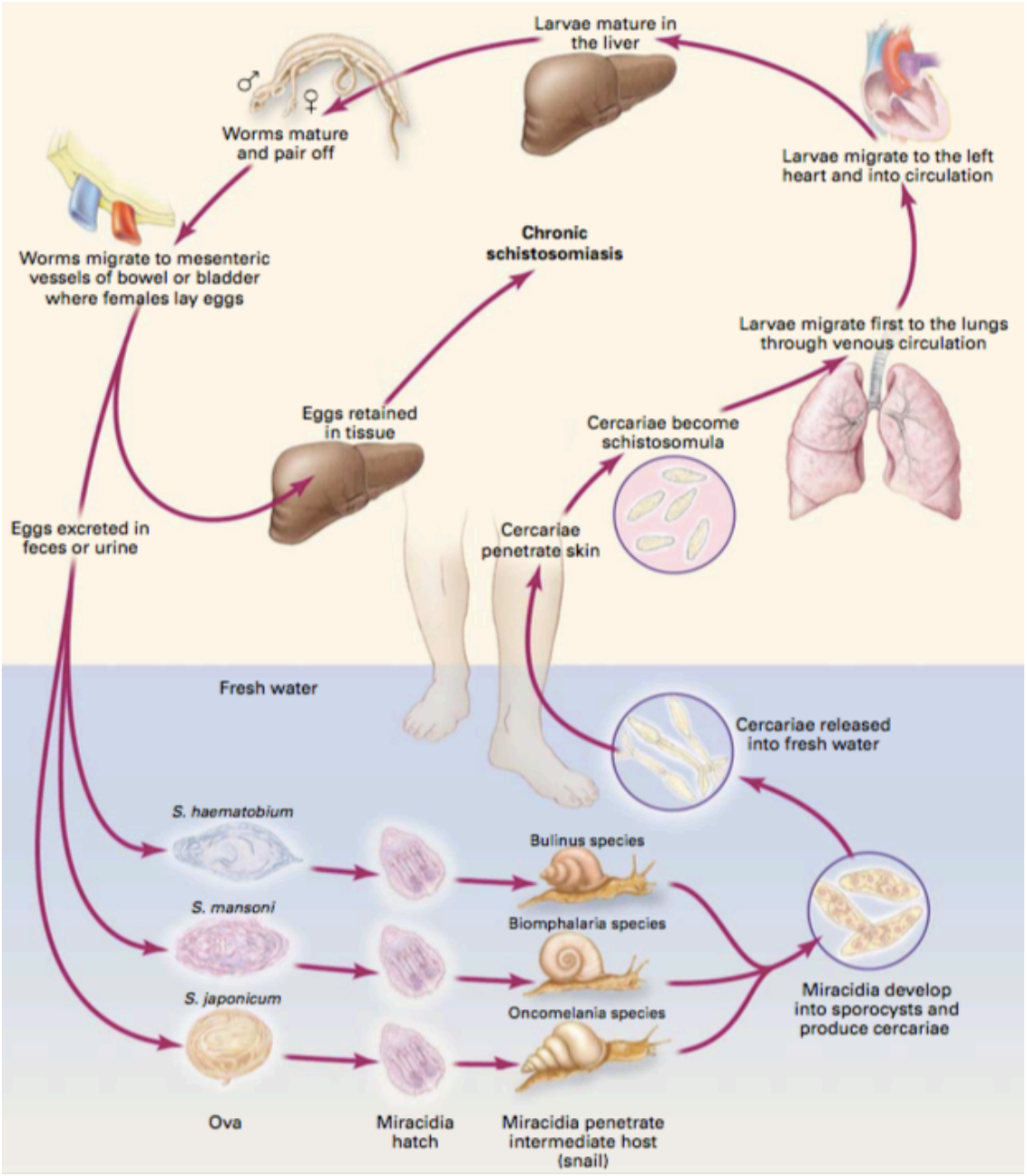

Figure 1. *Schistosoma* lifecycle. From: Ross et al. 2002 Schistosomiasis. New England Journal of medicine.

The cercariae are released in hundreds into the water, and are the *Schistosoma* parasitic form that can infect human (1). The cercariae penetrate the skin of the

mammalian host, loose their tail and transform into a schistosomula (18). The schistosomula forces its way into the vascular system and the follow the blood flow trough the lungs, heart and end up in the liver and the portal vein (1). Within the portal vein the schistosomulae mature into adult males and females, who then find their mate (2). The couple moves against the bloodstream and will lodge underneath any epithelial surface, where they lay their ova in submucosa (personal communication with Prof. Borghild Roald) (Figure 2).

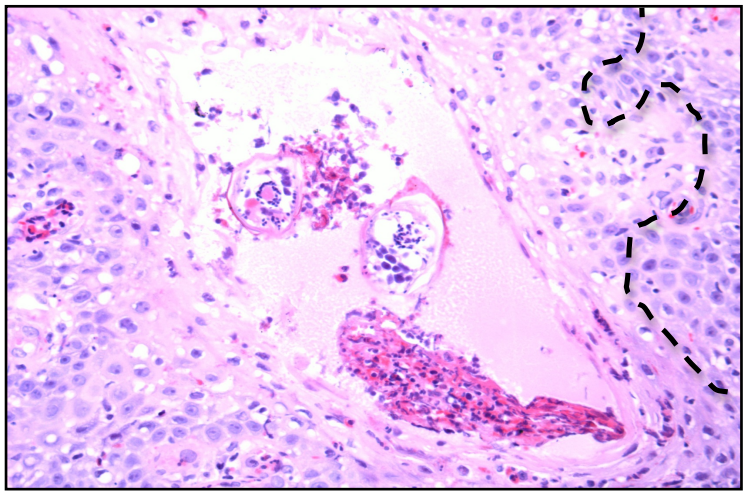

Figure 2. Viable ova inside a dilated submucosal vessel. The dotted line indicates the basal layer of the vaginal surface epithelium. The vessel also contains part of a thrombus. HE stained section objective. Picture published in Jourdan 2013, International journal of gynecological pathology

The various *Schistosoma* species have predilection sites in the human body. *S. mansoni* usually go to the mesenteric plexus, while S. *haematobium* mostly enters the pelvic plexus (1, 2). The ova contain enzymes, enabling them to penetrate the vessel wall and move through the stroma of the submucosa (1). Some ova will also move trough the epithelial surface (Figure 3).

