Diagnosis of Female Genital Schistosomiasis by Colposcopy: Feasibility and Options under Conditions of Sub-Saharan Africa

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II List of abbreviations

CAA	circulating anodic antigen
CCA	circulating cathodic antigen
CIN	cervical intraepithelial neoplasia
ECP	eosinophil cationic protein
FGS	female genital schistosomiasis
GSP	grainy sandy patch
HIV	human immunodeficiency virus
HPV	human papilloma virus
HSV-2	herpes simplex virus type -2
HYSP	homogeneous yellow sandy patch
IFCPC	International Federation of Cervical Pathology and Colposcopy
IgA	immunoglobulin A
LRT	lower reproductive tract
PZQ	praziquantel
QCBT	quantitative compressed biopsy technique
SSA	sub-Saharan Africa
TZ	transformation zone
S.h.	Schistosoma haematobium
S.m.	Schistosoma mansoni

1. Executive summary

More than 200 million people are affected worldwide by schistosomiasis, a parasitosis caused by blood flukes (Schistosoma). Usually, common adverse effects of schistosomiasis such as bladder, bowl and liver manifestations are in the focus of interest. SSA has the highest prevalence rate of infections caused by schistosomiasis (93 % of infections worldwide). Among the complex group of acute and chronic clinical manifestations one clinical picture still neglected is female genital schistosomiasis (FGS). In the majority of cases the human pathogen species causing FGS are Schistosoma (S.) haematobium and S. mansoni. In S. haematobium endemic areas of SSA it is estimated that 33% - 75% have a FGS co-manifestation. Currently FGS is in the global focus because of stated evidence that lesions caused by FGS can facilitate transmission of HIV. Diagnosis, treatment and prevention of FGS might have an impact on future HIV/AIDS prevention strategies.

However, a problem still unsolved is the diagnosis for FGS in resource-poor settings, although a gold standard with the quantitative compressed biopsy technique (QCBT) has been established. The applicability of QCBT is limited due to epithelium lacerations in the lower reproductive tract (LRT) and the risk of increasing the rate of HIV transmission in high endemic areas of SSA. For this reason ethical approval to perform QCBT on a routine basis is no longer granted. Physicians are faced with a diagnostic dilemma as FGS frequently occurs without egg excretion in urine and alternative direct procedures (egg detection in Pap smear or wet mount smear) and indirect diagnostic procedures (detection of schistosome antigens or proteins generated during the activation of infection such as eosinophil cationic protein, neopterin and IgA) are either not sensitive enough or not feasible in the setting of SSA. Diagnosis of FGS by disease-specific colposcopic findings would offer an elegant solution. Sandy patch and sub-classified grainy sandy patch (GSP) and homogeneous yellow sandy patch (HYSP) might be the pathognomonic finding in the LRT. Recent publications reported evidence that the validity of GSP to diagnose FGS is equal to egg detection procedures (i.e. QCTB, Pap smear and wet mount smear). The data published on FGS and colposcopy is limited. Furthermore, the nomenclature used in the literature and the classification of colposcopic findings are inconsistent. Uniform criteria to diagnose FGS by colposcopy have not been established. These aspects are the motivation for our study to assess the

diagnostic test quality of photo-colposcopic/colposcopic findings for FGS in SSA. We used a twofold study approach: First to analyse a data set of photo-colposcopic images gained in a Tanzanian study population and second a critical review of the literature dealing with colposcopy for the diagnosis of FGS. The two main study objectives are the evaluation of the results of photo-colposcopy findings and their relevance for FGS in our Tanzanian study group (Poggensee, personal data) and to assess the test quality presented in the published data on colposcopy for FGS. To assess the validity of the published data, we performed sensitivity and specificity analysis and estimation of predictive values. Category variables were compared by Chi-square test.

In our Tanzanian study group the test validity of the photo-colposcopic finding sandy patch (any type) as test criterion for FGS is not sufficient. The sandy patch is characterised by a sensitivity of 23.4% and a specificity of 94.8%. 76.6% of the FGS-positive females are missed by this criterion. However, only the sandy patch (any type) showed a significant association with the FGS status. The test quality was only minimally improved by adding additional colposcopic criteria by our pooled category 2. Notwithstanding that beside sandy patch (any type) four criteria were added; 61.7% of FGS-positive patients are missed by colposcopy.

The low sensitivity of colposcopic findings to diagnose FGS is confirmed in the literature. Helling-Giese et al. (1996b) compared the test quality of vital colposcopy for FGS with QCBT (Helling-Giese et al., 1996b). Here the sensitivity for sandy patch (not sub-classified) is 27.3% (9/33) and the specificity 100% (21/21). Comparable to our Tanzanian study group, the majority of FGS cases are missed by vital colposcopy (table 11). Kjetland et al. (2005) focused on the GSP as colposcopic finding pathognomonic for FGS. The sensitivity ranges from a low of 12.2% (reference Pap) to a high of 85.7% (reference genital biopsy). The specificity ranges from a low of 55.2% (reference genital biopsy) to a high of 97.2% (reference Pap). The majority of FGS-positive patients are not diagnosed based on this finding (table 9).

There are manifold reasons for the low sensitivity of colposcopy for the diagnosis of FGS. Physiological mechanisms such as hormone-dependent changes of the epithelium, pregnancy, ageing processes, post birth trauma and traditional local herbal applications are aggravating the colposcopic assessment. STDs with their high prevalence in SSA can cause multiple lesions

of the epithelium, reasonable for an unsatisfactory colposcopy. Colposcopic signs of specific and unspecific infectious diseases are seldom pathognomonic. Furthermore, the formation of a pathognomonic lesion is complicated by the fact that the main focus of interest (Cervix uteri) is characterised by a permanent variability of colposcopic findings based on metaplastic changes between two different types of epithelium in the transformation zone. Our results indicate that the sandy patch and the classified subtypes are not such constant findings as stated in the literature. The observed findings resemble more chronic post infectious lesions of variant morphology and size. Although evidence gained by our photo-colposcopy evaluation and by the re-evaluated literature data indicate that diagnosed GSP and sandy patch are pathognomonic for FGS, most of the FGS infections are not diagnosed by these findings. The explanations gained by our thesis are: frequently the sandy patches do not have such a characteristic presentation and because of this they are not diagnosed by colposcopy or FGS-infected women do not present any abnormal/suspect colposcopic findings.

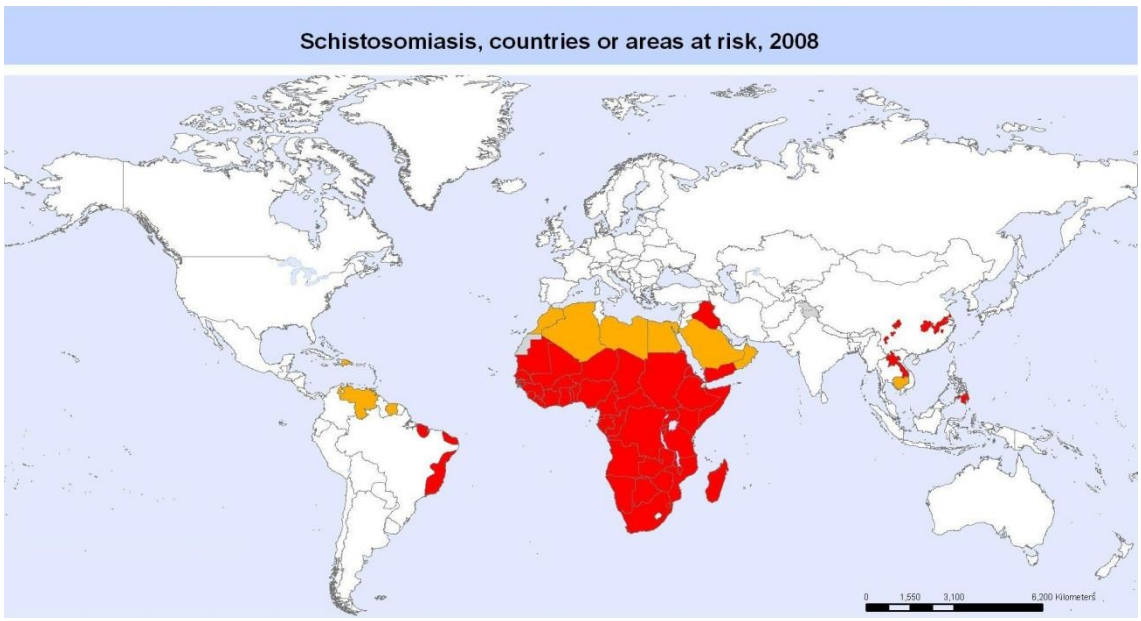
As consequence the test quality of photo-colposcopy/colposcopy for FGS is characterised by limited validity and reliability and thus not adequate for prevalence assessment. Because of the variability of presentation of colposcopic findings the assessment by colposcope usually needs a biopsy to maximise the sensitivity with adequate specificity.

At present colposcopy for FGS can be used for risk assessment and follow-up of diagnosed cases under therapy. Furthermore, FGS is an essential differential diagnosis for any colposcopic finding in regions with schistosomiasis and for any females who have been in countries where species of schistosomiasis are present. There is an urgent need for the development of a consistent terminology and guidelines for colposcopy of FGS. Observational cohort studies to follow-up and compare the colposcopic findings might offer further evidence of the prospects of colposcopy for FGS. Studies regarding the reproducibility of colopscopic findings indicating FGS have to be performed. It has to be concluded that a prevalence assessment of FGS by colposcopy is not valid. Statements based on these data are limited.

2. Introduction

2.1 Background

Schistosomiasis is an endemic disease in 74 countries with a population of 650 million living in the affected areas. More then 200 million people are infected by species of mammalian blood flukes (Schistosoma spp.). The five principal species responsible for human infections are Schistosoma (S.) mansoni, S. japonicum, S. intercalatum, S. mekongi and S. haematobium (WHO, 2007). S. mansoni, S. japonicum, S. intercalatum and S. mekongi are predominately affecting the intestine, whereas S. haematobium affects the urinary tract. S. mansoni occurs in Africa, South America and the Caribbean. In Asia there is a predominance of infections with S. japonicum and S. mekongi. However, in African countries infections with S. haematobium and S. mansoni are most frequent. The main burden of disease is caused by S. haematobium, S. mansoni and S. japonicum. S. mekongi and S. intercalatum are rarely reported causes of infections (WHO, 2007). Van der Werf et al. (2003) estimated that in sub-Saharan Africa (SSA) 112 million people are infected with S. haematobium and 54 million with S. mansoni. The prevalence rates are exceeding the 50% in local populations of endemic areas in parts of SSA. According to Hotez and Kanath (2009b) worldwide 93 % of infections caused by fluke worms (schistosomes) are apparent in SSA. In SSA, infections are mainly caused by S. haematobium and S. mansoni. Two thirds of the clinical cases of S. haematobium infections are affecting the urinary tract (WHO, 2007).



Countries or areas at high risk
Countries or areas at low risk

WHO, 2009

Schistosomiasis with its consequences is a disease of poverty, occurring mainly in areas without adequate safe water supply and sanitation. Women of childbearing age and children being the most vulnerable are frequently affected. Due to traditional gender roles and the subsequent division of workload with regard to water contact are responsible for the higher prevalence of schistosomiasis in females compared with males in SSA (Feldmeier, Poggensee and Krantz, 1993).

