An Atlas of Female Genital Schistosomiasis

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Short title: The First Atlas of Female Genital Schistosomiasis
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Abstract (PLoSNDT: 3 sections max 250-300 words)

Background: Female genital schistosomiasis (FGS) is a neglected tropical disease that affects women in *Schistosoma (S.) haematobium* endemic areas. It may have harmful consequences for those affected, such as abnormal discharge, infertility, ectopic pregnancies and increased HIV susceptibility. Symptoms may mimic several of the STIs and women with FGS have therefore likely been given the wrong diagnoses. A consensus meeting held in 2010 concluded that the following findings by visual inspection may serve as an adequate diagnosis in patients from *S. haematobium* endemic areas (i) grainy sandy patches, (ii) homogeneous yellow sandy patches or (iii) rubbery nodules. The scientific community has neglected this condition for many years and the clinical manifestations are not taught in medical school or presented in textbooks. The atlas is intended as a presentation of this neglected disease and diagnostic aid for clinicians working with patients from and in high-endemic areas.

Methodology / Principal findings: Between 1994 and 2012 in four different study sites highly endemic for *S. haematobium* in Malawi, Zimbabwe, South Africa and Madagascar photocolposcopic images were captured and laboratory analyses were performed. Sexually active women between the ages of 15 and 49 years were included. The best images were chosen and were reviewed by a panel of experts in tropical diseases, genital schistosomiasis and gynaecology. The state of the knowledge is briefly presented, the atlas shows photocolposcopic and some corresponding histopathological photographs of typical findings. There are some images of other diseases for differential diagnostic purposes.

Significance: The atlas presents, for the first time, the full range of characteristic clinical manifestations of female genital schistosomiasis. It provides a simple guide for clinicians and may be used in teaching sessions for gynaecologists, medical students and local nurses.
Author summary (PLoSNDT: 1 section max 150-200 words)

Female genital schistosomiasis (FGS) often remains undiagnosed due to lack of knowledge and difficulties in seeing the clinical manifestations during gynaecological examination. Millions of women in endemic areas may have FGS, and may suffer from potentially serious consequences such as infertility or increased susceptibility to HIV. This atlas provides an overview of the gynaecological manifestations of schistosomiasis. Our aim is to increase the likelihood of correct diagnosis in endemic areas and in areas where the disease is rare.
**Glossary and definitions**

Abnormal blood vessels - pathological convoluted (cork-screw), reticular, circular and/or branched, uneven-calibered blood vessels visible (by x15 magnification) on the mucosal surface.

Contact bleeding - fresh blood originating from the mucosal surface.

Female genital schistosomiasis (FGS) - having sandy patches or rubbery nodules and/or microscopically proven *S. haematobium* ova in genital tissue.

Grainy sandy patches (GSP) – constitute oblong yellow to white grains, each grain app. 0.05 by 0.2 mm long, found individually or clustered together, deeply or superficially situated in the mucosa.

Homogenous yellow sandy patches (HYSP) - sandy looking areas with no distinct grains using 15 times magnification. They are aceto-negative and may be situated both within and outside that transformation zone.

Nabothian cysts - retention cysts that may arise as the stratified epithelium of the ectocervix overgrows the columnar epithelium blocking the outlet of the cervical crypts during squamous metaplasia.

Pre-contact bleeding - darkened blood on the mucosal surface in the absence of recent or present menstruation.

Rubbery nodules - firm smooth beige to yellow lesions with pustuloid but firm protrusions 0.3 to 1.2 mm in diameter. Micro-focusing, blood vessels stand out like small spirals under the surface.

The finding was described already in 1919, in the bladder [1]

Sandy patches - described in the bladder and genital tract from 1910 [2].

Urogenital schistosomiasis (UGS) – a term recommended by the World Health Organisation to replace the term urinary schistosomiasis (*Schistosoma haematobium*).
Introduction

Schistosomiasis is one of the 17 “neglected tropical diseases”, affecting up to 300 million people and with 780 million people at risk in endemic areas (Figure 1) [3]. The disease is acquired from infested fresh water. Cercariae penetrate the skin, mature into adult worms in the venous system and then migrate to veins draining the intestines (Schistosoma (S.) mansoni, S. matthei and S. intercalatum) or the urinary tract and the genitals (S. haematobium) (Figure 2). Uro-genital infection is mainly caused by S. haematobium, although there are case reports on the other species as well.

The disease

In women the genital manifestations are referred to as female genital schistosomiasis (FGS) and constitute a disease affecting millions of women in endemic areas. They may have harmful consequences such as chronic pelvic pain or dyspareunia, abnormal bleeding, infertility, ectopic pregnancies and increased susceptibility to HIV [4-11].

The lesions of FGS as seen by colposcopical examination are found in the cervix, vagina and vulva (Figure 3), with lesions most commonly seen in the cervix [12-14]. However, autopsy studies report that S. haematobium ova are distributed throughout the genital tract [15]. In previous studies that have explored differential diagnoses lesions present as sandy patches, abnormal blood vessels and rubbery nodules [6,16-18](Rahandrianasolo, in progress). These highly focal lesions are not easily detected by visual inspection.

Age and FGS

Most endemic females acquire the disease in childhood during regular water contact for recreational and domestic purposes [19]. Six weeks after exposure a mature worm pair will find a location in the peripheral blood vessels in the uro-genital area, from where ova will be deposited in
seemingly arbitrary locations [15]. The symptoms and clinical signs will be a result of localised ova deposition. High worm loads after years of water contact are more likely to create clinical problems, but short exposure may sometimes also cause serious complaints [20,21].

There have never been systematic investigations of FGS in children, but several reports indicate that the problems start early in life [22]. For urinary schistosomiasis there is a well-known difference between adults and children. Bladder pathology is found more often in the young than in adults [23]. Urinary tract lesions have been found to be more persistent in adults, while in children, lesions reportedly resolve within 2 to 6 months of treatment after decline in egg excretion [23-35]. Generally *S. haematobium* ova excretion is lower in adults than in children, even though lesions may still be severe [23,36-38]. Whilst urinary ova excretion is significantly correlated with urinary tract pathology in the young, there is no such correlation in adults. This has been explained by the fact that the eggs have a limited lifetime, after which they die and calcify, leaving tissue pathology without egg excretion [4,39]. Hence, lesions may have become chronic while urinary ova excretion ceases or decreases.