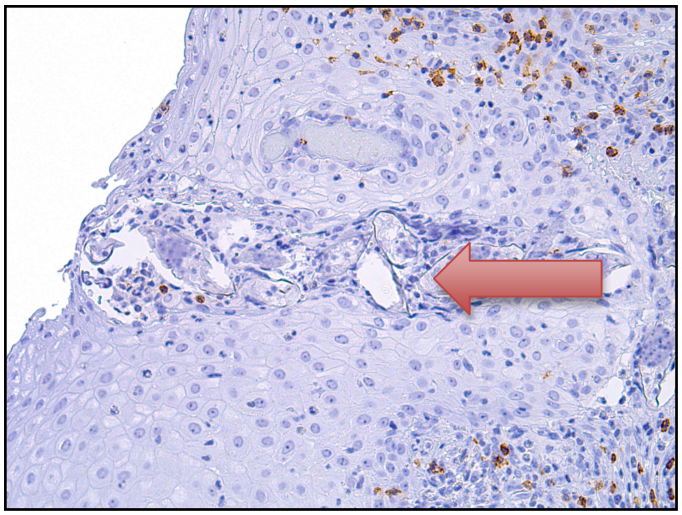

Figure 3. Large numbers of *Schistosoma* ova migrate through the vaginal squamous epithelium. A similar picture can be seen in the urinary mucosa, resulting in ova excreted in the urine. (Courtesy of Prof. Borghild Roald and Peter Jourdan)

The ova are then excreted in urine or stool (18). If these are passed into fresh water containing the right intermediate host snail, the cycle may start all over again (Figure 1). Adult *Schistosomes* will live in human body for three to four years in average. It is however reported that some may exist for up to 30 years, and can thus in their lifetime release thousands of ova (1, 2, 19).

Prevalence and risk factors

In terms of global public health impact, malaria is the most important parasitic disease followed by schistosomiasis. An estimated that over 800 million people are at risk of schistosomiasis, and more than 200 million are infected (20, 21). The disease is found in 149 countries, in tropical and subtropical areas. Approximately 93 % of the infected individuals live in the Sub-Saharan African countries (2, 22). The high prevalence in these countries is due to several factors. Many areas here are poor, with lack of access to clean and safe water. To meet some this problem, water reservoirs such as dams and irrigation systems have been established (21). In the same process the intermediate hosts of *Schistosoma* worms in the same process have expanded their habitats, thus making the

populations even more exposed to *Schistosoma*-contaminated water (21). People do their laundry in the rivers and the dams, children swim and play in the water. The agriculture is important to meet the demand for food. Poor sanitation often results in contamination by urine and feces into the rivers and lakes (23-25). As a result the transmission rate has increased (21).

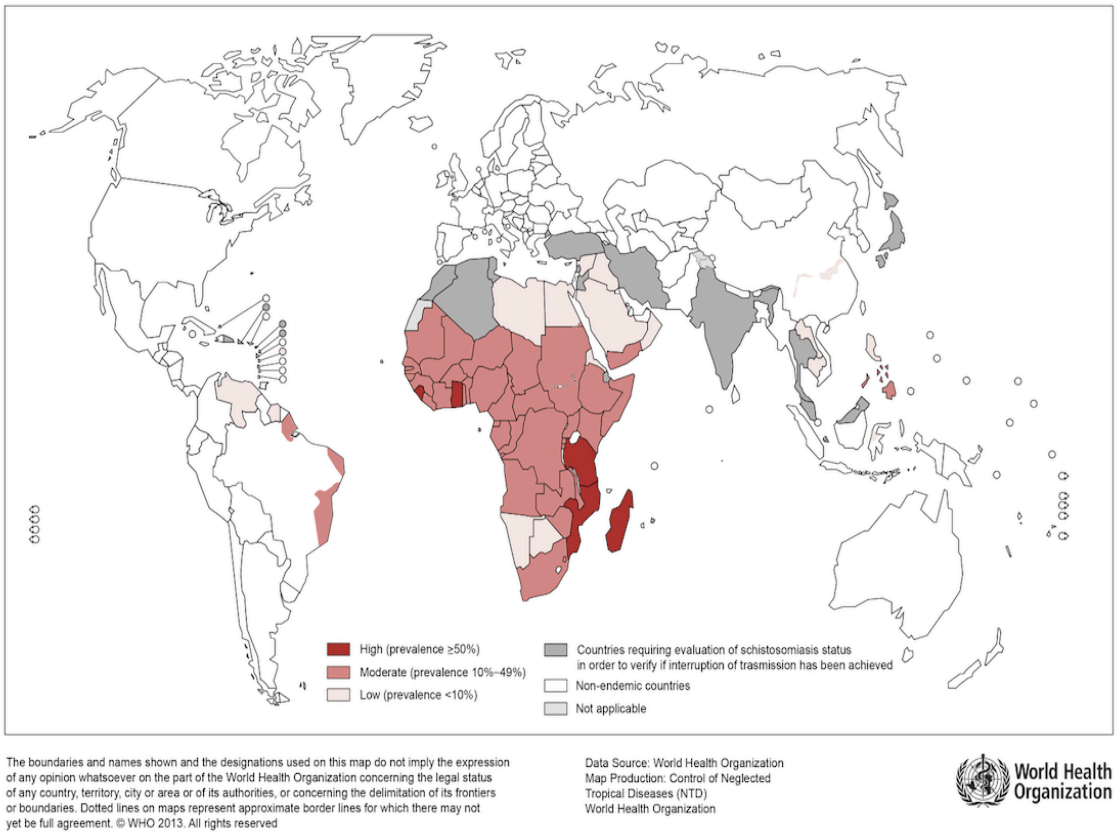

Figure 4. Distribution of schistosomiasis, worldwide 2012. Highest prevalence is found in Sub-Saharan African countries. http://gamapserver.who.int/mapLibrary/Files/Maps/Schistosomiasis_2012.png

Symptoms

In general, the patients symptoms will relate to the site where the *Schistosoma* couple lay their eggs (1). Symptoms are often unspecific and people may be misdiagnosed, which lead to insufficient treatment (26).

It is estimated that 261 million people have schistosomiasis related symptoms, and 20 million have severe disease (2, 22). Clinically, schistosomiasis may occur as either an acute or a chronic condition (1).

Acute infection

The acute reaction is described as itching and dermatitis at the site where the cercariae penetrate the skin. A more severe condition, probably caused by a hypersensitivity reaction, is called the Katayama syndrome. This may encompass symptoms like fever, headache, muscle pain, joint pain and bloody diarrhea (18, 27).