Among the complex group of acute and chronic disease manifestations a major, but still neglected clinical picture is female genital schistosomiasis (FGS). Even in most well-known medical textbooks FGS is not mentioned (Kjetland et al. 2008). This specific infection of the female genital tract is mainly caused by S. haematobium and S. mansoni. However, genital manifestations with all kinds of human pathogen schistosome species have been described (Poggensee et al., 1999). It has been estimated that in S. haematobium-endemic areas of SSA between 33% - 75% of women suffer from a FGS co-manifestation. Worldwide, FGS and its sequelae are affecting up to 13 million females (Poggensee et al., 1999). In Africa, as many as 10 million pregnant women per year are affected by schistosomiasis. Anaemia and underweight caused by schistosomiasis might lead to pre-term deliveries and low birth weight babies (Friedman et al., 2007). Despite this negative impact on women's health FGS has not been in the focus of international health until 1994. At that time the “Gender and Tropical Disease Task Force” was established by the WHO and the urgent need to support research for FGS was recognized (Vlassof, 1997). Although the negative consequences for the function of the female reproductive organs have been described for more than a century, no systematic research had been conducted. The mid-nineties were the starting point for systematic study activity in SAA (Kjetland et al., 1996; Helling-Giese et al., 1996b; Poggensee et al., 2000). A major reason for the growing interest in FGS research is actually due to the evidence of the association of FGS and the transmission of HIV and HPV transmission (Kjetland et al., 2005, Petry et al., 2003). FGS is now considered as a disease with major individual, national and global public health impact (Hotez, Femwick and Kjetland, 2009).

2.1 Anatomical and pathophysiological characteristics of FGS

After maturation, adult schistosomes have to reach the vascular plexus utero-vaginalis via the portal veins and deposit eggs in the genital organs to cause FGS. Therefore, they have to leave the ano-rectal plexus by crossing the recto-vaginal septum or by passing the vascular junctions between bladder and reproductive organs. The complex anastomoses provide a network of vessels favouring the spread of the fluke worms to any upper and lower genital organ. Due to lack of venous valves in the majority of vessels of the small pelvis the blood flow is not restricted to any direction. Furthermore, the migration of adult worms is favoured by the development of the complex and increasing pelvic blood supply of the reproductive tract with the onset of puberty with its impact of increasing sexual hormones. Pregnancy with its increased blood supply for the reproductive tract is further favouring FGS (Poggensee and Feldmeier, 2001).

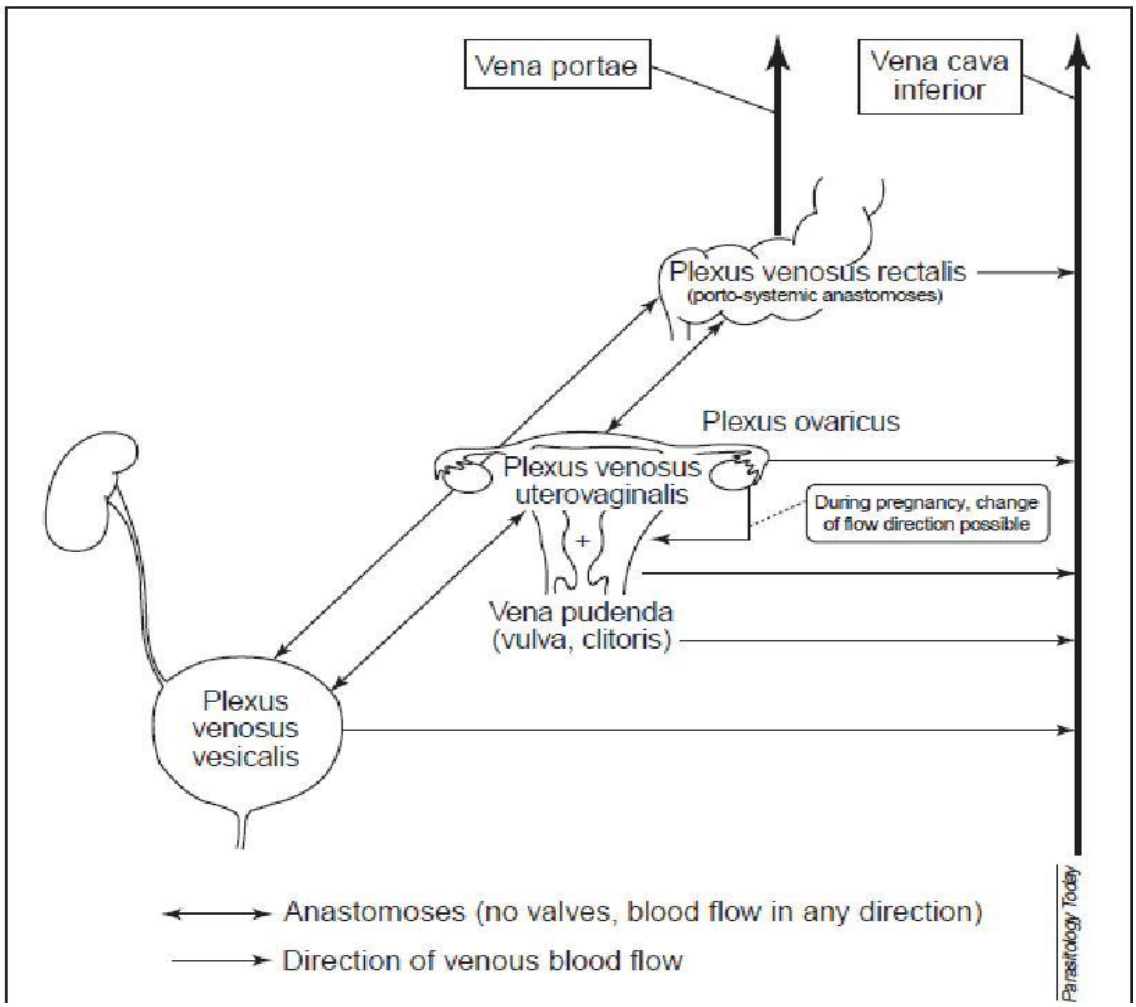


Figure 2. Female venous vasculature (from Poggensee, Feldmeier and Krantz, 1999)

Furthermore, adult worms have the tendency throughout their whole lifespan to migrate and to deposit eggs in various anatomic locations; this is increasing the likelihood of multiple organ manifestations in the small pelvis. Predominantly affected by FGS are the cervix uteri, whereas vagina, vulva and womb. Ovaries and Fallopian tube are less frequently affected organs of the reproductive tract (Poggensee and Feldmeier, 2001).

The pathology of FGS is largely caused by schistosome eggs and the consequent host immune system response rather than by the worms themselves. Contrary to the retained eggs, adult worms are tolerated by the immune system of the host (Poggensee and Feldmeier, 2001). Helling-Giese et al. (1996b) evaluated the histopathological findings in cervix biopsies and described two different types with characteristic findings:

- Type A is a severe inflammatory reaction of the tissue around viable eggs and the presence of lymphocytes, granulocytes and macrophages.
- Type B, found around non-viable eggs, is a fibrous reaction of the connective tissue characterised by the absence of reactive cell infiltration, similar to scar tissue.

Berry's study (cited in Poggensee and Feldmeier, 2001) indicates that the egg deposition preferentially takes place at the ecto-endocervical junction of the cervix uteri. Lesions in the LRT caused by FGS are most frequently evident in the epithelial and stroma layer of the cervix uteri. The findings of these lesions can be equal to any other infectious and non-infectious disease lesions in the female genital tract. Lesions with cauliflower-like growth and superficial or deep epithelial lacerations have been described (Helling-Giese et al., 1996b). The corresponding histopathological findings of cervical schistosomiasis can be even more complex due to possible disease co-manifestations like cervical intraepithelial neoplasia (CIN) indicating human papilloma virus (HPV) infection (Sharma et al., 2001). FGS in the Fallopian tubes is characterised by scars with granulomatous inflammation and fibrotic processes. This granulomatous tissue reaction can cause tubal obstruction with loss of organ function (Hoffmann and Bauerfeind, 2003). Swai et al. (2006) published a retrospective histopathological study on FGS in female genital organs. In the majority of these cases the

location was the cervix uteri, followed by vulva, vagina and Fallopian tube. Primary and secondary infertility due to FGS are mainly caused by motility impairment of the Fallopian tubes and/or impairment of the ovarian function. Tumour-like growths of FGS lesions, which can be misinterpreted as neoplasm, are another problem. Without the correct diagnosis this scenario can lead to harmful therapeutic approaches such as hysterectomies (Helling-Giese et al., 1996). Consequently, Helling-Giese et al. (1996) stated the importance of keeping in mind the likelihood of FGS as histopathological and clinical differential diagnosis in endemic regions of SSA. Poggensee, Feldmeier and Krantz, (1999) reviewed the possible consequences of FGS and described for any specific organ affected negative impacts. However, most of the consequences mentioned are not FGS-specific and can be confounded by several other infectious and non-infectious genital tract diseases.

Table. 1 Possible consequences of schistosomal lesions in the female genital tract (Poggensee, Feldmeier and Krantz, 1999)

Organs affected	Possible consequences
ovaries	hypogonadism, retarded puberty, infertility (primary/secondary)
tubes	ectopic/tubal pregnancy, tubal abortion, haemoperitoneum
uterus	anaemia due to chronic blood loss, metaplasia, miscarriage, preterm delivery
cervix	anaemia due to chronic blood loss, carcinoma, risk for sexually transmitted disease
vagina/vulva	destruction of hymen and/or clitoris, vesico-vaginal fistula, risk for sexually transmitted disease

These consequences have been mainly reported in case studies and prevalence figures are not available. Nevertheless, it has to be emphasized that the female reproductive tract with a normal macroscopy and histology presentation can be infected with FGS (Poggensee, Feldmeier and Krantz, 1999).

2.3 FGS and the potential consequences for human immunodeficiency virus (HIV) and human papilloma virus (HPV) co-infections

In recent publications it was concluded that there is evidence of the human host having an increased susceptibility for viral infections such as human immunodeficiency virus (HIV) (Secor and Sundstrom, 2007) and human papilloma virus (HPV) (Petry et al., 2003). The correlation was drawn by Secor and Sundatrom (2007) who could show that SSA is characterisd by the highest parasitic infection rate and the highest prevalence rates of HIV-1 globally. Superficial and deep epithelial lesions caused by FGS initiate breaks in the epithelium and offer entry ports in the LRT providing favourable conditions for the transmission of HIV. There is evidence that FGS-positive women have a threefold increased risk of being HIV infected by heterosexually transmission compared with females without FGS (Kjetland et al., 2006). Furthermore, inflammatory tissue response against FGS is impairing the local immune system of the affected organs. As consequence, transmission and replication of HIV and HPV can be favoured (Lawn, 2004). Schistosomiasis could be one of the co-infections responsible for an accelerated progress form HIV-1 infection to AIDS. FGS might increase the virus-host dynamics with all negative consequences for HIV/AIDS. These potential relationships can have a huge impact on the HIV survival rate (Lawn, 2004). Treating co-infections such as schistosomiasis might slow down the progress of HIV infection (Lawn, 2004). Treatment of schistosomiasis and the consequent decrease of systemic inflammation might reduce the HIV replication (Erikstrup et al., 2008). Preventing FGS-caused mucosa lesions and the subsequent vulnerability of the epithelium might offer additional preventive strategies regarding the spread of HIV. Hotez, Flenwick and Kjetland (2009) stated that the preventing FGS-caused lesions in young girls by drug treatment will have a massive impact on the HIV transmission rate in high endemic areas in SSA. The consequent result could be tremendous. Worldwide, SSA is the region with the highest HIV prevalence rate with 67% of the people living in this region being infected. Of note is that the number of females affected is disproportional high and this disproportion is even more evident among the young population (UNAIDS, 2008).