Case reports in girls below the age of 15 years are almost exclusively from the vulval region [40-49]. However, since intra-vaginal inspection is not usually done in virgins one cannot know if other genital sites are affected [50]. Moreover, there have not been any large-scale investigations in children.

There are a few case reports on lesions from non-vulval sites in young women and reports of stunting and late pubertal development, suggesting hormonal disturbances [40]. Similar effects have been shown in animal models, with decreased fertility and arrested development of corpora lutea [51-53]. A vaginal polyp has been found in a three-year old [54], a four cm by four cm
‘raised, reddened area’ in upper third of vagina was found in a 16-year old [55], and sandy patches have been found in the cervix of a 15-year old [56].

**Diagnostic approaches for schistosomiasis in the lower genital tract**

**Visual examination**

An FGS consensus meeting held in Copenhagen in 2010 concluded that, in patients from *S. haematobium* endemic areas, one of three clinical findings, may serve as an adequate diagnosis for genital schistosomiasis [15]. The three lesions types are aceto-negative

1. grainy sandy patches,
2. homogenous yellow sandy patches, or
3. rubbery nodules.

**Investigation of urine:**

Studies report that up to 40% of women with FGS do not have ova in their urine [16,57], hence urine analysis alone is not adequate for diagnosis. Urine investigations for *S. haematobium* is done by microscopy of filtered urine or the pellet after centrifuging a representative 10 ml sample (Figure 4). Where there is no centrifuge, or where it is not practical, the urine may stand in a conical sample container for some hours to sediment. Several urines should be investigated and in low intensity infections it may be necessary to explore large volumes over several days. Eggs hatch at room temperature, but storing in a fridge or adding formalin can prevent this.

**Biopsy of genital tissue:**

Ova may appear in clusters and may be missed even with several rounds of sectioning [58]. A bedside crushed biopsy may reveal ova and is likely the simplest technique, but removes the possibility for histological analyses. Ova may be present even in the absence of macroscopically visible pathology and may hence not always be the cause of a lesion [46,58]. Furthermore, women
in many areas where schistosomiasis is endemic may not have the possibility to choose to abstain from intercourse [50]. Therefore, this method may represent an HIV risk and should not be done routinely.

**Schistosoma PCR:**
Lesions seem to be chronic in adults and may be persist in the absence of live ova or worms [4]. *Schistosoma* real-time polymerase chain reaction (PCR) may be run in vaginal lavage and biopsy material [59] (Rahandrianasolo, in progress). The ova (which contain the explored DNA) live for some weeks and the worm may continue to lay eggs for a lifetime [60]. The average life span is five years, but occasionally live eggs have been found 30 years after exposure Therefore a negative PCR may mean that live ova have not been deposited in that location the last weeks. Old lesions may be present and live eggs may be found in other locations. The sensitivity and specificity in still under evaluation (Rahandrianasolo, in progress).

**Cytology:**
Pap smears have low sensitivity [16,61], and cannot be used to preclude genital schistosomiasis (Figure 5). However, results from Madagascar indicate that this test may be useful in some instances (Rahandrianasolo, in progress). A positive result may theoretically be caused by ova from sperm.

**Aim**
In patients from and in schistosomiasis endemic areas we aimed to increase the likelihood of visual diagnosis by presenting the full range of intra-vaginal mucosal morbidity caused by *S. haematobium*. 
Methods

Ethical clearance and permissions in four study sites

Study information was provided to the study population in the local languages and free informed oral or written consent were obtained. Following consent, all women who fulfilled the inclusion criteria were offered gynaecological examination (Table 1). Consent was also re-ascertained by the physician before each step of the investigations. Treatment and follow-up for schistosomiasis, sexually transmitted diseases (STIs), cancer and other conditions were given in all sites. In Zimbabwe permission was given by the Provincial and District Medical Directors, by the village headman and at village meetings. Ethical approval was given by the Medical Research Council of Zimbabwe and by the ethical committee of the Special Programme for Research and Training in Tropical Diseases Research (TDR), UNDP/WB/WHO. In Malawi approval was given by the Medical Ethical Committee of Malawi, Ministry of Health and Environmental Affairs 1993 and by UNDP/WB/WHO TDR. In South Africa four ethics’ committees granted permissions to do this research, Biomedical Research Ethics Administration (BREC), University of KwaZulu-Natal February 20th 2011(Ref BF029/07), Department of Health, Pietermaritzburg, KZN, February 3rd 2009 (Reference HRKM010-08), REK Eastern Norway September 17th 2007 (Ref 469-07066a1.2007.535), and The European Group on Ethics in Science and New Technologies 2011 (Ref IRSES-2010:269245). The Departments of Health and Education in KwaZulu-Natal gave local permission. In Madagascar ethical permission was obtained from the Ministère de la Santé, Comite d’Ethique N° 031-CE/MINSAN June 4th 2010.

Study populations

The images originate from four different rural study sites endemic for S. haematobium in Malawi, Zimbabwe, South Africa and Madagascar. Table 1 shows the selection criteria of consenting females in the different sites. All areas were highly endemic for S. haematobium but low-endemic
for *S. mansoni*. In all sites some women did have access to protected water but often rivers were used or had been used for laundry, playing and bathing (Figure 6).

**Clinical examination**

At the time of the examinations, the clinicians did not know the result of the *S. haematobium* examination in urine, except in Malawi where all were positive. All investigations were performed using autoclaved metal speculums. Examination was commenced by cervico-vaginal lavage. Saline (5 ml or 10 ml as per protocol) was sprayed on the vaginal wall and cervix twice, whereupon it was drawn back into a syringe and deposited into cryo tubes. This was followed by photocolposcopic examinations using an autoclaved metal speculum (Figure 7). The mucosal and vulval surfaces were inspected section by section with the colposcope according to a predefined protocol and mucosal abnormalities were captured by a photocolposcope. Thereafter Pap-smears were done in all consenting women. Upon suspicion and if the patient agreed, specimens for STI or cancer diagnosis were taken.

**Imaging and quality control**

In Zimbabwe, Malawi and South Africa photocolposcopic examinations were done with a Leisegang Photocolposcope (Script-O-Flash, Leisegang Feinmechanik Optik GmbH & Co, Germany, Magnifications 7.5; 15; 30). In Zimbabwe and Malawi the images were digitalised afterwards. In South Africa the colposcope was fitted with a Canon EOS 400 8000 megapixels. Further, in South Africa and in Madagascar an Olympus photocolposcope (OSC 500, Olympus America Inc., Center Valley, PA, USA) was used. Images were captured by a mounted SLR Olympus (E420, 10.0 megapixels, Olympus America Inc.), not by the medical capture equipment.