Chronic infection

The symptoms due to a chronic infection are caused by an inflammatory response to viable and non-viable ova (1). *S. mansoni* and *S. japonicum* mostly affect the liver and the intestine. Submucosal ova in the intestine results in polyposis, ulceration and bleeding, giving symptoms like chronic or intermittent abdominal pain, cachexia, or diarrhea with or without blood (1, 27, 28). Hepatic inflammation includes granulomas around the lodged ova, leading to fibrosis and occlusion of the portal veins. This may result in hepatomegaly, portal hypertension and ascites, changes that can be lethal (1, 18, 28).

S. haematobium predominantly go to the pelvic plexus around the urogenital tract (29). The tissue reaction can cause symptoms like hematuria, dysuria, pelvic pain, vaginal discharge and genital itch (30-32).

Even if the various *Schistosoma* species have their predilection sites, ova from all the species can also be found subepithelial in any tissue including the brain, kidney, lung, skin and skeletal muscle (27, 28). Besides the symptoms mentioned above, other symptoms reported are anemia and malnutrition (33, 34). This may result in fatigue, impairment of growth development and learning disabilities, especially in children (35, 36).

Diagnosis

The diagnosis of any *Schistosoma* species relates to the microscopic detection and identification of characteristic ova, each with their special morphology including the site of the spine (37) (Figure 5).

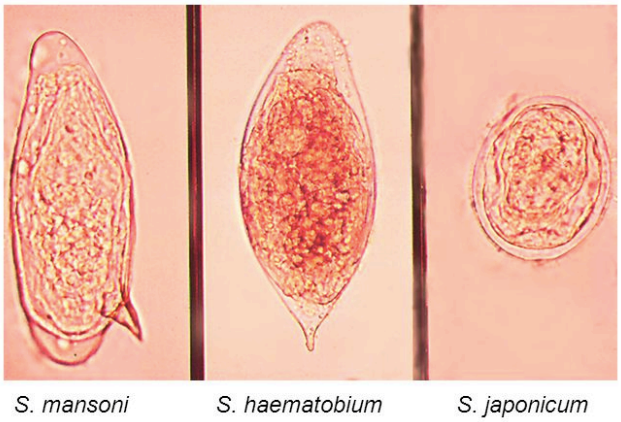

Figure 5. *Schistsoma* species (http://www.yourgenome.org/sites/default/files/images/photos/Schistosome%20eggs.jpg)

Serological tests to detect antibodies may also be used. The value is limited as antibodies may exist in the blood also when the worms are dead after treatment (18). Additionally the tests give no information about the location of infection (38). *S. mansoni* and *S. japonicum* are usually diagnosed by detection of ova in stool. This can be revealed by the Kato-Katz thick smear technique where feces are examined (18, 37). To diagnose *S. haematobium* infection, microscopy of urine is used to reveal ova (18, 37). Blood in urine can be detected with a dipstick, or by self-reported red urine (39, 40). Absence of blood and ova in urine can however not exclude infection in the female genital tract (15, 41), and a clinical examination with colposcopy should be performed (38). This may display characteristic findings in vagina and the cervix. It also allows a biopsy to be taken (38).

Treatment

Since the 1980s, praziquantel has been the drug of choice to treat schistosomiasis (42). This is a chemotherapeutic drug, killing adult worms, thus preventing further egg deposition (43). Immature worms will however not be killed, and may thus develop into adult worms after mono treatment. Retreatment should be given 4-6 weeks after the first dose of praziquintel to increase the efficiency (37, 44). The WHO recommended dose is 40 mg/kg body weight (45). Ongoing mass treatment regimen is carried out in schistosomiasis endemic areas, treating persons that are highly exposed to fresh water contact. This includes school-age children, fishermen, irrigation workers and women doing laundry in the rivers and dam. The aim is to prevent that infected people

develop severe morbidity due to schistosomiasis (42). Praziquantel rarely gives side effects, but nausea, dizziness, vomiting, urticarial rash, abdominal pain and diarrhea with or without blood are reported (46). Furthermore, the tablets have a disgusting and bitter flavor, which may affect the compliance (47).

In addition to medication, efforts are made to decrease infection risk by providing clean and safe water, give education in health, develop adequate sanitation and organize chemical snail control (22, 46, 48).

FEMALE GENITAL SCHISTOSOMIASIS

S. haematobium is the predominantly *Schistosoma* species resulting in clinical manifestations in the female genital tract (13, 31, 32, 49, 50), but *S. japonicum* and *S. mansoni* may also be found (50-52). FGS may be defined as the tissue response that ova of *S. haematobium* induces in the genital tissue (29). It is estimated that 85 % of women with schistosomiasis live in the rural parts of Africa (53). Of the approximately 100 million women with the parasitic disease (9), 45 million may be affected with urogenital schistosomasis (17).

Relation between urinary schistosomiasis and FGS

In a metaanalysis published in 2006, Swai found that FGS often coexists with urinary schistosomiasis (26). The number of women reported to have urinary schistosomiasis and simultaneous FGS varies from 15 to 75 % (12, 41, 49, 54). Urinary schistosomiasis may occur without genital tract findings (12, 55). FGS may also be seen in women without urinary ova excretion or symptoms (13, 31), reported in a range from 23 to 41 % (12, 41). Studies seem to indicate that while

the prevalence of urinary schistosomiasis decrease when the women are getting older, the prevalence of FGS seems to be relatively constant in different age groups (12, 55, 56).

Age groups

S. haematobium infection is often acquired during childhood (30, 57). Gynecological examination is usually not performed prior to sexual debut (29). As a consequence, knowledge on genital manifestations of FGS in children is lacking (29). A case-control study, investigating women aged 15-45, found FGS lesions in all age groups (56). The percentage of FGS lesions in age group 15-19 was as high as 33 % in one area. This suggests that FGS probably also is present in females younger than 15 years (13). A cross-sectional study of schoolgirls in age group 10-12 years from costal KwaZulu-Natal in 2013, reported urinary schistosomiasis associated with genital symptoms that seemed to be of intra-vaginal origin (e.g. malodorous discharge)(53).