Furthermore, FGS is discussed as possible cofactor in the genesis of cervix carcinoma. There is compelling evidence of high-risk type HPV infections of the

cervix uteri being the main global cause of cervical cancer (Mosunjac et al., 2003, Petry et al., 2003). Mucosa lesions caused by FGS might also promote HPV transmission. The local immune system is depressed by the local infection with the host clearing mechanisms for HPV being impaired. Persistent HPV infection increases the risk of cervix cancer (Petry et al., 2003). With an estimated 70.700 new cases in 2002, cervix carcinoma is the most frequent cancer among the female population of SSA (Jamison et al., 2006, p. 292). FGS favouring a persistent HPV infection might have a tremendous impact on this scenario (Petry et al., 2003).

2.4 Diagnostic procedures for FGS

The clinical diagnosis of FGS is difficult due to the unspecific symptoms. The spectrum of clinical signs include any history of menstrual disorders, lower and upper abdominal pain, dyspareunia, post-coital bleeding and primary or secondary infertility (Feldmeier and Poggensee, 2001). All symptoms can be associated with other specific and unspecific infections and non-infectious diseases of the genital tract. Furthermore, signs and symptoms of chronic and acute infections can be minor or even completely inconspicuous (Kjetland et al., 1996). As consequence the diagnosis of FGS in the upper and/or lower reproductive tract cannot based on clinical signs.

Usually, FGS in the upper genital tract (ovaries, tubes, uterus except cervix) is diagnosed by chance in histopathology specimens taken from the upper genital organs. Ultrasound of the pelvic organs might provide some indirect indications by complications caused by FGS like an abdominal mass or complications such as ectopic pregnancies (Helling-Giese et al., 1996, Richter, 2000). Contrary to ultrasound for hepatosplenic schistosomiasis and late complications of urinary schistosomiasis, no criteria have been established for ultrasound diagnostic of FGS in the upper genital tract. Furthermore, it could be shown that it is an unreliable diagnostic procedure (Richter, 2000). In fact no other diagnostic tests apart from histopathology have been established for FGS in the upper reproductive tract (Helling-Giese et al., 1996).

FGS in the lower reproductive tract (LRT) can be diagnosed by Papanicolaou-stained smears (Pap). The smear is primarily obtained from the cervix uteri.

Shennan and Gelfand (cited in Feldmeier, Helling-Giese, Poggensee, 2001) diagnosed in only 2.3% (44/1905) of PAP smears schistosome eggs in an endemic area in South Africa. Feldmeier, Helling-Giese and Poggensee (2001) reported comparably poor results. In a study population with 65% QCTB-diagnosed FGS cases only 3.9% were diagnosed by Pap smear. The anatomic location of the schistosome eggs and the procedure of the Pap smear technique explains these results. Peri-oval granulomas are located in the interface between the epithelium and the stroma layer. The Pap smear technique accesses primarily the superficial layers of the epithelium (Helling-Giese, 1996b). Furthermore, the smear analysis is complicated by the formation of cell artefacts and the varying developmental stages of the eggs. This leads to a consequent heterogeneity of presentation in the Pap smear and aggravates the diagnosis of schistosome eggs. Feldmeier, Poggensee and Helling-Giese (2001) conducted the only study in which Pap was compared with QCBT. The diagnostic test quality is characterised by an insufficient sensitivity (6.06%). Evidence indicates that Pap smear is not a valid diagnostic test for FGS.

Urine analytic techniques are inadequate to diagnose FGS. The correlation between urinary schistosomiasis and consequent egg excretion by micturition and FGS is inadequate. Egg verification by urinalysis has high false-positive and false-negative results and is characterised by low sensitivity. Although a standardised technique to collect and stain the urine samples was used by Poggensee et al. (1998), in 23% of biopsy-diagnosed FGS cases, schistosome eggs were not confirmed by urine analysis (Poggensee et al. 1998). Clinical signs of urinary tract schistosomiasis like haematuria or proteinuria can only provide indications for FGS. Gundersen et al. (1996) concluded that test results to diagnose FGS by reagent strips are not valid. A combined reagent strips index (RSI) adding proteinuria and leukocyturia could not improve the results (Poggensee et al. 1998).

The presence and verification of circulating adult worm antigens is an established diagnostic tool for different schistosomiasis species. Two antigens, the circulating anodic antigen (CAA) and the circulating cathodic antigen (CCA), are primarily used as diagnostic markers. The CAA is a negatively charged proteoglycan with an anodic migration and CCA is a polysaccharide with a

cathodic migration, both makers are excreted from the gut of the adult worms (Pereira e Siva et al., 1999). These serodiagnostic techniques are based on the verification of the specific antigens in serum or urine. The value of these serodiagnostic techniques for FGS is limited by the fact that these techniques have their limitations when it comes to distinguish between general or loco regional disease manifestations (Van Lieshout, Polderman and Deelder, 2000).

Midzi et al. (2003) assessed the diagnostic value of eosinophil cationic protein (ECP), a cytotoxic protein of eosinophil lymphocytes. ECP is elevated in helmet infections like schistosomiasis, which are associated with eosinophilia. They analysed ECP levels obtained by vaginal lavages of women living in a S. haematobium-endemic area in Zimbabwe. Any kind of genital infection in the upper and or lower reproductive tract increased the ECP levels. A correlation between the ECP level and egg density in urine samples and biopsy specimens taken could not be shown. The sensitivity of the ECP test was not higher than 35%. Therefore, they concluded a limited validity of this test to diagnose FGS. Contrary to this report, Poggensee et al. (1996) described a significant correlation between the level of ECP and the quantity of eggs in the biopsy specimens. The level of ECP in the vaginal fluid did not correlate with the number of eggs in specimens.
Indirect diagnostic methods using markers in blood serum, excreted in vaginal discharge or urine have never been used as routine diagnostic procedures for FGS. Neither ECP, a cytotoxic protein of eosinophils, neopterin - a second messenger of macrophages, nor IgA as indicator of local B-cell activation are established diagnostic tests in SSA. Factors explaining the impracticability are the need of expensive equipment, labile reagents and skilled personal in the low resource setting of SSA.

Feldmeier et al. (1981) inaugurated the quantitative fresh compressed biopsy technique (QCBT), a direct diagnostic test to diagnose FGS. This technique is primarily used to diagnose and follow-up intestinal schistosomiasis. To diagnose intestinal schistosomiasis biopsies are taken from the rectum. For the analysis the biopsy sample is placed on a slide and a drop of 1% malachite green in glycerol is added. After compression between two slides the sample is examined under a microscope with 100 x magnification. The intensity of

infection is semi-quantified by the number of eggs detected per millimetres of compressed biopsy tissue (stated by Poggensee et al., 2001). Biopsies to diagnose FGS are primarily taken from the cervix uteri. The reasons to obtain material from the cervix are that the cervix is the location in the LRT were biopsy samples can be taken with minor pain and as it is the location with the highest probability to confirm ova in the LRT (Helling-Giese et al., 1996). To date QCBT represents the gold standard for the FGS diagnosis (Poggensee et al., 2000). The biopsy is most promising when performed at the squamocolumnar junction of the cervix uteri. The likelihood to confirm FGS is increasing with the number of biopsies conducted (Poggensee and Feldmeier, 2001). Although QCTB represents the standard, a diagnosis of FGS can be missed because the eggs are positioned in focal clusters in the deeper stroma layer (Helling-Giese, 1996b). QCTB is a more sensitive and specific diagnostic procedure than the histopathological examination of formaldehyde-stored specimens (Poggensee et al., 2001). However, this method requires a gynaecological speculum examination with visualisation of vagina and cervix uteri. Furthermore, a test based on punch biopsy can cause complications such as bleeding and infections. It is questionable to use a test like this as screening test for diagnosing FGS in prevalence studies (Poggensee and Feldmeier, 2001). The major unsolved problems are the iatrogenic lacerations caused when performing the biopsy, which can favour the transmission of infections such as HIV. Because of this scenario ethical approval in FGS studies to utilise this biopsy-based technique is no longer granted (Kjetland et al., 2006).

The wet mount technique is a workaround between Pap smear and QCBT. Accessible, vulnerable lesions favourable on the vulva can be ablated by a glass slide and the sample is stained and analysed by microscope. Although it seems to be a valid method for FGS it is limited to vulva lesions (Poggensee and Feldmeier, 2001).

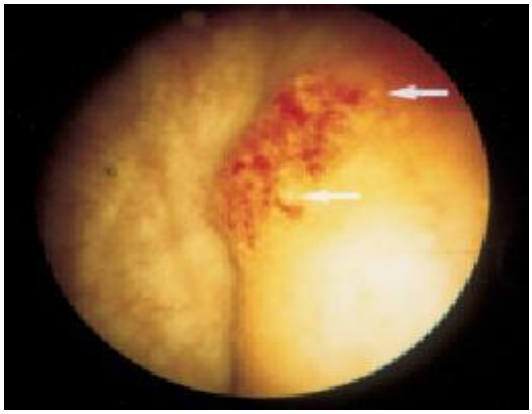
To date no reliable and valid non-invasive diagnostic test appropriate for low-resource settings is available. Diagnostic guidelines for FGS have not been established. In publications dealing with FGS no uniform diagnostic procedure is used. However, there is consensus that a valid and reliable direct diagnostic test is based on ova detection in the female genital organs (Poggensee, Feldmeier and Krantz, 1999, Helling-Giese et al., 1996b).

2.5 Colposcopy and FGS

With increased research activity in the field of FGS, colposcopy has become an integral part of the gynaecological examination for FGS (Helling-Giese et al., 1996b, Kjetland et al., 2005, Kjetland et al., 2008). The colposcope being a stereoscopic binocular field microscope with an integrated intensive light source enables the optimal visualisation of the lower genital tract under different magnifications (Sellors and Sankaranarayanan, 2003). The colposcopic evaluation of characteristic findings might help to diagnose the underlying disease. Furthermore, photo-colposcopy offers the opportunity to record the findings and estimate the reproducibility of the visual characteristics by an assessment of the pictures (Jeronimo et al., 2007). The diagnosis of FGS by disease-specific colposcopic findings is stated as an elegant non-invasive option (Kjetland et al., 2005). Furthermore, colposcopy is used to follow-up regression or progression of lesions caused by FGS after therapy (Richter et al., 1996, Kjetland et al., 2006). The stated relevance of colposcopic findings to diagnose FGS is increasing in the literature (Kjetland et al., 2006, Kjetland et al., 2008, Kjetland et al., 2008b). In current publications reporting evidence of FGS favouring HIV transmission the diagnosis of FGS is mainly based on pathognomonic, colposcopic findings (Kjetland et al., 2006, Hortez, Fenwick and Kjetland, 2009).