**Selection of images.** The atlas portrays intra-vaginal lesions. The selection of images was based on the characteristic findings in FGS described previously, such as sandy patches, abnormal blood
vessels and rubbery nodules. For the atlas, the best images were chosen, independent of patient history. Several images were chosen for each lesion in order to present the full range of findings. Findings were reviewed by a panel of experts in tropical diseases, genital schistosomiasis and gynaecology.
The images and the population

In the four study sites around 4000 colposcopic images were captured between 1994 and 2012 patient ages range between 16 and 29 years. The mean age per study site is presented in Table 1. The best images were chosen. Figure 8 shows that sandy patches are found in all adult age groups whereas the presence of abnormal blood vessels increases significantly with age.

Technical and teaching aspects in the visual diagnosis of FGS

The findings may be subtle and focal. It may take several months to learn how to recognise the lesions (personal communication). One cannot preclude FGS without the systematic use of a colposcope viewing every part of the intra-vaginal surface, including the fornices and the cervix, rotating the speculum in order to view the posterior and anterior vaginal walls. The vaginal wall lesions may be overlooked due to difficulties in rotating the speculum and some speculums have been found to be impossible to use for this purpose (Figure 7). Most importantly the patient must be given enough information and privacy to be completely relaxed.

Using a colposcope for FGS diagnosis

Oculum, magnifying glasses, torches, lamps, bulbs, or surrounding light conditions may have to be changed or focused and applying more than 15 times magnification may be necessary. One will have to use the micro-meter focusing function. It will require some practice for the clinician to look at the entire vaginal surface and it may be necessary to tilt the gynae chair. Furthermore, if the clinician does not have an adjustable gynae chair / very adjustable colposcope / lamp it may be necessary to sit on the ground or stand on a (stable) chair in order to see the anterior and posterior vaginal surfaces respectively.

Some medical equipment currently in use is not good enough for FGS diagnosis and commercial products may be better. A mounted SLR Olympus E420, 10.0 megapixels, or Canon EOS 8
megapixels provided good levels of detail, whereas the MediCapTM USB200 (Medical Capture Inc., PA, USA) could not be used as it did not provide enough detail.

**Using a computer screen, a projector or a TV monitor to identify lesions**

The room should be dark. The screens or projectors may have to be focused, light adjusted, contrasted or screen tilted. The resolution must be good. A larger magnification may be necessary and it may be necessary to look at a screen from different angles.

**Summary of the clinical manifestations**

**Sandy patches**

The sandy patches are often but not always accompanied by other lesion types such as abnormal blood vessels or general signs of inflammation. There are two types of sandy patches, grainy sandy patches and the homogeneous yellow sandy patches. These may cover the whole vaginal or cervical surface (Figure 9), but sometimes only one grain is found (Figure 10). The grainy and homogeneous sandy patches can be found individually (Figures 11, 12, 13, 15, 16) or concurrently (Figures 17a, 17b, 18, 19, 20a, 20b). They do not respect the squamo-columnar junction and their localisation is not confined to the transformation zone. The sandy patches are not aceto-white.

**Homogenous yellow sandy patches**

(Figures 17a, 17b, 18, 16, 19, 20a, 20b, 21b, 22a)

**Localisation**

The homogeneous yellow sandy patches are most often seen on the ectocervix and in the vagina.

**Morphological description**

The homogeneous yellow sandy patches are sandy looking areas with no distinct grains using 15 times magnification [16].
**Differential diagnoses**

Nabothian cyst (Figures 23a and 23b), Herpes simplex virus, LSIL (Figures 24 and 25)

**Associated findings**

In some instances grains (see below) may be embedded into the typical homogeneous lesions. These grains often seem to be lying superficially in a mucosa that has a deeper yellow discolouring (Figures 17a, 17b, 18, 20a, 20b, 21b).

**Grainy sandy patches**

(Figures 9, 10, 11, 12, 13, 15, 17a, 17b, 18, 19, 20a, 20b, 21a, 21b, 22a, 22b, 26a, 26b, 27a, 27b, 28a, 28b, 29, 30, 31a, 31b, 32a, 32b, 33, 34, 35, 36, 37)

**Localisation**

Grainy sandy patches may occur on all intra-vaginal and cervical surfaces.

**Morphological description**

The grains (app. 0.05 by 0.2 mm long, and shaped as minuscule rice grains in clusters of up to 300) may be individual or clustered. They are deeply or superficially situated in the mucosa [16], with a characteristic yellow, off-white or golden colour (Figure 27b). The deeply situated grains may merge into sub-mucosal plaque-like formations with uneven edges and shades of texture (Figure 27, 28a, 32a). Sometimes the mucosa is mottled beneath the surface (Figures 9, 20a, 20b, 28b, 37). The mucosal surface over the deeply grained patches is smooth and grains are not moveable. Superficial grains may be situated within the mucosa. Occasionally, with a metal spatula movable distinct minuscule crust-like superficial protrusions can be felt and sometimes even heard.
**Differential diagnoses**
None

**Histological findings**
Moderate hyperplastic epithelium (Figure 32b). Calcified and viable looking ova are typically scattered in the stroma. There may be ample plasma cells, lymphocytes, fibroblasts and occasional eosinophils. However, the tissue may also characterised by collagen tissue and scant fibroblasts.

**Associated findings**
The most common manifestation of the grainy sandy patches in the ectocervix, are the clusters of visible single grains surrounded by convoluted (cork-screw), reticular, circular and/ or branched, uneven-calibre blood vessels (Figures 13, 19, 21b, 27b, 28a, 28b, 35). In the endocervix, clusters of grains are contrasted to the darker colour of the columnar epithelium (Figures 9, 11, 12, 15, 17a, 21a, 22a, 22b, 27a, 30, 31a, 31b). Pathological blood vessels (see below) are also seen in close correlation with these grains (Figure 11). In some cases with clusters of grains, the underlying mucosa is hyperaemic or inflamed (Figures 17a, 20a, 20b). The mucosa is often fragile, and the surfaces may bleed on touch.

**Abnormal blood vessels**
(Figures 11, 13, 17a, 19, 21b, 27b, 28b, 30, 31a, 31b, 35, 36, 37, 38a, 38b, 39a, 39b)

**Localisation**
Abnormal blood vessels may occur anywhere on the vaginal wall or on the cervix and do not respect the squamo-columnar junction.