Symptoms

Schistosoma lesions in the genital tract can lead to a variety of symptoms (52), but may also be asymptomatic (58). The most common symptoms reported with association to FGS are abnormal vaginal discharge, genital itch, (31, 32, 55), pelvic pain, (31) dyspareunia (29), post-coital bleeding (56) and spot bleeding (32). Lesions in the upper genital tract are associated with spontaneous abortion (31) and infertility (59), possibly related to involvement of the Fallopian tubes (26).

Women with FGS may also complain of symptoms from the urinary tract such as hematuria and dysuria (31), frequent urination (pollacisuria) and stress incontinence (32).

The vague and often nonspecific symptoms (31) are clinically a challenge in the differential diagnosis between FGS and sexually transmitted infections (STIs) (13). The fact that these infections often coexist (12, 58), makes it even harder clinically. It is however, a problem that health care providers, doctors and nurses alike, have little awareness of FGS and its symptomatology, and thus do not consider the diagnosis of FGS (43).

Histopathological findings

Biopsies taken from the female genital tract have been used for diagnostics and in order to understand the underlying tissue reaction for *S. hematobium* (13). Several changes are found associated with both worms and ova, yet the pathogenesis is not fully understood (11, 16).

Inflammation

Both viable and non-viable ova may cause a local inflammatory response in submucosa (15). The overlying mucosa may be ulcerated (60). The infiltrate mostly consists of chronic inflammatory cells, especially lymphocytes and macrophages as shown in figures 6 and 7. In addition, a varying number of eosinophilic granulocytes may be seen (11, 60). The lymphocytes are predominantly CD4+ T-cell. The macrophages are CD68+. These cell types both have membranous CD4 receptors, and can be a biological explanation on the

increased risk of sexually transmitted HIV (60, 61). Furthermore, we cannot preclude that there is a correlation between schistosomiasis and transmission and persistence of human papilloma virus (HPV)(62).

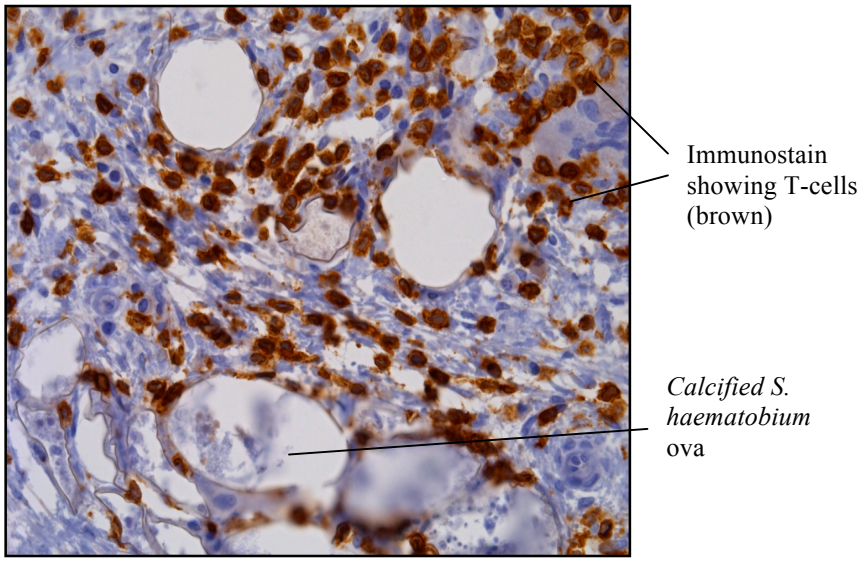

Figure 6. Immunohistochemical detection of T-cell, mostly CD4+ surrounding calcified ova. Magnification, objective 40.
Published in Jourdan 2011. American journal of tropical medicine and hygiene

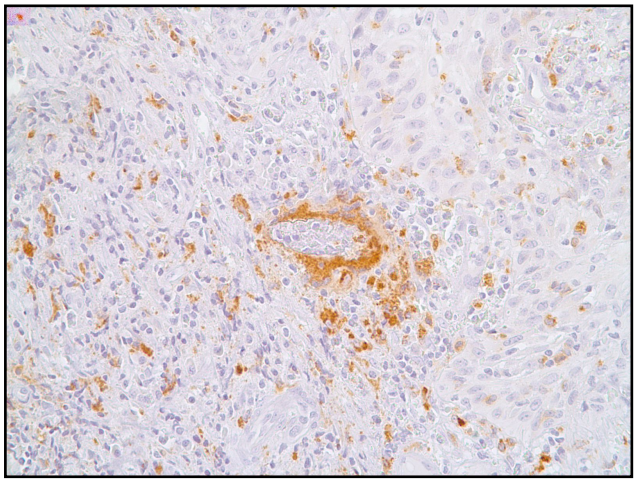

Figure 7. Immunohistochemical detection of $CD68^{+}$ macrophages markers. Magnification, objective 40 (Courtesey of Jourdan and Prof. Borghild Roald)

Dilated blood vessels

Histopathology reveals dilated vessels (14, 63). In an experimental study from Egypt with monkeys, distention of the venule wall was seen close to the female worm. As she migrated into the vessel, her body was bigger than the vascular diameter, the lumina were dilated and vessel stretched (63). This observation has not been repeated in other studies, but it is part of the hypothesis for the abnormal dilation of the submucosal vessel. (14, 63)

In 2013, Jourdan reported a thrombus surrounding ova (Figure 8). The mechanisms are not known.

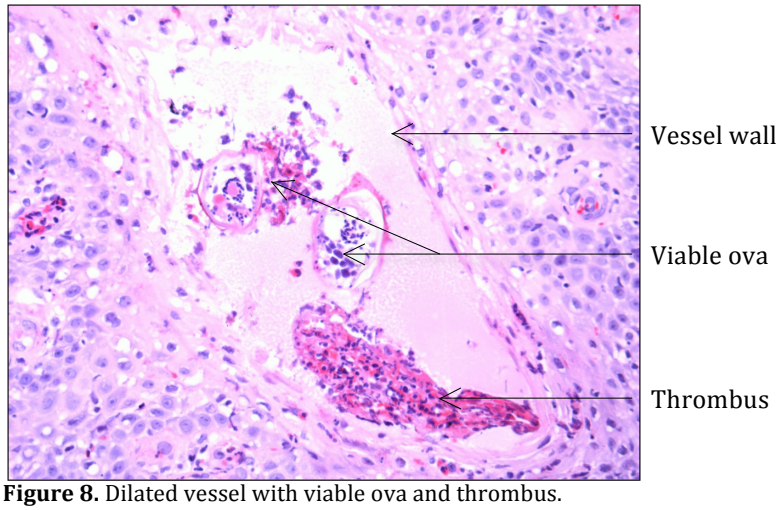

Figure 8. Dilated vessel with viable ova and thrombus. Published in Jourdan 2013. International journal of gynecological pathology