There is no correlation of unspecific colposcopic findings like erosion, ulceration, oedema, swelling and leukoplakia and FGS (Kjetland et al., 1996). The colposcopic finding of most interest in the context with FGS is the sandy patch (Kjetland et al., 1996; Poggensee and Feldmeier, 2001). For decades, the sandy patch has already been described as a lesion indicating FGS in the LRT. Gibson, 1925; Badaway, 1962; Youssef et al., 1970 and Friedberg et al., 1991, had reported of sandy patch lesions in the LRT and concluded that the sandy patch is a pathognomonic lesion of diagnostic relevance for genital schistosomiasis (cited in Kjetland et al., 1996). The sandy patch in the LRT is the genital equivalent of the pathognomonic finding by cystoscope in the bladder in cases with urinary schistosomiasis. The sandy patch in the bladder is a pathognomonic lesion of diagnostic relevance for urinary schistosomiasis. The statement that the presumption diagnosis of urinary schistosomiasis can be confirmed by visualisation by cystoscope of a sandy patch in the bladder makes common sense. The lesion is characterised by greyish-yellow mucosal

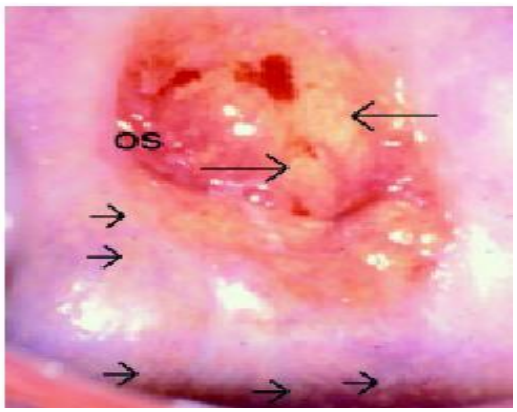
irregularities surrounded by dense fibrous tissue. Neighbouring calcifications are common, and vital and devitalised schistosome eggs are found by histopathology (Döhrig, Mand and Zimmermann, 1999).



Cystoscopic view of a hyperaemic lesion and sandy patch (bladder)

Figure 3: Cystoscopic image of a haematobium manifestation in the bladder, arrow= sandy patch area (Döhring, Mand and Zimmerman, 1999)

Although the relevance of the colposcopic finding sandy patch to diagnose FGS in the LRT is increasing, evidence of the diagnostic test quality is limited. The sandy patch of the LRT is preferentially located on the cervix uteri. Helling-Giese et al. (1996b) were the first to publish a correlation of sandy patch, colposcopic presentation and histopathology. They described the sandy patches as “slightly elevated lesions, with irregular borders, covered by a finely granular epithelium”. The characteristics of the histology are equivalent to their published type B histopathology generated by FGS (fibrous connective tissue around non-viable eggs). The colposcope provides visualisation of the sandy patch in more detail by magnification and its intensive source of illumination. Additional characteristics visualised by colposcopy like concentric vessels around the sandy patches were described as additional characteristics. Based on the observations by colposcope Kjetland et al. (2005) inaugurated a sub-classification of the sandy patch into the grainy sandy patch (GSP) and the homogeneous yellow sandy patch (HYSP).

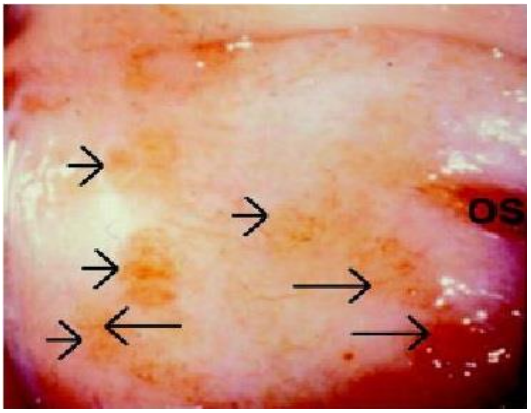


Colposcopic view of a GSP (superficial and deep) on cervix uteri

Figure 4: Superficial and deep grains on a cervix of a women positive for FGS. Long arrow= superficial GSP, short arrow= deep GSP; OS= uterine os (image from

Kjetland et al., 2005)

Kjetland et al. (2005) describe the GSP as in average 0.05 x 0.2 mm long minuscule rice-like grains positioned in clusters up to 300. These grains are positioned either deep or superficially in the mucosa. Deeply positioned GSP are covered by smooth mucosa, whereas superficial grainy patches are located within the mucosa. They emphasised that the distinction between superficial and deep grainy patch is given by the manoeuvrability and palpability of superficial grainy patches in comparison to deep grainy patch.



Colposcopic view of a homogeneous yellow patch (cervix uteri)

Figure 5: HYSP of a female with a cervix-positive FGS, short arrows= HYSP; long arrows= convoluted blood vessels; OS= uterine os (image from Kjetland et al., 2005)

HYSP is described as sandy, yellow and homogeneous areas with no distinct grains visualised under a colposcopic magnification of 15 x. A strong light source and magnification are important for the detection of sandy patches. The colposcope is an essential tool for the recognition of the sandy patch and the sub-classified GSP and HYSP. Kjetland et al., (2005) stated 39% of the sandy patches, GSP and HYSP could only be diagnosed without the aid of the magnification by colposcope. Furthermore, they stated a significant correlation of colposcopic findings like atypical neo-vascularisation, mucosa oedema and erosion with FGS (Kjetland et al., 2005). To date no manual or guidelines for the use of colposcopy as diagnostic procedure for FGS has been established.

Based on the fact that no criteria had been established, Helling-Giese et al. (1996b) recorded the colposcopic findings according to the “Manual for the Standardisation of Colposcopy for the Evaluation of Vaginally Administered Products”. This manual was developed to evaluate epithelial changes caused by intra-vaginally applied contraceptive drugs (WHO, 1995). Despite this fact, colposcopy has an increasing impact as non-invasive diagnostic procedure for

FGS. In current publications reporting on the diagnostic test quality of pathognomonic colposcopy like sandy patch for FGS is equal to egg detection procedures such as Pap smear, wet mount and biopsy combined with QCBT (Kjetland et al., 2005, Kjetland et al., 2006, Kjetland et al., 2008). In contrast to the current trend, to diagnose FGS by pathognomonic findings without confirmation by biopsy requires the colposcopic assessment for cervical intraepithelial neoplasia (CIN), a biopsy to obtain a histopathology result: The colposcopy-guided biopsy is taken from the suspect area to confirm the diagnosis (Sellors Sankaranarayanan, 2003). Therefore, the question arises whether or not colposcopy without biopsy is a valid and reliable diagnostic tool for FGS. To date there is almost no data available regarding the test quality of colposcopy to diagnose FGS. In addition, colposcopy is rarely practised in SSA and adequate information regarding the feasibility and options in a low-resource setting with its challenging working conditions are non-existent (Muwonge et al., 2009). In conclusion, there is a persisting need for clarification of the significance of the colposcopy procedure as diagnostic tool for FGS.

2.6 Treatment for FGS

Until now no specific therapy regime for FGS has been established. However, a treatment strategy for urinary and intestinal schistosomiasis is recommended by WHO (WHO, 2006). The WHO policy is based on mass treatment with praziquantel (PZQ) for the population most at risk like school children, pregnant women and those in occupations involving a high risk of contact with infested water. The focus is on morbidity control. The therapeutic regime is adjusted to the schistosomiasis prevalence of the evaluated communities and the endemic risk situation. The treatment varies from once a year in high risk communities to every two years in moderate risk communities, down to two times during the complete period of school attendance. The announced global target is a chemotherapy administration to at least 75% of all school children at risk of morbidity by 2010. The WHO-recommended dose is 40mg/kg (PZQ). The treatment of pregnant and lactating women with PZQ is recommended (WHO, 2006).

Kjetland et al. (2008b) stated evidence that treatment of school children before and during their period of education can prevent FGS lesions and their negative consequences in adulthood. They emphasise the importance of treatment

provided before the chronic lifelong lesions in the genital tract have developed. Richter et al. (1996) followed up eight women with biopsy-confirmed FGS after therapy (PZQ). The interval biopsies diagnosed persistent ova only in three cases. Although the study was limited by the small study population they claimed evidence that FGS-induced lesions decrease after drug therapy. In contrast, Kjetland et al. (2008) did not describe a reduction of established colposcopic findings like sandy patches in a study conducted over a 12-months period in Zimbabwe.

Drug treatment before the age of 13 years might offer the best opportunity to prevent FGS lesions in the female LRT. Women who are treated before this age might have lower rates of FGS-induced lesions and their subsequent complications. Adapted to the general policy the actual strategies for FGS are favouring the treatment of young females to prevent genital lesions. Hortez, Fenwick and Kjetland (2009) claimed evidence that this strategy to prevent FGS-induced lesions reduces the increased susceptibility for HIV transmission.

3. Study aims and objectives

The overall objective was to assess the diagnostic test quality of photo-colposcopic/colposcopic findings for FGS in endemic areas of SSA. There are two main study objectives. The first main objective is to evaluate the results of photo-colposcopy findings and to assess the validity to diagnose FGS in a study population of an FGS endemic area in Northern Tanzania. The study results can be exclusively compared with the diagnostic gold standard QCTB. In addition, there were two sub-objectives of the first main objective:

- To evaluate photo-colposcopic findings of a study population from an FGS endemic area in Tanzania (SSA) and compare the results with the available literature to identify consistencies and differences.
- To assess the validity of photo-colposcopic/colposcopic findings and our developed colposcopic criteria (normal and abnormal/suspect) to diagnose FGS and compare them with the literature.

The second main objective was to analyse the validity of the stated pathognomonic colposcopic findings to diagnose FGS by a critical review of the available literature. The respective two sub-objectives are:

- To re-evaluate the published data about the test validity of colposcopic findings by sensitivity and specificity analysis together with an estimation of the positive and negative predictive value
- To compare the stated pathognomonic findings for the diagnosis of FGS by colposcope with the pre-existing nomenclature and its recommended use defined by the “International Federation of Cervical Pathology and Colposcopy” (IFCPC)

4. Methods

The study design is based on a twofold study approach. The first step is an analysis of photo-colposcopic images obtained in a cross-sectional survey carried out in an S. haematobium and S. mansoni endemic area in northern Tanzania. The second step is a critical review of the existing literature on colposcopy and FGS in SSA.