**Morphological description**
The blood vessels in genital schistosomiasis are pathological convoluted (cork-screw), reticular, circular and/ or branched, uneven-calibre blood vessels [16].
**Differential diagnoses**

Cervical cancer, cervicitis (Figures 40, 41), Trichomoniasis (Figure 42)

**Histological findings**

The findings may represent thromboses in the blood vessels or blood vessels established at the time of egg deposition (Jourdan 12, in press). Histopathology shows tissue with densely, well-established blood vessels [62]. Cases with viable ova may contain granulation tissue rich in sprouting blood vessels [62]

**Associated findings**

The blood vessels are adjacent to or surround the sandy patches. Small blood vessels / capillaries may be seen encircling clusters of grains (Figures 13, 19, 21b, 27b, 28a, 28b, 35). Abnormal blood vessels of a bigger calibre are often not adjacent to the sandy patches (Figures 11, 35). Blood vessels may surround the rubbery nodules or be present as spirals inside the nodules (Figures 38a, 38b, 39a, 39b).

**Rubbery nodules**

(Figures 38a, 38b, 39a, 39b)

In this multi-site investigation rubbery nodules were only found and documented in Madagascar. However they have been seen by other scientists in the bladder in Egypt [18]; and possibly also in the genital tract in patients from Egypt and South Africa [40,41].

**Localisation**

Rubbery nodules are found on both the cervical surface, the vaginal wall, and most of them stretch into the fornices.
**Morphological description**

The rubbery nodules are spheroid, pustuloid and firm (hence rubbery) beige nodules in the cervicovaginal mucosa [18,40,41]. The 0.3-1.2 mm papulous lesions are easy to spot with the naked eye. They give the mucosa an irregular surface.

**Differential diagnoses**

Human papillomavirus warts (Figure 43), Nabothian cyst (Figure 44)

**Histological findings**

Inflammatory immune cells, eosinophilic abscesses, slight epithelial hyperplasia and epithelial erosion.

**Associated findings**

The rubbery nodules may stand alone, or be found concurrent with sandy patches. They are often surrounded by various degrees of vascularisation at their basis (Figures 38a, 39b), both blood vessels and petechiae, and mucosal bleeding may be seen.

**Images section**
Management of FGS

In the urinary tract, the effect of praziquantel has largely been determined by resolution of lesions detectable by ultra sound scan and decreased egg excretion in urine [27,33]. However, praziquantel kills the egg-laying worms and lesions may remain and continue to develop around eggs already deposited in the tissues [63,64]. Once egg deposition has induced lesions in the genital tract the egg excretion and lesion development are two independent processes, with praziquantel affecting the former almost immediately, but not the latter [37,63,64]. After less than two years, treatment has been described to resolve schistosomal infertility (with pregnancy) in six of 13 infertile women [65,66]. However, only one study has followed gynaecological lesions after treatment [67]. It showed no significant change in the adult sandy patches and contact bleeding over a 12-month period, even though urinary egg excretion ceased. The outcome of treatment in the urinary tract has been found to be variable, depending on four factors: (i) the age of patient, (ii) the pre-treatment intensity of infection, (iii) the degree of fibrosis or calcification, and (iv) the site of the lesion [27-29,33,68]. In younger patients the urinary tract lesions are more responsive to treatment; this may be so in the genital tract as well [64]. However, given the same age group and exposure rates, lesions in the bladder decrease faster than do lesions in the upper ureters after treatment [27-29,33,68].

WHO has recommended treatment for women and school-based mass-treatment of children in schistosomiasis endemic areas in order to prevent long-term morbidity [19] Mass drug administration frequency is recommended yearly in high-risk communities, every second year in moderate-risk communities and twice during the schooling years in low-risk communities. Studies have found that the prevalence of schistosomiasis is higher in children not enrolled in school [69]. This may affect populations differently, the poor are often under-represented in schools, as are teenagers and females [69]. Water contact patterns can also vary according to gender and culture.
In one Egyptian study only 18% of the infected girls were reached through the school programmes [69].

Based on a number of reports, WHO has decided to recommend praziquantel to pregnant and lactating women [70]. Treatment for urinary schistosomiasis has been found equally effective in HIV positive and negative, it does not seem to influence plasma HIV viral load significantly [71-73]. Studies indicate that some worms may stay alive after treatment and that treatment should be repeated [19]. Moreover, even though treatment is efficient and the worms die, lesions may remain for years after correct use of praziquantel [37,63,64]. For the time being praziquantel should be given as a single oral dose of 40 mg/kg, or 60mg/kg in two divided doses, with food and drink in order to increase absorption [19] Reinfection is rampant, and the suggestion that treatment creates immunity against reinfection in the individual is disputed [74].

**Differential diagnostic challenges**

The diagnosis of FGS in low-income countries may be hindered by several factors. Firstly, STIs and schistosomiasis coexist, and adults at risk of FGS are also at risk of STIs. Syndromic treatment for STIs is available in many Sub-Saharan countries and when presenting with a genital ulcer the patient will be treated for *Haemophilus ducreyi, Herpes simplex* and *Treponema pallidum* infections [75]. Similarly the treatment protocol for discharge targets three diseases, *Neisseria gonorrhoeae, Chlamydia trachomatis* and *Trichomonas vaginalis* [76]. The syndromic management of STIs, are based on concepts of aetiology and monitoring resistance patterns [77]. Furthermore, since symptoms of FGS may be the same as for the STI´s, there is a risk that women receive wrong treatment for their genital symptoms, over treatment and waste of antibiotics [4,6,77]. Having FGS in mind when interviewing patients for genital symptoms and when performing gynaecological examinations will make it easier to provide the correct diagnosis and treatment.
Secondly, FGS may mimic other potentially serious genital conditions, such as various degrees of cervical dysplasia and cancer. One of the first signs of invasive cervical cancer is the appearance of abnormal blood vessels. The finding of abnormal vessels should therefore always raise the suspicion of malignancy. However, if the vessels are caused by FGS and not cancer, the preferred management would be different. In some African settings where pathology services are lacking or scarce a mistaken cancer diagnosis may have devastating consequences. Hysterectomies have been performed under the suspicion of cancer, when the pathology was actually caused by FGS [16].