Neovascularization/granulation tissue

Women with FGS have a more vascularized tissue in the genital tract than non-infected women (16). Microscopically, it is seen as a granulation tissue, characterized by sprouting capillaries

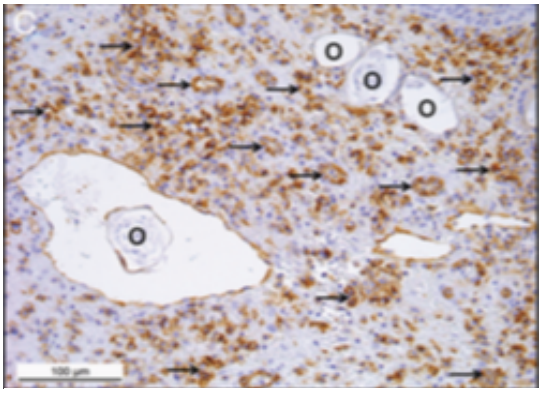

Figure 9. Granulation tissue. The arrows shows sprouting capilarries Published in Jourdan 2013. International journal of gynecological pathology

(Figure 9). This is mostly around viable ova (16). Studies with *S. mansoni* indicate that *Schistosoma* ova secrete factors including antigens that activate endothelial cells in capillaries. This stimulates angiogenesis through proliferation, tube formation and decreased apoptosis (14, 64).

Fibrosis

Fibrosis is mostly seen around non-viable and calcified ova (11). This implies that ova were deposit some time ago, and that the lesions are old (15). The fibrous tissue is dominated by mature fibroblasts and collagen fibers (Figure 10), and the number of inflammatory cells is minimal (15). This is thought to be the end-stage pathology of the *Schistosoma* infection (11, 16).

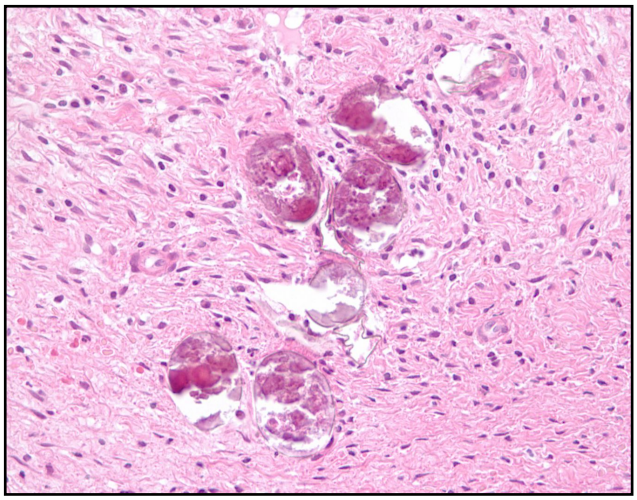

Figure 10. Cluster of calcified ova surrounded by fibrosis. No inflammation cells are present here. Seen as the end-stage pathology of schistosomiasis. Courtesy of Prof. Borghild Roald

Clinical findings related to the schistosomiasis lesions in FGS

Ova may be distributed and lodged in the submucose in all parts of the genital tract (50). The clinical finding depends on the anatomic site where the worms have deposited them (56). The cervix has been suggested to be the most common location for FGS (13, 49, 50), however, it is also the most common genital investigation site and FGS is equally common in the vagina, ovaries,

Fallopian tubes and vulva (13, 50, 65). Autopsy studies have also revealed ova in the myometrium and parametrium of the uterus (50).

The most common lesions in the lower female genital tract seen by gynecological examination are sandy patches (homogenous or grainy), abnormal blood vessels and rubbery papules (38). Recently, WHO has published an atlas: "female genital schistosomiasis: a pocket atlas for clinical health-care professionals," with images visualizing the clinical characteristics of FGS (43).

Sandy patches

Sandy patches are clinically described as patchy, yellow, and often slightly lifted lesions, sometimes with a rough surface at touch (11, 12). Two different types of sandy patches are described, grainy and homogenous. These may be seen concurrently (12, 38), and both are found associated with *S. haematobium* ova (12).

Grainy sandy patches

Grainy sandy patches (figure 11 and 12) may appear with single or clustered grains, and they may be seen widespread or as just a few areas (38). They are thought to be pathognomonic for FGS, and are found strongly associated with an inflamed and easily bleeding mucosa (12). The grains may be located deep or superficially in the mucosa. The deep grains cannot be moved and have a smooth mucosal surface, while the superficial may bulge out and be movable. The single grains are shaped like small rice-grains (12). It has been suggested, supported by a roughly size measurement and microscopically examination of the grains, that the single grains consist of a single *Schistosoma* ovum (12, 66). Kjetland et al

have reported a correlation between the size of the grainy lesions (in diameter) and the number of *S. haematobium* ova pr mm^2 tissue (13). The colors of the grains are in different shades of yellow, but can also be more off-white, beige or golden (38).

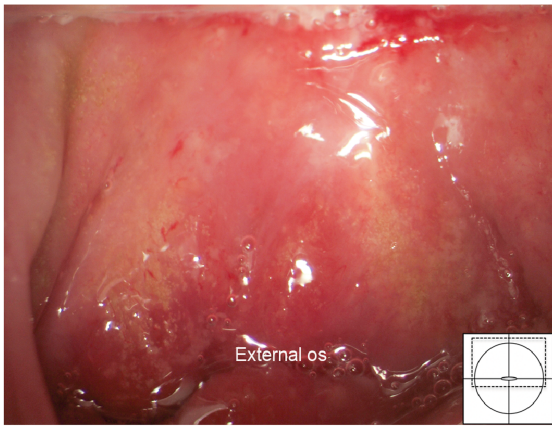

Figure 11. Grainy sandy patches on the cervix. They are thought to be pathognomonic for FGS, and appear in different shades of yellow. Norseth 2014, PLoS Neglected Tropical Diseases

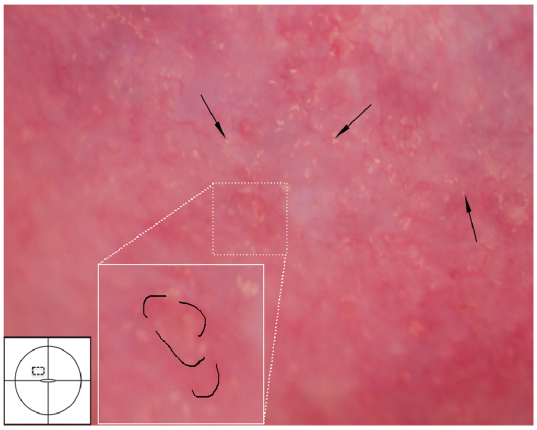

Figure 12. Clustered and single grains. Arrows show single grains. Norseth 2014, PLoS Neglected Tropical Diseases

Homogenous sandy patches

Homogenous sandy patches (figure 13) are yellowish lesions without distinct grains when viewed in the colposcope at 15 times magnification (12).