4.1 Tanzania study

4.1.1 Background

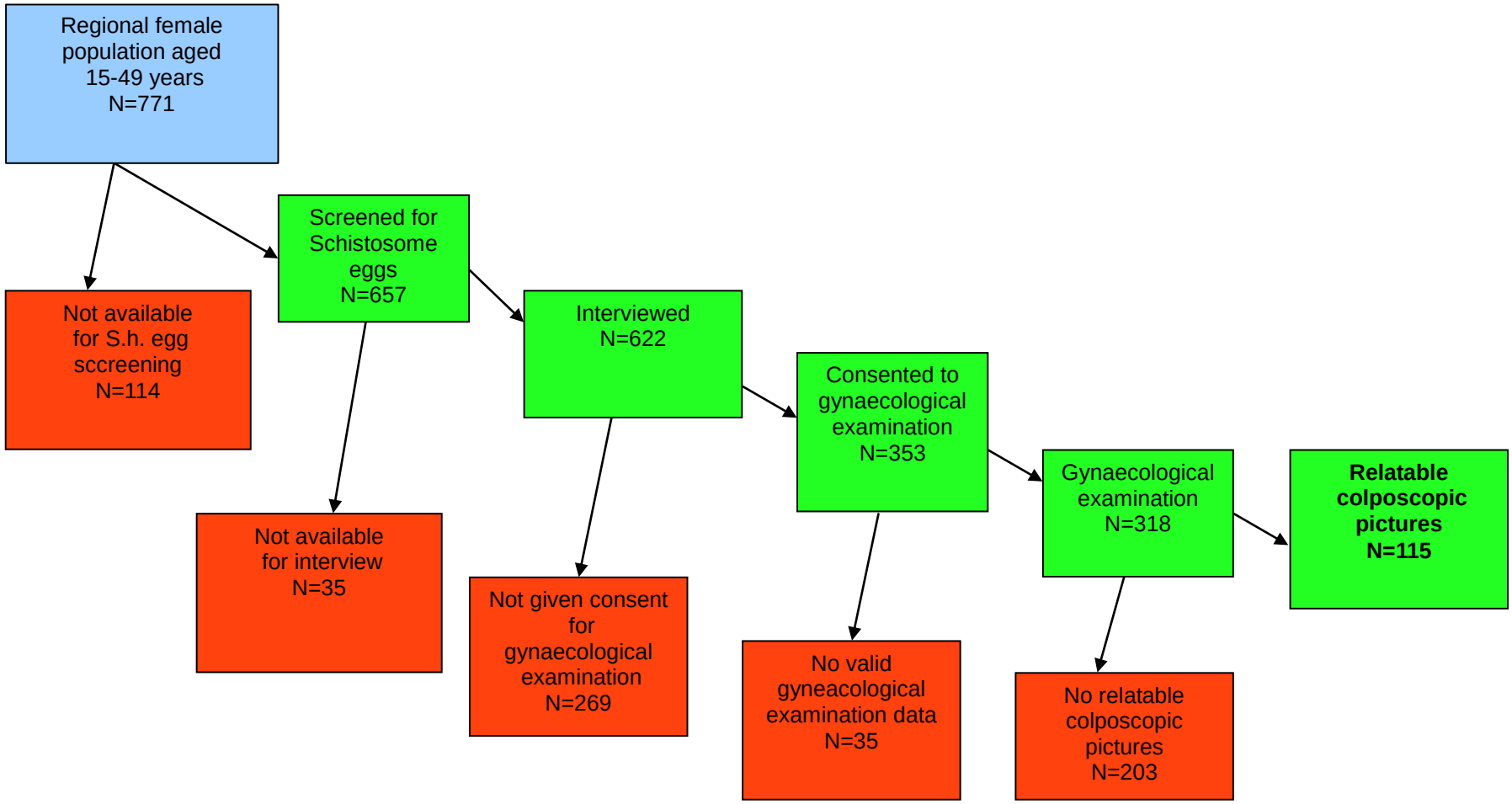
The study was carried out in two villages (Kileo and Kivulini) in the Mwanga District in Northern Tanzania between October 1996 and January 1997 (Poggensee, 2002). The initial study aim was to investigate the prevalence of FGS and to analyse the consequences of S. haematobium and S. mansoni in an endemic area in SSA. All women of the two villages aged 15 to 45 (n= 771) excluding virgins and pregnant women were asked to participate in the study. 657 (87%) of the women were screened for schistosome eggs by urinalysis. To increase the sensitivity urine samples were screened on three consecutive days. 622 (81%) of the women were interviewed with the aid of standardised questionnaire regarding their medical and reproductive health history, socio-demographic background and water contact situation (annex 9.1). 353 women (47%) consented to a complete gynaecological examination. The gynaecological examination included inspection of the vulva, visualisation of vagina and cervix uteri by speculum and bi-manual palpation of the lower abdomen. If feasible, the colposcopic procedure included photo-documentation, a Pap and a routine punch biopsy from the squamocolumnar junction of the cervix uteri. The biopsy was used for QCBT and in some cases for additional histological examination. The routine application of 3%-5% diluted acetic acid and lugol's iodine solution was not an essential part of the study protocol.

This study protocol guaranties that all photo-colposcopic findings can be compared to the gold standard diagnostic procedure: FGS by QCTB. This approach is unique and has never been undertaken at any time. A systematic evaluation of the photo-colposcopic findings and FGS has never been done before.

4.1.2 Study population

Among the 353 women who had a gynaecological examination in the cross-sectional study, data were available for retrospective analysis of 318 (90.08%) and relatable photo-colposcopy images of 115 (32.57%) women. Women for whom photo-colposcopic images were available are named “study group” (N=115) and women without photo documentation of the colposcopy are named “referent group” (N=203).

Figure 6: Available study population for photo-colposcopic evaluation



4.1.3 Colposcopy and classification criteria for the photo documentation

The used colposcope had the option of two magnifications (7.5x and 15x) for the photo-colposcopy (Leisegang Photocolposcope; Leisegang Feinmechanik-Optik GmbH, Berlin, Germany). Regardless of suspect colposcopic findings for FGS a cervix biopsy was performed whenever feasible. The results were documented in a standardised form. For the thesis work all available and relatable pictures are scanned and digitalised. Due to the fact that no established colposcopy score to diagnose FGS is available, the evaluation categories for the study photo-coloposcopy analysis are consistent with the finding classification and colposcopy terminology of 2002 (Barcelona Score 2002) as set out by the "International Federation for Cervix Pathology and Colposcopy" (Walker et al., 2003). Additional criteria for the categories were taken from the "Manual for the Standardisation of Colposcopy for the Evaluation of Vaginal Products" (WHO and CONRAD, 2004) and from the manual "Colposcopy and Treatment of Cervical Intra-epithelial Neoplasia" (Sellors and Sankaranarayanan, 2003). For the sandy patch and the sub-classified GSP and HYSP the definition for these findings inaugurated by Kjetland et al. (2005) was used.

Three categories were used to evaluate the photo-colposcopic findings: normal, abnormal/suspect and unsatisfactory. Abnormal/suspect photo-colposcopic findings were categorised as (2.1) suspect feature on the cervix; (2.2) atypical vascular pattern; (2.3) disrupted status of epithelium and tumour formation; (2.4) inflammatory lesions of the cervix; (2.5) sandy patch (any type). Appropriate to the 2002 IFCPC classification (Barcelona Score), abnormal findings include the criteria for minor and major changes of the epithelium and suspect findings were considered suggestive for invasive cancer (Walker et al., 2003). Images were categorised as normal if none of the aforementioned criteria applied. The photo-colposcopy was termed unsatisfactory if the cervix uteri could not be visualised was of poor quality or bloodiness or major mucus contamination were present. Images taken by unsatisfactory colposcopy were excluded from the evaluation.

Table 2

Classification criteria for the evaluation of the photo-colposcopic findings

1. Normal photo-colposcopic findings: no suspicion of FGS	2. Abnormal/suspect photo-colposcopic findings: suspicion of FGS or other co-infections or neoplasia (co-infections+FGS and neoplasia+FGS)	3. Unsatisfactory photo-colposcopy: basic prerequisite to evaluate the image is not fulfilled
1.1 Original squamous epithelium, columnar epithelium, normal transformation zone (TZ) (b)	2.1 Suspect feature on cervix: coarse punctation/mosaik, suspect surface (a)	3.1 Cervix uteri not visible (b) (not accessible)
1.2 Normal vascular pattern: regular vascular network, regular branching vascular tree (a), (annex 9.2)	2.2 Atypical vascular pattern: corkscrew, tree-like and bizarre branching vessels (a) (annex 9.3), colposcopic feature suggestive of invasive cancer (b)	3.2 Poor/unsatisfactory quality of image, bloodiness, major mucus contamination (not accessible)
1.3 Benign miscellaneous findings: nabothian cyst, ectopy, polyp (a)	2.3 Disrupted status of epithelium: ulceration, erosion, leukoplakia, condylomata (a)	
1.4 Intact status of epithelium (c)	2.4 Inflammatory lesions of the cervix: inflammatory punctation/vascular congestion/ulceration not restricted to the TZ (a)	
	2.5 sandy patches of any type: homogeneous yellow sandy patches and/or grainy sandy patches (superficial and/or deep) (d)	

a. Sellors and Sankaranarayanan (2003), b. Walker et al., (2003), c. WHO and CONRAD, (2004), d. Kjetland et al., (2005)

The selected categories to evaluate the photo-colposcopic findings include the essential criteria, which were used to define normal and abnormal/suspect colposcopic findings in the literature. The main focus was on clinical presentation of the squamous and columnar epithelium surface, vascular pattern, general signs of cervical inflammation and on colposcopic findings suspect for invasive cancer (Sellors and Sankaranarayanan, 2003, WHO and CONRAD, 2004, Walker et al., 2003). The definition for the sandy patch and the sub-classified grainy sandy patch (GSP) and homogeneous yellow sandy patch

(HYSP) is based on the definition inaugurated by Kjetland et al., (2005) and Helling-Giese et al., (1996b). Because of the small study population HYSP and GSP were pooled in the criteria 2.5. For the additional data analysis a sub-classification into GSP and HYSP was used. The criteria stated by Kjetland et al. (2005) to palpate potential grains on the cervix for differentiation between deep and superficial GSP is not practicable in a photo-colposcopic assessment. As consequence a sub-classification into deep and superficial GSP was not feasible. Furthermore, due to the limited image resolution and the size of the grains (0.186 mm) a retrospective measurements of the grains demonstrated in the images was technically impossible by our approach. Therefore, we decided to refrain from this option stated by Kjetland et al. (2005).

After identification of the patient, the first step was the quality assessment of the image. Unsatisfactory images had to be excluded. Once the prerequisite was assured, the aforementioned criteria of the categories for the assessment were systematically prompted and the images were matched with the appropriate criteria of the categories. Any abnormal/suspect findings were termed as the main criterion, whereby any additional criteria could also be matched. The major normal criterion was ranked as main criterion if only normal findings were present. This process permits matching of each image with one main and a maximum of 5 additional criteria. The following figures exemplify the criteria used to evaluate the images of our study:

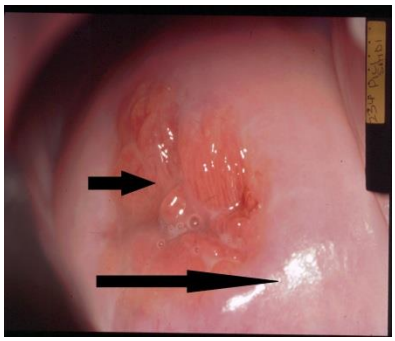


Figure 7
image (FGS-) with good quality, the cervix is in the centre, original squamous epithelium and columnar epithelium and normal transformation zone (long arrow, criteria 11) and ectopy (short arrow, criteria 13) with clearly visible squamocolumnar junction is presented (Tanzania study population, Poggensee, personal data)

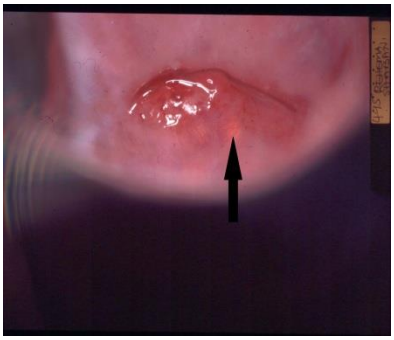


Figure 8

image (FGS-) with a benign miscellaneous finding of two nabothian cysts (arrow, criteria 13) and normal vascular pattern of a regular vascular network (arrow, criteria 12) (Tanzania study population, Poggensee, personal data)