Nabothian cysts finding may be mistaken for the yellow colour seen in homogeneous yellow sandy patches. However, unlike the homogeneous yellow sandy patches the Nabothian cysts are most often crossed by characteristic blood vessels. The Nabothian cysts are also always confined to the transformation zone, unlike the sandy patches that can be found anywhere on the cervical or vaginal surface.

**Limitations of the atlas**

This atlas focuses on the intra-vaginal manifestations of FGS. To date the vulva has not been explored satisfactorily for us to present the clinical findings. In the community based studies very few vulval lesions were found and there was no association between them and e.g. urinary *S. haematobium* ova or genital ova [16,17,56,78,79]. Furthermore, *S. haematobium* ova may be found in lesions without being the actual cause [16]. None of the case reports that have found *S. haematobium* in ulcers or tumours have performed satisfactory differential diagnostic tests for e.g. human papillomavirus, syphilis, herpes or other possible causes [15,16,80,81]. Furthermore, children with schistosomiasis in the largest questionnaire-based study to date seem to have had more ulcers and tumours than their peers (Hegertun, accepted). These have not yet been documented.
We have chosen the images with characteristic lesions, however, we cannot rule out the possibility that in some cases co-morbidities influence the macroscopic manifestations. We do not have differential diagnoses for all the cases. Furthermore, we do not have histopathological correlates for all the cases.

All the women included in the four studies were between the ages of 15-49 years, which means that we do not know what lesion look like in pre-pubertal girls or post-menopausal women.

The lesions of FGS can be very difficult to spot with the naked eye without the use of a good colposcope or an imaging device. This applies especially to sandy patches that constitute a few single grains focal changes or generalised homogenous yellow surfaces. Since this atlas will be of most use in resource-poor settings where high-tech equipment is lacking, good light and a systematic investigation technique covering the entire surface is important.

**Differences between the study areas.**

Rubbery nodules were only found in Madagascar, and here the cytological smears were found to be sensitive and specific indicators of genital schistosomiasis in women (Rahiandrasolo, in progress). The intensity of infection was relatively high in Madagascar, but similar levels were investigated in Malawi and Zimbabwe. They were relatively young (mean age 22) but the South African study population was as young. There was one common clinician in all the studies, information and images were captured in the same way. At this stage we do not know if the findings in Madagascar constitute genetic differences (in parasites or populations) or a summation of factors such as exposure to infested water, other diseases and age. Further studies are needed to explore this.
Furthermore, in Madagascar cervices were soft as if pregnant (they were not). In Malawi, Zimbabwe and Madagascar it was easy to rotate the speculums, in South Africa not (personal communication). Culturally there were differences that influenced the clinical consultations. In Malawi and Zimbabwe husbands had to be involved in decisions on treatment and referral, this was not so in Madagascar where women seemed surprised over the query and made independent decisions every time.
Box 1. Key learning points

- One of three aceto-negative clinical findings may serve as an adequate diagnosis for genital schistosomiasis, namely grainy sandy patches, homogenous yellow sandy patches, or rubbery nodules.
- Do a systematic investigation looking at all mucosal surfaces using excellent light
- The disease is acquired in childhood and it may pose a risk for other infections
- The traditional treatment of chronic infections may not work. Several rounds of treatment may be needed.

Box 2. Five key articles


Box 3. Outstanding questions

1. How can we best see the gynaecological manifestations of FGS without the use of a colposcope?
2. Can schistosomiasis cause papillomatous or polypous tumours, or ulcers?
3. What do vulval lesions look like?
4. What is the natural history of the macroscopic FGS lesions?
5. What are the main differences between the abnormal blood vessels in FGS and malignancies?
6. Why are some women in endemic areas more heavily affected than others?
7. Is there are difference in parasite genetics in Madagascar and Africa mainland that cause different disease manifestations?
8. How do co morbidities influence the appearance of the FGS lesions?
9. What are the most common manifestations of FGS in pre-pubertal girls and post-menopausal women?
10. In the genital tract what do Schistosoma mansoni and Schistosoma japonicum do?
11. How do the FGS lesions influence female fertility, abortions and ectopic pregnancies, transmissions of STD and HIVs?
12. What is the optimal time and dosage of treatment to avoid the potential serious consequences of FGS?

Box 4. Interview of the patient

1. Have you ever, in your lifetime lived in a tropical or sub-tropical country? When and where?
2. In these areas do you recall having had contact with fresh water where plants could grow?
   a. Did you maybe cross streams to get somewhere?
   b. Did you ever fetch water in a river or a lake?
c. Did you go on a boat or fish?

d. Is there any possibility that your tank water was taken from an insecure water source? Are you sure they used chemicals to clean it?

3. Have you ever had red urine, genital ulcers, tumours or genital discharge? Has anyone in your family had this?

4. Have you ever been treated for Bilharzia? When and where?
Acknowledgements

The atlas draws on information acquired from all the four studies. The Zimbabwean teams from Blair Research Institute, University of Zimbabwe and Biomedical Research and Training Institute are thanked for prolonged hard work under very difficult circumstances. Institute Pasteur, Antananarivo, Madagascar and Aarhus University Hospital, Denmark are thanked for efficient field work as is Freie Universität Berlin, Germany. We thank the team from University of KwaZulu-Natal for hard recruitment work. We thank for Figure 5 by Pavitra Pillay, Figures 32b and 38c by Peter M. Jourdan. All other images were captured by the authors.
References


84. CDC Schistosomiasis life cycle. Centres for Disease Control and Prevention.


FIGURE LEGENDS

For the reviewers: please note that the codes will be taken out in the submitted version

Figure 1  Code 1. Geographic distribution of schistosomiasis

In 2009 WHO stated that urinary should henceforth be called urogenital schistosomiasis [82,83].

Figure 2  Code 2. Schistosomiasis life cycle.

The most common species found to be pathogenic to humans; Schistosoma (S.) mansoni, S. japonicum and S. haematobium [84]. Eggs secreted through faeces, urine and likely through vaginal discharge from infected individuals may hatch if they come in contact with water, releasing miracidia that penetrate specific snail hosts where they can multiply producing free-swimming cercariae that eventually may penetrate the skin of human hosts. The cercariae mature in the portal venous system and then migrate to veins draining the intestines, the urinary tract or the genitals, where they may deposit up to 300 eggs every day. Some of these eggs will be trapped in the tissue inducing a localised host response, while others will penetrate the vessel wall and the mucosa of the intestines, bladder or the genitals, are excreted in faeces, urine or vaginal discharge into freshwater in order to begin the parasite life cycle again. This figure denotes the venous plexus of the bladder but it should also be for the genital tract.