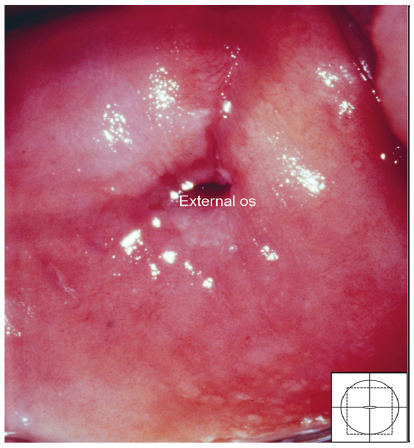

Figure 13. Yellow homogenous sandy patches Norseth 2014, PLoS Neglected Tropical Diseases

Hemorrhagic mucosa with contact bleeding

The surface surrounding the genital lesions is often fragile, edematous and hyperemic (12, 14, 38). It may look eroded (12, 49), and tends to bleed at touch under examination (15, 38) (figure 14).

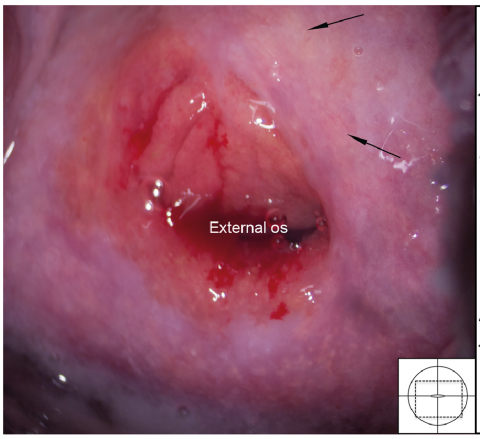

Figure 14. Mucosal bleeding around the external cervical os. Surrounded by areas with sandy patches Norseth 2014, PLoS Neglected Tropical Diseases

Abnormal blood vessels

Occasionally, dilated abnormal blood vessels (figure 15) are seen surrounding the other schistosomal lesions (13, 14). These submucosal vessels have been described as circular, corkscrewed and uneven-calibered (12, 67). The biological and morphological correlate is not known.

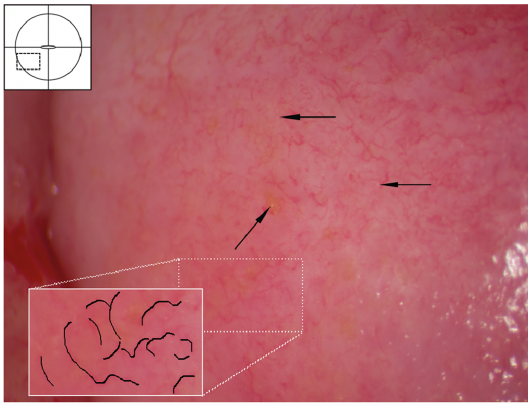

Figure 15. Abnormal blood vessels surrounding grainy sandy patches Norseth 2014, PLoS Neglected Tropical Diseases

Rubbery papules

Rubbery papules (figure 16) are so far only documented in Madagascar (15). They are beige 0,3-1,2 mm papules that look like pustules. They got their name "rubbery" because on touch they are firm like rubber (15). Microscopically, these contain inflammation with massive eosinophils, surrounding mostly viable ova (15). Rubbery papules may be seen alone or concurrently with sandy patches, abnormal blood vessels and bleeding (38).

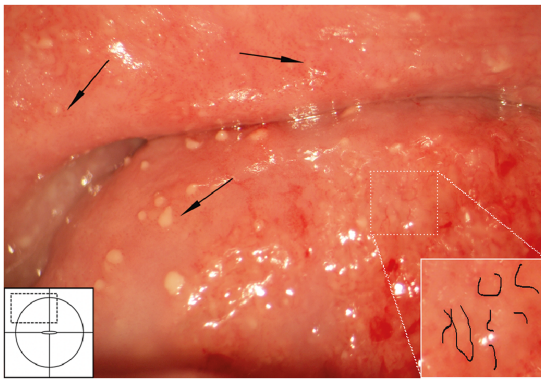

Figure 16. Arrows pointing at rubbery papules. Abnormal blood vessels are also seen. Norseth 2014, PLoS Neglected Tropical Diseases

Table 2. The table summarizes present hypothesis regarding correlation between clinical and histopathological findings in FGS.

Clinical/Colposcopic/ cystoscopic/findings	Histopathological findings	References
Sandy patches	• Associated with ova, mostly non-viable and calcified • Fibrosis • Mature fibroblasts and collagen fibers • Few immune cells	(11, 12, 15)
Hemorrhagic mucosa with contact bleeding	• Granulation tissue with neovascularization surrounding viable and non-viable ova.	(13, 16)
Abnormal blood vessels	• Dilated submucosal vessels with intraluminal ova • Thrombus • Possibly worm related	(14, 63)
Rubbery papules	• Infiltrate predominantly eosinophilic granulocytes • Mostly viable ova	(15, 38)

Diagnostic tools

A consensus meeting in 2010, decided that visualizing one of three main clinical findings (grainy sandy patches, homogenous sandy patches and rubbery papules) in the female genital tract, should be sufficient to diagnose FGS clinically (29). These lesions are best seen with a colposcope (a low power microscope) (figure 17) (13, 38) where this is available. Alternatively, the lesions may be visualized with a proper strong light source (12). Sandy patches may however easily be missed without using colposcope (11, 13).