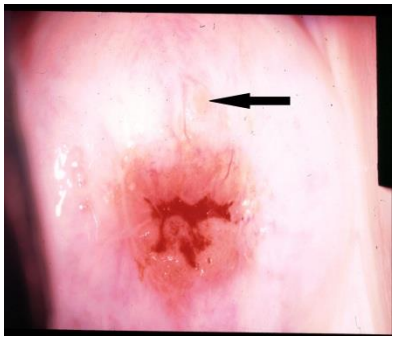


Figure 9

image (FGS+) with homogeneous yellow sandy patch (arrow), distinct fine, branching vessels (normal vascular pattern) and intact epithelium (Poggensee, personal data)

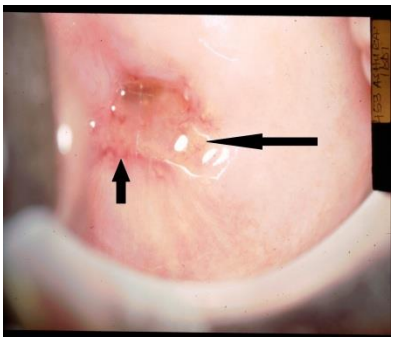


Figure 10

image (FGS+) with HYSP (long arrow) and prominent normal arborizing vessels (short arrow), the squamocolumnar junction is at the uterine os (Poggensee personal data)

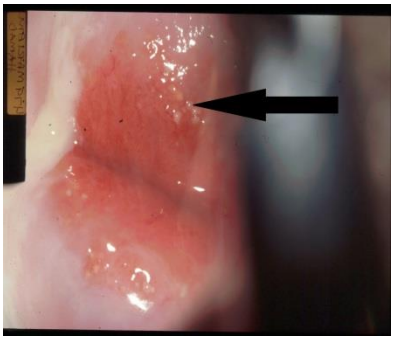


Figure 11

image (FGS+) with ectropion on the anterior and posterior lips of the cervix, GSP (arrow) and normal vascular pattern (Poggensee, personal data)

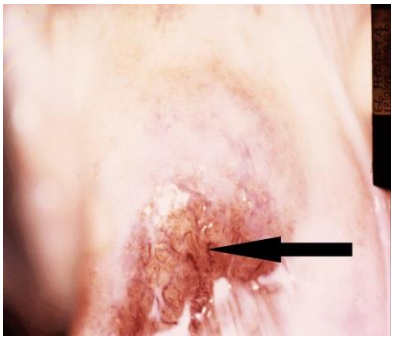


Figure 12

image (FGS+) with atypical vascular pattern (arrow) on the anterior lip of the cervix (Poggensee, personal data)

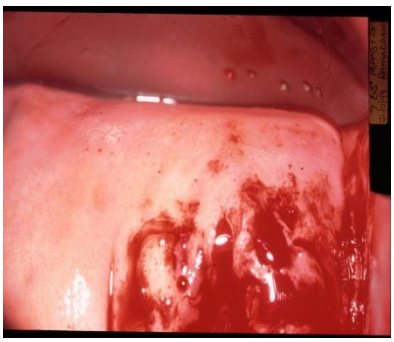


Figure 13
unsatisfactory image, invisible cervix and bloodiness, no evaluation is possible (Poggensee personal data)

The evaluated colposcopic criteria were documented in an Excel sheet and statistically evaluated. As a result of this the diagnostic test quality of photo-colposcopic/colposcopic findings were assessed. Furthermore, a comparison of the available study population (N=115) was made with a view to reproductive health, socio-demographic aspects and QCTB results; included in this comparison were all females who had been examined without relatable photo-colposcopic images (N=203). The evaluated colposcopic findings and the reproductive/clinical health data taken from the questionnaire was used to compare the study population with satisfactory and relatable images (N=106). The results are discussed with the available literature on colposcopy and FGS.

4.2 Literature review - description and criteria

The second step of our study was a critical review of the existing literature on colposcopy to diagnose FGS. Wherever possible, sensitivity and specificity analysis together with an estimation of positive and negative predictive values for the disease were performed using the published data.

4.2.1 Identification of existing literature

To identify the published literature on FGS and coloposcopy a systematic literature review was performed. The literature review was conducted using the data base PubMed [accessed online 15 December 2009]. “MeSH is the U.S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/PubMed” (U.S. National Library of Medicine, 2009). MeSH terms was used to build a literature search strategy to retrieve scientific articles dealing with medical concepts and information.

The search was done using the following MeSH terms: schistosomiasis including the subheadings classification, complications, diagnosis, aetiology, pathology,

physiology and colposcopy using the used subheadings: classification, contraindication, methods.

The used search terms are:
("Schistosomiasis"[Mesh] AND ("Schistosomiasis/classification"[Mesh] OR "Schistosomiasis/complications"[Mesh] OR "Schistosomiasis/diagnosis"[Mesh] OR "Schistosomiasis/aetiology"[Mesh] OR "Schistosomiasis/pathology"[Mesh] OR "Schistosomiasis/physiology"[Mesh])) AND ("Colposcopy/classification"[Mesh] OR "Colposcopy/contraindications"[Mesh] OR "Colposcopy/methods"[Mesh]).
With this search strategy only one result was obtained. Therefore, a different search strategy was applied. In the second literature search only keywords were used to identify relevant articles. The PubMed database was searched by using the keywords: female genital schistosomiasis, colposcopy and sandy patch.

The search for female genital schistosomiasis yielded 251 results, and in combination with the keyword colposcopy only 9 results were found. In order to identify all relevant literature for the aforementioned objectives it was necessary to review all available 251 abstracts found in the first keyword search. The literature was selected using the following selection criteria: geographic region (SSA), gained data under study condition, colposcopic examination included in the study protocol, integration of an egg detection procedure to diagnose FGS.

4.2.2 Comparison of colposcopic criteria

Colposcopy criteria to identify FGS like neo-vascularisation, contact bleeding, pre-contact bleeding, leukoplakia, sandy patch, GSP and HYSP found by literature research were compared with the pre-existing nomenclature by the “International Federation of Cervical Pathology and Colposcopy” (IFCPC) and its recommended use (Walker et al., 2003).

4.3 Sensitivity and specificity analysis and other statistical procedures

All statistical analyses were performed using the statistical software STATA 10.0 (StataCorp. 2007). Sensitivity and specificity analyses and the estimation of predictive values for FGS were being performed using the optional Stata procedure "diagti". Sensitivity and specificity are commonly used to assess the clinical validity of a diagnostic test. In general, a new test method to identify a

disease was compared to a gold standard test method. Sensitivity was defined as the proportion of correctly identified patients with a given disease. The specificity was defined as the proportion of healthy patients identified by the test. The positive predictive value shows the probability of patients tested positive having truly the disease. The negative predictive value shows the probability of patients tested negative, who are truly healthy. In the following study data derived by literature research data from the original study were also used to calculate sensitivity, specificity, positive and negative predictive value (Geordis, 2004, p. 71-94). These different diagnostic criteria were compared to different test measures. Categorical variables were compared by using the chi-square test. Instead of chi squared-test Fisher's exact test was applied when expected cell counts were smaller than 1.

4.4 Ethical consideration

The data set used was from the community cross-sectional survey carried out between October 1996 and January 1997 in Tanzania. The study protocol was approved by the Research and Ethical Committee of the Kilimanjaro Christian Medical Centre. The authorisation was confirmed by the local authorities (Regional Medical Officer, Kilimanjaro Region, Moshi). The basic prerequisite for participation was informed consent. The local languages (Kiswahili and Kipare) were used for all explanations. Colposcopy with photodocumentation was an inherent part of the informed consent (Poggensee, 2002). Ethical clearance for our thesis in Tanzania or any clearance by ethical commission of the Charité was not necessary. The source for this secondary data analysis was project-approved. All data were used anonymous in order to protect the privacy of the patients. The performed literature research includes aggregated data already published without any personal data, therefore ethical approval was unnecessary.

5. Results

5.1 Tanzanian study: socio-demographic and reproductive/clinical health data (questionnaire based)

The following tables present the socio-demographic and reproductive/clinical health data of the Tanzanian study population with gynaecological examination: study group and referent group. Furthermore FGS negative and FGS positive women of the study group are compared with this data. The used data is taken from the standardized questionnaire (annex 9.1) and statistically evaluated.

Table 3 shows the differences in socio-demographic variables (age and living children) and FGS status (QCBT diagnosed) and diagnosed urinary schistosomiasis (ova detected by urine analysis) in the study participants (study group and referent group). Totally, the proportion of positive FGS cases (verified by QCTB) is 34.3%. 42.6% of the study group and 29.6% of the referent group are FGS positive. The difference between both groups is significant.

Table 3: Basis socio-demographic data and status of urinary tract schistosomiasis and FGS (study and referent group); Tanzanian study

socio-demographic and status of urinary schistosomiasis/FGS	referent group (N=203)	study group (N=115)	P-value of difference between samples	samples combined / total sample (N=318)
Age mean (S.E., 95% CI) N	31.14 (0.61; 29.94 – 32.35) N=203	33.09 (0.91; 31.29 – 34.88) N=114	0.069	31.84 (0.51; 30.83 – 32.85) N=317
number of living children mean (S.E., 95% CI) N	3.47 (0.22, 3.03 -3.91) N=146	3.96 (0.29; 3.38 – 4.54) N=72	0.200	3.63 (0.18; 3.28 – 3.98) N=218
FGS diagnosis with QCTB % of positive cases(S.E.; 95% CI) N	29.56 (0.03; 23.37 – 36.35) N=203	42.61 (0.05; 33.43 – 52.17) N=115	0.018*	34.27 (0.03; 29.07 – 39.78) N=318
Schistosoma haematobium ova in urine % of positive cases(S.E.; 95% CI) N	43.28 (0.03; 36.32 – 50.44) N=201	39.47 (0.05; 30.44 – 49.06) N=115	0.510	41.90 (0.03; 36.40 – 47.57) N=315

S.E. = standard error, 95% CI = 95% confidence interval; N = in the column gives the number of valid data for the respective cell of the table; * $p<0.05$

Table 4 shows data about self-reported gynaecological problems during the lifetime. The most common lifetime gynaecological problem was vaginal discharge followed by menstrual problems. Dysuria was the third most common condition.

Table 4: Self reported data about lifetime gynaecological problems and urinary tract related problems of FGS positive and FGS negative women (study group); Tanzanian study

lifetime gynaecological problems	**FGS negative** Freq., %, N	**FGS positive** Freq., %,N	**Total** Freq., %,N*
Miscarriage	1 2.44 41	2 5.71 35	3 3.95 76
menstrual problems (dysmenorrhoea)	21 56.76 37	12 42.86 28	33 50.77 65
post-coital bleeding	8 19.51 41	3 8.57 35	11 14.47 76
lower abdominal pain	18 45.00 41	11 31.43 35	29 38.67 76
Dysuria	16 39.02 41	16 45.71 35	32 42.11 76
Haematuria	3 7.32 41	4 11.43 35	7 9.21 76
vaginal discharge	19 51.35 41	18 48.65 35	37 48.68 76

*N is smaller than 115 due to missing information

Table 5 shows results (study group) of the self-reported gynaecological and other physical problems during the 14 days prior to the gynaecological examination. Because of missing data the number of women (N,%) is differing for the evaluated aspects. The most commonly reported physical problem was backache followed by low abdominal pain. The most common gynaecological problem was vaginal discharge and urinary tract related problem dysuria.