Figure 3  Code 3. Gynaecological predilection sites for FGS [85].

Manifestations in the cervix and vagina are seen colposcopically

Figure 4  Code 4: Urine microscopy.

The S. haematobium ova are seen as xx times longer than the diameter of the red blood cell.
Figure 5 Code 6: *S. haematobium* ova in a Pap smear

Figure 6 Code 7: A typical transmission site.

River water is used for personal, household, husbandry and recreational purposed. Even where taps are present the queues are often long and water that is not for drinking purposes is acquired from places such as these.

Figure 7 Code 8: Different speculums.

In our experience speculum A was the only speculum that allowed rotation for full inspection if the vaginal walls. The others caused discomfort.

Figure 8 The relationship between the sandy patches, the abnormal blood vessels and age.

Figure 9 Code 28 (HNM-11): Grainy sandy patches.

Grainy sandy patches in all visible areas of the ecto-and endocervix and mucosal bleeding. This entire cervix is covered, mottled with both single grains and clusters. The dashed line follows the squamo-columnar junction and portrays the manifestations of FGS under squamous (peripheral) or columnar (central) epithelium.

Figure 10 Code 27 (mdcs 66): Grainy sandy patches in the fornix.

Grainy sandy patches (circles) and mucosal bleeding (a) in the right fornix (left on the image). These grains are difficult to see, even with the help of a colposcope.

Figure 11 Code 10 (mdcs 46): Grainy sandy patches and abnormal blood vessels.

Grainy sandy patches (a) and abnormal blood vessels (b). The yellow lesions seen near and around the external os are grainy sandy patches, here seen as clusters of grains, each grain approximately 0.05 by 0.2 mm. Around six o’clock are also single grains (arrows point to some examples), where one can see the rice-grain shape of the FGS grains. The grains are yellow in colour.
Abnormal blood vessels radiate from the external os. The vessels are of uneven calibre, some dilated (c).

**Figure 12**  
**Code 11 (mcds 73): Grainy sandy patches.**  
Grainy sandy patches in the transformation zone in the anterior and posterior lips of the cervix close to the squamo-columnar junction (dashed line), mostly on the anterior lip. Some of the grains are clustered together (a), while others seem to lie independently (arrows point to some examples). No abnormal blood vessels are seen.

**Figure 13**  
**Code 13 (7090): Grainy sandy patches and abnormal blood vessels.**  
The ectocervical surface is mottled with grainy sandy patches (circles around most examples) surrounded by a network of blood vessels.

**Figure 14**  
No image (mistake)

**Figure 15**  
**Code 15 (7443): Grainy sandy patches and mucosal bleeding.**  
Clusters of grainy sandy patches (a) and some single grains (arrows point to some examples) in close proximity to the squamo-columnar junction (dashed line). We also see fresh blood from the endocervix. Five o’clock there is a cluster of yellow grains. No pathological vessels are seen.

**Figure 16**  
**Code 31 (HMN-39): Homogeneous yellow sandy patch.**  
Homogeneous yellow sandy patches (ovals) of the ectocervix. There is also some white discharge at six o’clock.

**Figure 17a**  
**Code 19a (7456 A): Grainy sandy patches, homogeneous yellow sandy patches, abnormal blood vessels and mucosal bleeding.**  
Covering the entire cervical surface are mottled areas of grainy sandy patches and also some homogeneous yellow sandy patches (ovals), two of which have grains (arrows) embedded. The whole transformation zone looks yellow, likely due to the extensive amount of grains. The ectocervical mucosa is also covered
with abnormal blood vessels. We also see mucosal bleeding from around the cervical os.

**Figure 17b** Code 19b (7456 B): **Grainy sandy patches embedded in a homogeneous yellow sandy patch.**

Enlarged section of a part of the ectocervix in Figure 17a (7456 A). Single grains (arrows) are seen around and embedded in the homogeneous yellow sandy patch (oval).

**Figure 18** Code 30 (HMN-36): **Homogenous yellow sandy patch with some grains embedded.**

Homogeneous yellow sandy patch (between the lines) and some single grains (arrows). The homogeneous yellow sandy patch can be seen as a vague yellow discolouring of the mucosa. A lesion like this can be very difficult to spot if one doesn’t have the correct light source.

**Figure 19** Code 32 (HMN-34): **Grainy sandy patches and abnormal blood vessels.**

Grainy sandy patches (some shown by circles) and abnormal blood vessels on the posterior lip of the ectocervix. In some areas the surface also has a diffuse yellow discolouring (a), possibly reflecting underlying homogeneous yellow sandy patches. The abnormal blood vessels constitute a network of vessels of variable calibres that surrounds the clusters of grains.

**Figure 20a** Code 14a (7101 A): **Grainy sandy patches in the vaginal wall.**

Clusters of grainy sandy patches (arrows point to some examples) and mucosal bleeding of the lateral and posterior vaginal walls. Some of the grains are deposited in areas with a more diffuse yellow colour, representing homogeneous yellow sandy patches (see Figure 20b). The vaginal mucosa looks hyperaemic, but no clear vessel structures are seen.

**Figure 20b** Code 14b (7101 B): **Grainy and homogeneous sandy patches of the vaginal wall.**
Enlarged section of a part of the vaginal wall in Figure 20b (7101 A). Here we can see the single grains (arrows point to some examples) and their characteristic rice-grain shape and colour, and also the mottled appearance (circles around some). We also see areas of homogenous yellow sandy patches (ovals), two of which have grains embedded.

**Figure 21a** Code 12a (7061 A): **Grainy sandy patches.**

Grainy sandy patches (arrows) in close proximity to the squamo-columnar junction (dashed line). The mucosa underlying the grains is yellow. This might be due to an underlying homogeneous sandy patch (see below), but the same yellow shade may be seen in the squamo-columnar junction in healthy women. In the right and left lip of the cervix close to the columnar epithelium are two yellow, Nabothian cysts (ovals).

**Figure 21b** Code 12b (7061 B): **Grainy and homogeneous yellow sandy patches surrounded by abnormal blood vessels.**

Enlarged section of the ectocervix in *Figure 21a* (7061 A). Small clusters (arrows point to some examples) of grainy sandy patches with a gold-like colour are seen in a network of blood vessels. If looking at this on a computer screen it may have to be tilted / brightness adjusted to see the homogenous yellow sandy patch (in ovals, two of which have grains embedded). The whole surface is covered with abnormal blood vessels.