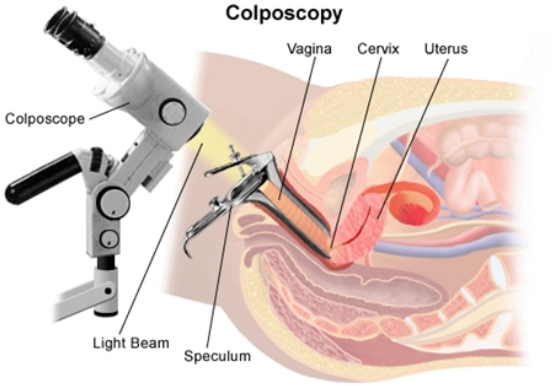

Figure 17. Colposcope
http://www.womenhpv.com/wp-content/uploads/2016/03/Colposcopy_procedure.jpg

Histology, visualizing the living or dead ova in the lesions, has been regarded as the gold standard for diagnosing FGS (68). However, examination of tissue in the genital tract has shown that the ova often lie in focal clusters (50), with the risk for being missed on a few tissue sections (38, 68). Biopsies will leave small ulcers that may increase the risk of HIV transmission, and is therefore not recommended in clinical African guidelines (69, 70).

Due to the prevalence of women with genital lesions without ova excretion in urine, urinary-based diagnostics (urinary filtration or dipstick) are insufficient (29, 32). PCR in vaginal lavage may be an alternative, but in a pilot study, the sensitivity was estimated to 53 % only (69). There is no schistosomal DNA if ova are long dead and calcified. The fact that PCR will be present if there are viable

ova and schistosomal DNA (71, 72), may be suggested to be the reason for this low sensitivity. Wet smears and Papanicolaou (Pap) smears also show a low sensitivity (12, 13, 73, 74). In younger girls, an appropriate tool for diagnosing FGS has not yet been found, as they rarely have gynecological examinations (53). Lesions in the upper genital tract are not seen during a routine clinical examination. They are thus more difficult to detect (52).

Relation between HIV and FGS

An epidemiological overlap between women with high prevalence of HIV and areas endemic for urogenital schistosomiasis exists (Figure 17). In Sub-Saharan Africa, more women than men are infected with HIV (75), and a correlation between the prevalence of HIV and *S. haematobium* in these countries is documented (76).

Figure 2: Geographical overlap of SCH and HIV distribution

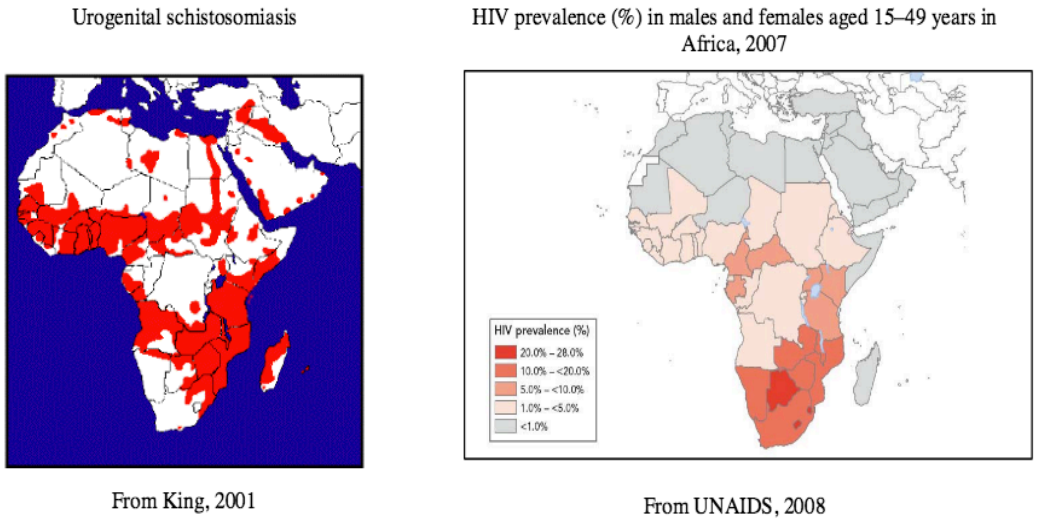

Figure 18. Geographical overlap between women with high prevalence of HIV, and areas endemic for urogenital schistosomiasis. http://apps.who.int/iris/bitstream/10665/70504/1/WHO_HTM_NTD_PCT_2010.5_eng.pdf

Women with genital schistosomiasis have a three- to four-folded risk for HIV infection (7, 8). The high density of HIV target cells (CD4+ T lymphocytes and macrophages) in the schisto-lesions, are thought to explain the FGS/HIV association (60). With an additional defect mucosal barrier caused by genital lesions, this might increase the risk for HIV infection in women with FGS (10, 12, 77). The hypothesis is that infection acquired in childhood may increase the tendency for HIV infection later in life, when the girls get sexually active (78). It has been suggested that anti-schistosomal treatment might be a target for HIV prevention (9, 79).

Treatment of FGS

Praziquantel has a reported impact of reducing the prevalence and intensity from *S. haematobium* infection when given to children (80, 81). Though, the effect of praziquantel on FGS-lesions is limited (8, 82). Established lesions like sandy patches may still be present and unchanged after treatment (8, 15), despite decreased ova excretion in urine (8). In a cross-sectional study, Kjetland et al found that anti-schistosomal treatment had the best effect on the sandy patches and contact bleeding when women were treated before the age of 20 (83). Treatment of younger females may thus be crucial for prevention of morbidity in the female genital tract (83, 84). Even though older pathology may not disappear during treatment; praziquantel kills the worms. It thus impedes further ova deposits, in turn preventing new genital lesions from being established (29).

PART 2: FIELD WORK IN KWAZULU-NATAL

In January 2016 we visited the province KwaZulu-Natal in South Africa. The main reason for our trip was to get insight in the work in a research group, and to participate in the preparatory work in the planning of a large hospital based study. The project title is *"Management of Female Gynaecological Bilharzia through better understanding A hospital based study in schistosomiasis endemic KwaZulu-Natal exploring the correlations between optical diagnostic tools and histopathology."* The study will be based at Port Shepstone Provincial Hospital in a schisto-endemic area, south of Durban in KwaZulu-Natal, where the predominant schistosoma specie is *S. haematobium* (85). The project will be a collaborate study between Port Shepstone Hospital, Oslo University Hospital, University of KwaZulu-Natal and University of Oslo.