Table 5: Self reported data about gynaecological and other physical problems during the last 14 days before the gynaecological examination of the study group; Tanzanian study

gynaecological and other physical problems during the last 14 days	**FGS negative** Freq., %, N	**FGS positive** Freq., %,N	**Total** Freq., %,N*
post-coital bleeding	8 19.51 41	5 14.71 34	13 17.33 75
Backache	30 73.17 41	26 74.29 35	56 73.68 76
Diarrhoea	0 0.00 41	3 8.57 35	3 3.95 76
low abdominal pain	30 73.17 41	25 71.43 35	55 72.37 76
Dysuria	16 39.02 41	15 42.86 35	31 40.79 76
Haematuria	4 10.00 40	1 2.86 35	5 6.67 75
vaginal discharge	18 43.90 41	14 40.00 35	32 42.11 76

* Due to missing data the sample is smaller than N=115

Table 6 shows the results of the gynaecological examination by FGS status (study group). Cervical discharge (different qualities) was most often observed (FGS neg. and FGS pos.). Slightly less common was vaginal discharge related to STDs. It was diagnosed in 59 women (56.7% of total; FGS neg. = 56.67%; FGS pos. = 56.8%).

Table 6: Table 6: Gynaecological examination results and FGS status of the study group (N=115); Tanzanian study

gynaecological examination result	**FGS negative** Freq., %, N	**FGS positive** Freq., %,N	**Total** Freq., %,N*
vaginal discharge (any kind, including physiological discharge)	50 75.76 66	43 87.76 49	93 80.87 115
cervical discharge (any kind, including physiological discharge)	60 90.91 66	45 93.75 48	105 92.11 114
tentative STD-Ulcer	0 0.00 61	0 0.00 45	0 0.00 106
tentative STD-lymphadenopathy	0 0.00 59	0 0.00 45	0 0.00 104
**tentative STD-discharge (different kinds)	34 56.67 60	25 56.82 44	59 56.73 104

*Due to missing data the sample is sometimes smaller than N=115

**Tentative STD-discharge (dis.) included: cervical dis. yellow: gonorrhoea; mucopurulent dis.: chlamydia; greenish dis.: trichomoniasis; fish smell dis.: bacterial vaginosis; whitish, curdled, milk like dis.: candidiasis

5.3 Tanzanian study: assessment of the photo-colposcopic findings of the study group

From the study group (N=115), 9 women presented unsatisfactory colposcopic images (category 3) and had to be excluded from the following evaluation. A total of 106 women were classified by evaluable pictures and data can be presented. All evaluated results of the image evaluation can be compared with the reference test to diagnose FGS: QCBT.

Table 7 shows the results of the evaluation of photo-colposcopic findings by defined classification criteria of the category 1 and 2 (table 2). For the association between a single classification criteria and FGS status a chi squared test was performed, which means the association between the respective class and FGS was tested against FGS status of the combined other criteria. In all cases where any of the expected cell counts for these 2x2 tables were smaller than 1, Fischer exact test was applied. This was true for the criteria 1.4, 2.1, 2.3. In addition an overall chi-square test was performed to test the general association between photo-colposcopic criteria and FGS status. Only criteria 2.5 had a significant association to positive FGS status.

Table 7: Photo-colposcopic classification (evaluated main criteria) and FGS status (detailed) (study group)*; Tanzanian study

photo-colposcopic criteria	**FGS negative** Number of cases, %	**FGS positive** Number of cases, %	**Total** Number of cases, %	**Chi ^{2} / Fisher's exact** p value
1.1 (normal epithelium/TZ) number of cases column % row %	 29 49.15 64.44	 16 34.04 35.56	 45 42.45 100.00	 0.118
1.2 (normal vascular pattern) number of cases column % row %	 1 1.69 50.00	 1 2.13 50.00	 2 1.89 100.00	 0.871
1.3 (benign miscellaneous findings) number of cases column % row %	 21 35.59 63.64	 12 25.53 36.36	 33 31.13 100.00	 0.266
1.4 (intact status of epithelium) number of cases column % row %	 1 1.69 100.00	 0 0.00 0.00	 1 0.94 100.00	 1.000**
2.1 (abnormal feature on cervix) number of cases	 0	 1	 1	

column % row %	0.00 0.00	2.13 100.00	0.94 100.00	0.443**
2.2 (abnormal vascular pattern) number of cases column % row %	 0 0.00 0.00	 2 4.26 100.00	 2 1.89 100.00	 0.110
2.3 (disrupted status of epithelium and tumour formation) number of cases column % row %	 1 1.69 100.00	 0 0.00 0.00	 1 0.94 100.00	 1.000**
2.4 (inflammatory lesions of the cervix) number of cases column % row %	 3 5.08 42.86	 4 8.51 57.14	 7 6.60 100.00	 0.480
2.5 sandy patch (GSP and or HYSP) number of cases column % row %	 3 5.08 21.43	 11 23.40 78.57	 14 13.21 100.00	 0.006
total number of cases column % row %	59 100.00 55.66	47 100.00 44.34	106 100.00 100.00	 0.064

* Due to not assessable pictures only 106 cases were classified
** In all cases where any of the expected cell counts for 2x2 tables were smaller than 1, Fisher's exact test was applied

Figure 14 shows the distribution of the diagnosed sandy patches (any type) (N=14), Tanzanian study. All 6 of 6 diagnosed grainy sandy patches, 3 of 5 homogeneous yellow patches and 2 of 3 grainy and homogeneous yellow sandy patches were positive for FGS.

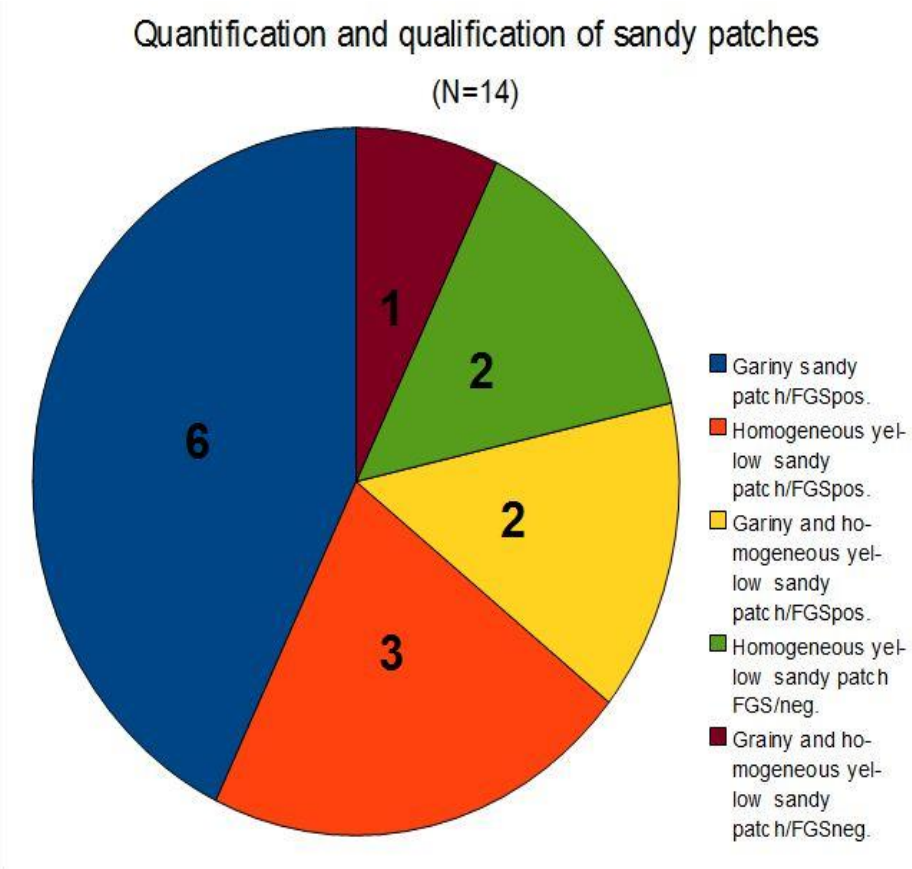


Table 8 shows the results of the evaluation by the pooled classification criteria (category 1: normal and category 2: suspect/abnormal) of the photo-colposcopic findings (table 2). A total of 47 cases were tested FGS-positive giving a sample prevalence of 44.3 %.

Table 8: Photo-colposcopic classification (pooled criteria) and FGS status (study group)*; Tanzanian study

Photo-colposcopic classification (1 + 2)	**FGS negative**	**FGS positive**	**Total**
normal criteria (category 1)			
number of cases	52	29	81
column %	88.14	61.70	76.42
row %	64.20	35.80	100.00
abnormal/suspect criteria (category 2)			
number of cases	7	18	25
column %	11.86	38.30	23.58
row %	28.00	72.00	100.00
Total	59	47	106
	100.00	100.00	100.00
	55.66	44.34	100.00

* Due to not assessable pictures only 106 cases were classified

Table 8a shows the results for the pooled photo-colposcopic classification criteria (category 2: abnormal/suspect) as test indicator for FGS compared to QCBT. The sensitivity is 38.3% [(18/47)*100] and the specificity is 88.1% [(52/59)*100]. The positive predictive value is 72.0% [(18/25)*100], that means the proportion of test positives, who were tested positive by the QCBT test. The negative predictive value is 64.2% [(52/81)*100], meaning the proportion of test negatives (normal finding) who have a negative QCBT test result.

Table 8a: Sensitivity, specificity, and predictive values using the pooled photo-colposcopic criteria (abnormal/suspect) as test for FGS status against QCBT result (study group); Tanzanian study.

	photo-colposcopic finding							
FGS status diagnosed with QCBT	Normal findings (-)	abnormal/suspect findings (+)	total	prevalence Pr(A)	sensitivity Pr(+|P)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	52	7	59					
FGS positive (P)	29	18	47	44.34 %	38.3%	88.1%	72.0%	64.2%
total	81	25	106					

Table 8b shows the results of the sensitivity, specificity and predictive value analysis for the sandy patches (any type) diagnosed by photo-colposcopy, as test indicators for FGS compared to QCBT. The sensitivity of the test is 23.4% [(11/47)*100] and the specificity is 94.4% [(56/59)*100]. Positive predictive value is 78.6% [(11/14)*100] and the negative predictive value for sandy patches as test for FGS is 60.9% [(56/92)*100].

Table 8b: Sensitivity, specificity, and predictive values using the photo-colposcopic finding sandy patch (any type) as test for FGS status against the QCBT result (study group); Tanzanian study.

	photo-colposcopic finding							
FGS status diagnosed with QCBT	other findings (-)	sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	Positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	56	3	59	44.34 %	23.4%	94.9%	78.6%	60.9%
FGS positive (P)	36	11	47					
Total	92	14	106					

5.3 Literature review: assessment of the diagnostic validity of stated pathognomonic colposcopic findings for FGS

The literature research revealed only three studies presenting primary data on FGS and colposcopy in SSA. The studies were conducted in Malawi (Kjetland et al., 1996; Helling-Giese et al., 1996), Tanzania (Poggensee et al., 2001) and Zimbabwe (Kjetland et al., 2005) between 1994 and 1999. The published data from the Malawi and Zimbabwean study are re-evaluated regarding the test validity of stated pathognomic colposcopic findings to diagnose FGS. Sensitivity and specificity analysis, together with an estimation of the positive and negative predictive value, are performed whenever possible. The data from the Tanzanian study have to be excluded from the re-evaluation as they are already used for our photo-colposcopic assessment.