**Figure 22a** Code 20a (7389 A): **Grainy and homogeneous sandy patches.**

Grainy sandy patches (arrow) around six o’clock in the columnar epithelium in close proximity to the squamo-columnar junction (dashed line) and a homogeneous yellow sandy patch (oval) around five o’clock in the ectocervix.

**Figure 22b** Code 20b (7389 B): **Grainy sandy patches in the endocervix.**
Enlarged section of the grainy sandy patches in Figure 22a (7389 A). The shapes of the individual grains are discernible although they are clustered together.

**Figure 23a** Codes 37 (7022 DD) and 38 (7312_6 DD): **Nabothian cyst.**

and 23b  
The underlying mucosa is pale yellow adjacent to the squamo-columnar junction (dashed line). The typical regular vascular network shows regular branching. These are Nabothian cysts.

**Figure 24**  
Code 40 (7171_10 DD): **Low-grade squamous intraepithelial lesion (LSIL).**

Aceto-white lesion in the transformation zone abutting the squamo-columnar junction (dashed line). The aceto-white area is dense and with feathery margins (arrows) possibly with some mosaic pattern (ovals). This finding probably represents cervical intra-epithelial neoplasia (CIN) stage one to two. CIN refers to the premalignant neoplastic changes taking place in the squamous epithelium in the transformation zone of the cervix before the possible development of cervical squamous carcinoma. These changes can be divided into three groups based on the proportion of epithelium thickness involved in the dysplastic process. Early stages of CIN may be confused with homogenous yellow sandy patches, and late stages may involve some of the same vessels pattern as we see in schistosomal lesions. However, the schistosomal lesions are not aceto-white, and they are not confined to the transformation zone.

**Figure 25**  
Code 41 (7174_0 DD): **Low-grade squamous intraepithelial lesion (LSIL)**

Transformation zone before the application of acetic acid. The entire transformation zone has a yellow discolouring (outlined) with abnormal blood vessels of varying calibre (a). This yellow colour could resemble the one we see in homogeneous yellow sandy patches. However, in this case the yellow area covers and is limited to the transformation zone, and the overlying vessel
structure is not typical of the homogeneous yellow sandy patches.

**Figure 26a** Code 16a (7109 A): **Grainy sandy patches surrounded by a hyperaemic mucosa and encircled by pathological vessels.**

Clusters of grainy sandy patches (arrows) on the posterior lip of the ectocervix are both superficial and deep, millimetres to centimetres from the squamo-columnar junction (dashed line). This case is however also positive for *Trichomonas (T.) vaginalis* and an erythematous surface is seen with microscopic, punctate haemorrhages typical for trichomoniasis (the so-called ‘strawberry cervix’). We also see fresh blood from the mucosal surfaces (b), both diseases may be the cause.

**Figure 26b** Code 16b (7109 B): **Grainy sandy patches, petechiae and mucosal bleeding.**

Enlarged section of a part of the ectocervix in Figure 26a (7109 A). We see single grains (arrows point to some examples) scattered over the ectocervical surface. Petechiae are surrounding the grains. We also see fresh blood from the mucosa (b). The surface is uneven. Running a narrow metal spatula over the surface one can feel, or even hear the ‘crepitations’.

**Figure 27a** Code 17a (7121 A): **Grainy sandy patches.**

Single grains (arrows) in the anterior lip of the ecto- and endocervix, on both sides of the squamo-columnar junction (dashed line).

**Figure 27b** Code 17b (7121 B): **Grainy sandy patches and abnormal blood vessels.**

Enlarged section of a part of the ectocervix in Figure 27a (7121 A). Single grains are spread over the ectocervical surface. The grains are surrounded by network of convoluted blood vessels.

**Figure 28a** Code 18a (7760 A): **Grainy sandy patches and abnormal blood vessels.**

Grainy sandy patches (ovals) in the ectocervix both close to the squamo-columnar junction (dashed line) and spread out over the whole cervical surface.
Large parts of the ectocervix are also covered with abnormal blood vessels.

**Figure 28b** Code 18b (7760 B): **Grainy sandy patches and abnormal blood vessels.**

Enlarged section of a part of the ectocervix in Figure 28b (7760 A). The first one notices is a network of abnormal blood vessels typical for FGS. However, looking closely, one can see that the blood vessels are surrounding pale yellow / golden areas mottled with deep grains (ovals).

**Figure 29** Code 22 (HMN-79): **Grainy sandy patches.**

In the anterior lip of the cervix close to the external os are two yellow areas (ovals) with a sharp demarcation and a characteristic yellow colour. It is rare to see it so clearly.

**Figure 30** Code 23 (HMN-30): **Grainy sandy patches and abnormal blood vessels.**

The abnormal blood vessels (a) immediately make you look for other signs of FGS and grainy sandy patches (b) are found around the external os. The abnormal vessels are dilated and of uneven calibre, some of them branched. The grains are situated in the endocervix around seven o’clock. A large blue venous vein is encircled. Schistosomiasis has been found to cause thrombosis (Jourdan, in press), but such areas are rarely biopsied and pathogenesis unexplored.

**Figure 31a** Code 24a (mcds 78 A): **Grainy sandy patches.**

Grainy sandy patches (a) in the left lateral lip of the endocervix in close proximity to the squamo-columnar junction (dashed line). There are also some convoluted blood vessels (oval) five o’clock, over a mottled area of deep grainy sandy patches.

**Figure 31b** Code 24b (mcds 78 B): **Grainy sandy patches.**

Enlarged section of the lesion in Figure 31a (mcds 78 A) shows clusters of grains (a) and some abnormal blood vessels (arrows).

**Figure 32a** Code 25a (mcds 43): **Grainy sandy patches and mucosal bleeding.**
Grainy sandy patches (ovals) and mucosal bleeding (a) on the whole anterior lip of the cervix, the endo- and ectocervix, into the anterior and lateral fornices. Note the different shades of yellow; some areas are bright yellow, whereas other areas are beige to white.

**Figure 32b**  
Code 25b (Mad43iiHE20b): **Histological correlate to Figure 32a**  
Calcified (a) and viable-looking ova (b) are typically scattered in the stroma beneath the epithelium. It is not possible to see the terminal spine of *S. haematobium*, except maybe in one ovum (c). There are ample plasma cells, lymphocytes, fibroblasts and occasional eosinophils. If in doubt about the type of schistosomiasis (not found in stool or urine) a modified Ziehl-Neelsen stain of a biopsy section would show the difference.