The correlation study is planned with a two year recruiting and specimen collecting period, hopefully from January 2017 to December 2019. Females referred to Port Shepstone Hospital for elective surgery (conisation, prolapse operations or total hysterectomies) will be asked to participate. The consenting patients will have a gynecological examinations including colposcopy with photo documentation of lesions prior to surgery. Furthermore a series of serologic and STI related tests will be made. Tissue sections will be sampled from the surgically removed specimens for histopathology examination. A one-to-one identification to the colposcopic findings will be done, in addition to regular diagnostics related to the clinical indication for surgery. The study will provide access to larger tissue samples, than small superficial biopsies. It will give an

invaluable opportunity to explore many unsolved questions and to better understand the pathological processes behind the clinical findings in female genital schistosomiasis.

During our stay, we also got insight in the health challenges and health care system in South Africa. We visited the rural St. Andrews hospital, the regional Port Shepstone Hospital and the university clinic King Edwards VIII Hospital.

We went to Port Shepstone Hospital and observed operations to get a "hands-on" insight in the practical set of routines and procedures regarding the cervix-related operations, including the postoperative handling of the specimens.

Gynaecological procedures for cervix specimens

We observed the doctors in three gynaecological operations related to removal of the cervix. One hysterectomy and two conisations (cone biopsies) (figure 19) were performed, and done vaginally. The indication for the hysterectomy was abnormal uterine bleeding due to multiple leiomyomas, diagnosed by explorative laparoscopy. Indication for the conisations was cervical epithelial atypia and cancer. These two patients we observed, previously had done a Large Loop Excision of the Transformation Zone (LETTZ), with histopathology revealing atypia and cancer in the resection margin.

LETTZ is the preferred treatment for CIN2 and CIN3 (cervical intraepithelial neoplasia) (figure 18). Diathermy with a thin wire loop is used to make a loop

biopsy. This removes the transformation zone of the cervix, the interface zone between squamous cells and columnar epithelium, the usual site of neoplastic changes. The procedure takes about 5-10 minutes, and is most commonly preformed in local anaesthesia (86). The specimens will be sent to the laboratory for histological examination, to verify the tissue diagnosis and ensure that the atypia is removed with free resection borders, i.e. with no abnormal cells left behind.

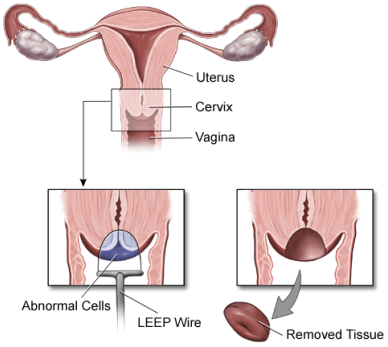

Figure 19. Large Loop Excision of the Transformation Zone (LLETZ) http://www.fullcirclehealthcareinc.com/uploads/4/1/6/7/41671693/5875074_orig.gif?425

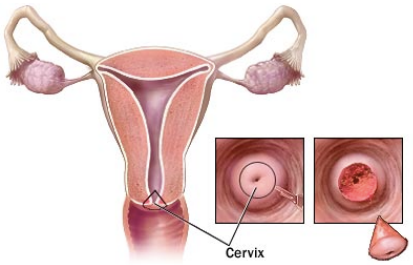

Figure 20. Cone biopsy from the cervix. https://cancercervical.wikispaces.com/file/view/c7_conebiopsy.jpg/389993356/440x305/c7_conebiopsy.jpg

The specimens

The uterus from the hysterectomy had a cervical part of approximately 2x2 cm. One of the cervical cone biopsies had definite borders, while the other was more uneven and roughly cut. They used a liquid on the cervix to view the transformation zone and possible dysplasia, and removed the cervix area 1-2 mm lateral to this.

The removed tissue material was put in a plastic container with 4 % formalin and identified with the patients name and data. The container was kept in the

operation theatre until the end of the surgery. A requisition was completed with relevant patient data and clinical history, and taped to the container. All specimen containers were then stored with other specimens in room temperature right outside the operation theatre. In the afternoon, they were taken to the pathology lab for further examination, including histology.

The women were admitted to the hospital the day prior to the operation, to ensure that they were ready for surgery. Anamnesis, clinical examination and laboratory tests were administered this day, and the women spent the night in the hospital department.

Reflection on planning a research project

Trough our fieldwork in South Africa we got a brief insight in how to participate in a research project. It was easy to understand that there are many aspects and logistics to think through when planning a bigger scientific project. Our small fieldwork was just a minor brick in the preparation of a study protocol. To make a good and complete protocol, it is important to have good knowledge of the routine and procedures at the hospital. The protocol needs
a good and clear description of the procedures for staff and research assistants that will participate in questioning the patients and collection of specimens. It is important to have standardized procedures to ensure equality, and that nothing get lost or are mistaken along the way. This can be accomplished be using an "easy to understand"-flowchart where staff can tick off as tasks are preformed.

DISCUSSION AND CONCLUSION

Schistosomiasis is a neglected tropical disease, even though 200 million people are infected, and a much greater number are at risk (21). Infection is often acquired in childhood (30). Due to continuing exposure to contaminated water, people are often reinfected (21). In women, genital manifestations are common, and referred to as FGS (12, 54). It seems like morbidity with these lesions in the female genital tract persist into adultness (56, 83). Recent years, focus on this disease has increased, especially when studies indicate that women with vaginal and cervical FGS lesions may be more susceptible to HIV (7, 79).

The symptoms of FGS are often unspecific, and may easily be misinterpreted as STIs. This, together with clinical unawareness of the manifestations of FGS, represents challenges in diagnostics and efficient treatment (26, 55).

Visualizing the *Schistosoma* lesions in the genital tract are diagnostic for FGS. They are best seen with a colposcope (13, 38). WHO has published an atlas with colposcopic pictures of clinical characteristics of FGS lesions. This atlas may work as a diagnostic tool to help recognize these clinical manifestations, and make clinical health-care workers aware of the disease. Even though studies have documented the characteristic clinical manifestations of lesions, the correlation to the underlying pathology is only partially understood (11, 14). More research is thus needed. The hospital-based study, were we participated in preparatory work, aims to collect specimens from women coming for elective cervical surgery (conisation, cervix amputation and total hysterectomy).

A clinical examination with colposcopy will be preformed pre-operative to reveal lesions, and the samples will be examined histopathologically. This yields a

unique opportunity to correlate these findings. Increased knowledge of the correlation might contribute to a better understanding of FGS, which may be crucial for a more precise diagnostics, risk assessment and adequate treatment.

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