**Figure 33**  
Code 26 (7517): **Grainy sandy patches in the ectocervix.**  
Clusters of grainy sandy patches (oval) in the second upper quadrant of the ectocervix, around two 2 o’clock. This case shows how difficult it can be to spot the characteristic grainy sandy patches when only a small part of the lower genital tract is affected.

**Figure 34**  
Code 29 (7810): **Grainy sandy patches off the vaginal wall.**  
Grainy sandy patches (arrows) in the vaginal mucosa. There are also some green areas here that are not typical of FGS, this could be a super-infection or hemosiderin?

**Figure 35**  
Code 33 (7584): **Grainy sandy patches and abnormal blood vessels.**  
Grainy sandy patches (a) surrounded by small, irregular shaped blood vessels in a small section of the ectocervix close to the external os. Some of the vessels a crescent-shaped (arrows), encircling the grains, this is quite characteristic of the vessels pattern seen in FGS.

**Figure 36**  
Code 34 (mcds 11): **Abnormal blood vessels and some grainy sandy patches.**
Grainy sandy patches (arrows) and abnormal blood vessels near the columnar epithelium in the transformation zone. The vessels are pathologically dilated, branched and of uneven calibre. In one area (circle) the vessels seem to send of branches towards each other, suggesting that there may be an underlying process stimulating vessels growth. Since the vessels are confined to the transformation zone, cancer must be precluded as a differential diagnosis. This vessel-pattern may also be seen as a manifestation of other causes of cervicitis.

**Figure 37** Code 21 (7247): **Grainy sandy patches, abnormal blood vessels and mucosal bleeding.**

Grainy sandy patches (a) and abnormal blood vessels (b) in the ectocervix in close proximity to the external os. Some individual grains (arrows) and a mottled area of grainy sandy patches (oval) can be seen. The blood vessels are irregular. Small amounts of mucosal bleeding are also seen.

**Figure 38a** Code 35a (mds 65 A): **Rubbery nodules and abnormal blood vessels.**

Rubbery nodules (a) and mucosal bleeding (b) on the cervical surface and anterior fornix. Nodules look like pustules but are firm like rubber, the diameters range between 0.3 to 1.2 millimetres. Nodules are often surrounded by fine blood vessels at the base (arrows).

**Figure 38b** Code 35b (mds 65 B): **Rubbery nodules and mucosal bleeding.**

The whole surface is uneven with confluent rubbery nodules (some shown by circles), there is mucosal bleeding (b). The nodules’ diameters range between 0.3 to 1.2 millimetres (some are circled). The blood vessels are finely convoluted and there are occasional grains (arrows).

**Figure 38c** Code 35c (Mad65iiHE20b): **Histological correlate of a rubbery nodule to Figure 38a.**

In rubbery tubercles viable-looking (with intact structures) schistosomiasis ova
are surrounded by intense eosinophilia, whereas the histological findings in sandy patches show a larger assortment of immune cells and fibroblasts.

**Figure 39a** Code 36a (mcds 85 A): **Rubbery nodules.**

Rubbery nodules (arrows) in the posterio-lateral fornix and minute abnormal spiral blood vessels

**Figure 39b** Code 36b (mcds 85 B): **Rubbery nodules.**

Enlarged section of the lesion in Figure 39a. Near the nodules are minute-spiral blood vessels (arrows).

**Figure 40** Code 42 (7578 DD): **Cervicitis due to Bacterial Vaginosis.**

Oedematous and erythematous cervical mucosa with dilated vessels (arrows) in close proximity to the external os and in the transformation zone. We also see small areas of mucosal bleeding (a). Cervicitis could be the result of FGS, but the clusters of *S. haematobium* ova are most often focal and the surrounding inflammation rarely covers the whole endocervical surface, as we see in this case.

**Figure 41** Code 43 (7602_2 DD): **Cervicitis of unknown cause.**

Intensely red columnar epithelium with dilated blood vessels (arrows) in all four quadrants of the endocervix and the adjacent transformation zone (original squamo-columnar junction seen as dashed line) and bleeding from the cervical surface. This inflammation involves the whole endocervical surface while FGS is rarely so generalised.

**Figure 42** Code 44 (7488 DD): **Trichomonas (T.) vaginalis infection.**

Clusters of punctuated blood vessels (some of them encircled) in both the cervix and vagina forming a characteristic ”strawberry” pattern characteristic of *T. vaginalis* infection. Typically, these red spots are found in combination with a greenish-yellow, frothy, mucopurulent discharge. The red spots neither contain
grains nor the mottled yellow areas seen in FGS (for example in Code 13).

**Figure 43**  
**Code 45 (7403 DD): Condylomas.**

Multiple white lesions (arrows) with clearly demarcated, raised margins and irregular surface contours spread over the cervical and vaginal surface, characteristic of condylomas caused by low-risk HPV infection. Condylomas can be seen anywhere on the vulva or the vaginal or cervical surface. Unlike CIN and cancer there may be multiple condylomas, and they are not confined to the transformation zone. Unlike FGS condylomas are aceto-white and the plaque may be elevated from the surface.

**Figure 44**  
**Code 39 (mcds 12_036 DD): Nabothian cyst.**

Normal cervical surface with a small yellow lesion (arrow) around 11 o’clock in the anterior lip of the transformation zone, probably representing a Nabothian cyst. These may be confused with rubbery nodules but the Nabothian cysts are often bigger, do not protrude so acutely, and they are only found in the transformation zone. Rubbery nodules, however, may be situated anywhere over the vaginal and cervical surface. Encircled four o’clock is a mottled area, likely deep clusters of grains. Also note, next to the Nabothian cyst a small dinosaur-shaped area that could be an HPV infection.

**Figure 45a**  
**Code 46 (7173): Normal cervix.**

Cervical surface with a major part covered by columnar epithelium. In the epithelium are small reflections (arrows) that could be mistaken for grainy sandy patches. However, when looking closely, one can see that these small reflections lack the typical rice grain shape that characterises the grainy sandy patches. When looking at this with a colposcope the speculum can be moved; or the computer screen should be tilted to easily distinguish the two.

**Figure 45b**  
**Code 9 (mcds 16): Normal cervix.**
Normal cervix with squamo-columnar junction (dashed line).