Table 9 shows the re-evaluated data published by Kjetland et al. (2005). The results are based on the colposcopic finding GSP as diagnostic test for FGS. The results have to be compared to different diagnostic test for FGS used. The reference test procedures are direct diagnostic tests like Pap smear; wet mount smear and in selected cases biopsy specimens. The diagnosed prevalence of FGS is related to the reference test and ranging from a low of 19.4% [(7/36)*100] (reference ova by genital biopsy) to a high of 51.6% [(28/39)*100) (reference ova in wet mount).

Table 9 Sensitivity, specificity, and predictive values on colposcopic finding grainy sandy patch as test for FGS status against the detection of S. haematobium ova by different diagnostic procedures*; literature data

	colposcopic findings							
FGS status diagnosed with S.h. ova in pap smear	other findings** (-)	grainy sandy patch (+)	total	Prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	318	9	327	31.2%	12.2%	97.2%	66.7%	71.0%
FGS positive (P)	130	18	148					
Total	448	27	475					
	colposcopic findings							
FGS status diagnosed with S.h. ova in wet mount	other findings** (-)	grainy sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	35	11	46	51.6%	57.1%	76.1%	71.8%	62.5%
FGS positive (P)	21	28	49					
total	56	39	95					
	colposcopic findings							
FGS status diagnosed with S.h. ova in genital biopsy	other findings* (-)	grainy sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	16	13	29	19.4%	85.7%	55.2%s	31.6%	94.1%
FGS positive (P)	1	6	7					
total	17	19	36					
	colposcopic findings							
FGS status diagnosed with S.h. ova in any genital specimens	other findings** (-)	grainy sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	311	30	341	30.7%	30.5%	91.2%	60.5%	74.8%
FGS positive (P)	105	46	151					
Total	414	76	492					

* Data from Kjetland et al. (2005), table 3, page 315, **other colposcopic findings: grainy sandy patches excluded

Table 10 shows additional results based on the publication by Kjetland et al., 2005. Homogeneous yellow sandy patch was used as test indicator for FGS and Herpes simplex-type 2, respectively. Prevalence of FGS is related to the used reference tests, ranging from a low of 28.2% [(134/475)*100] (reference ova in Pap smear) to a high of 70.7% [(65/92)*100] (reference ova in wet mount). The prevalence of herpes simplex was 27.9% [(133/476)*100] diagnosed by laboratory test.

Table 10 Sensitivity, specificity, and predictive values on the colposcopic finding HYSP as test for FGS status against the finding of S. haematobium ova in different egg detection procedures* and HYSP as test for HSV-2 against laboratory test; literature data

	Colposcopic findings							
FGS status diagnosed with S.h. Ova in pap smear	Other findings** (-)	homogeneous yellow sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	328	13	341	28.2%	10.4%	96.2%	51.9%	73.2%
FGS positive (P)	120	14	134					
Total	448	27	475					

	Colposcopic findings							
FGS status diagnosed with S.h. ova in wet mount	other findings** (-)	homogeneous yellow sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	24	3	27	70.7%	50.8%	88.9%	91.7%	42.9%
FGS positive (P)	32	33	65					
Total	56	36	92					

	Colposcopic findings							
FGS status diagnosed with S.h. ova in genital biopsy	other findings* (-)	homogeneous yellow sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	12	13	25	30.6%	54.5%	48.0%	31.6%	70.6%
FGS positive (P)	5	6	11					
Total	17	19	36					

	colposcopic findings							
FGS status diagnosed with S.h. ova in any genital specimens	other findings** (-)	homogeneous yellow sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	319	28	347	29.2%	33.6%	91.9%	63.2%	77.1%
FGS positive (P)	95	48	143					
Total	414	76	490					

	colposcopic findings							
Herpes simplex virus type 2 laboratory test	other findings** (-)	homogeneous yellow sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
H. simplex negative (N)	132	211	343	27.9%	72.2%	38.5%	31.3%	78.1%
H. simplex positive (P)	37	96	133					
Total	169	307	476					

* Data from Kjetland et al. (2005), table 4, page 315
**other colposcopic findings excluding Homogeneous yellow sandy patches

Table 11 shows the re-evaluated results of the sensitivity, specificity and predictive value analysis for sandy patch (not sub-classified) and papillomatous/polypous tumor to diagnose FGS. The results are based on data published by Helling-Giese et al. (1996). The prevalence of FGS diagnosed by QBTC is 61.1%.

Table 11 Sensitivity, specificity, and predictive values using literature data on the colposcopic findings (sandy patch or papillomatous/polypous tumour) as test for FGS status against the finding of S. haematobium (S.h.) ova in QCTB*; literature data

	colposcopic findings							
FGS status diagnosed by QCTB	other findings** (-)	sandy patch (+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	negative predictive value Pr (N|-)
FGS negative (N)	21	0	21	61.1%	27.3%	100.0%	100.0%	46.7%
FGS positive (P)	24	9	33					
Total	45	9	54					
	colposcopic findings							
FGS status diagnosed by QCTB	Other findings*** (-)	papillomatous/ polypous tumour(+)	total	prevalence Pr(P)	sensitivity Pr(+|N)	specificity Pr(-|N)	positive predictive value Pr (P|+)	Negative predictive value Pr (N|-)
FGS negative (N)	8	13	21	61.1%	60.6%	38.1%	60.6%	38.1%
FGS positive (P)	13	20	33					
Total	21	33	54					

* Data from Helling-Giese et al., (1996), table 1, page 260
** Other colposcopic findings excluding sandy patches
*** Other colposcopic findings excluding Papillomatous/polypous

6. Discussion

The questionnaire data of the Tanzanian study population (study group and reference group) does not reflect significant differences in sociodemographic and reproductive/clinical health data. The higher FGS prevalence in the study group can be explained by the higher quality of the gynaecological examination leading to relatable photo-colposcopic images and sufficient biopsies. The pathognomonic colposcopic finding indicating FGS are SP and GSP in our study group. Literature data confirm this conclusion. However, any colposcopic findings can be diagnosed in FGS-positive and FGS-negative patients and none of our considered classification criteria of colposcopic findings can exclude the probability of FGS in our study group. SP and GSP do not have such a constant and characteristic presentation as stated in the literature. The findings indicating FGS rather resemble chronic post-infectious lesions of variant morphology and size. The sensitivity of colposcopic findings indicating FGS is not sufficient, although specificity, positive predictive value and negative predictive values are excellent in our study group. The re-evaluated published data obtained by literature research confirmed this result. The test validity of colposcopic findings to diagnose FGS is limited by bacterial community, specific and unspecific genital infections, hormone-dependent changes, pregnancy and physiologic/pathological changes of the LRT. There are no consistent criteria of colposcopic findings published indicating FGS. Nomenclature and standardized colposcopy are focused on CIN. The colposcopy-guided biopsy remains essential for the diagnosis of abnormal/suspect colposcopic findings to maximise the sensitivity. The present scope of colposcopy is risk screening for FGS. A prevalence assessment of FGS based on colposcopic findings is not valid and statements regarding disease associations based on these data are limited. The development of guidelines based on a consistent terminology and coherent colposcopic criteria indicating FGS are essential prerequisites for further research concerning FGS and colposcopy based on valid and reliable data.

6.1 Comparison of the sociodemographic and reproductive/clinical health data of the Tanzanian study population with the literature

The mean age of females (N=318) who underwent a gynaecological examination with available data is 31.8. The mean age of the study group is higher (33.1 years) compared to the referent group (31.1) years (table 3). The

age difference is only marginal and a clear reason cannot be stated. The mean number of children is 4.0 for the study group and 3.5 for the referent group. These figures are consistent with the published data in the “Tanzanian Demographic and Health Survey 1996” (TDHS, 1996). In 1996, Tanzanian women gave birth to >3 children by age 30 on average. The higher mean age (2.0 years) might explain the higher mean number of children (table 3). Poggensee, Feldmeier and Krantz (1999) described primary and secondary infertility as an important complication of FGS. This is not reflected by our data. The prevalence rate of FGS is significantly higher in the study group compared to the referent group (42.6% versus 29.6%) (table 3). The quality of the gynaecological examination might provide an explanation. In the study group successful photo-colposcopy points out a good quality examination which correlates with a more sufficient biopsy (Dexeus, S., Cararach and Dexeus, D., 2002). There is evidence stated that egg detection by QCBT is related to the optimal quantity and quality of the biopsy material (Helling-Giese et al., 1996b).

Urine positivity is higher (43.3%) in the referent group compared to 39.5% in the case group (table 3). This result is contrary to the published data that the intensity of urinary schistosomiasis increases the risk for FGS (Poggensee et al., 2000). However, the prevalence of urinary schistosomiasis is generally declining with increasing age (Ndhlovu et al. 2007). The higher mean age of the study group might explain the lower rate of prevalence of urinary schistosomiasis in comparison to the reference test.

The majority of self-reported lifelong gynaecological problems in the study group are vaginal discharge and menstrual disorders. Although Kjetland et al. (2008) stated a significant association between discharge and FGS there is no significant difference between the FGS-positive and FGS-negative cases. Women who consented to a gynaecological examination might suffer, regardless from the FGS status, on the same level from problems like discharge and menstruation disorders. Menstruation disorders are a well known major problem in SSA. Women are focussing on their monthly period because irregularities are well known reasons for not conceiving and bearing children. Blocked or delayed menses are accepted signs of something being wrong and create a high degree of suffering (Van de Walle and Renne, 2001; p 157-171). Therefore, it might be reasonable that 56.8% of FGS-negative cases and 42.9% of FGS-positive cases

mention this as problem in their lifetime (table 4). Although dysuria and haematuria can be indirect clinical signs of urinary schistosomiasis (Gundersen et al., 1996), there is no statistical significance between FGS-positive and FGS-negative cases. Though lower abdominal pain can be associated with upper genital tract schistosomiasis our data do not show a difference between the case group and reference test (table 4).

Kjetland et al. (2005) described contact bleeding and pre-contact bleeding as being significantly associated with FGS. Our data do not confirm this statement. In our study group FGS-negative women complained more frequently about postcoital bleeding (table 4).

All self reported gynaecological problems (vaginal discharge, post-coital bleeding, lower abdominal pain) and other physical problems (urinary tract related problems like dysuria, haematuria) 14 days prior to the gynaecological examination are more often complained by the FGS-negative female of the study group. The women might have been motivated by the high level of suffering from gynaecological problems regardless of FGS to participate in the gynaecological examination. Only backache and diarrhoea are more often complained by the FGS-positive cases. However in both groups backache is the main non-gynaecological problem. African women are frequently exposed to great work loads and used to carry heavy burdens (personal observation). A consequence might be backache on an equally distributed between FGS negative and FGS positive women (table 5). The number of diarrhoea cases is too small to assume any correlation.

Although tentative STD-discharge is a major problem in the referent group and study group, tentative STD-ulcer and tentative STD-lymphadenopathy were not present in either group (table 6). According to the syndromic approach to diagnose specific STDs can be concluded that specific STDs like syphilis, lymphgranuloma venererum, donovantiosis and cancroids are not present in our study group (Amaral, 1998). The reported tentative STD-discharge might be mainly caused by STDs like chlamydia, trichomoniasis and candidiasis, whereas ulcers and lymphadenopathy are not present in the clinical picture. A further differentiation of the STDs is not feasible due to the quality of discharge not mentioned. The published association between FGS and vaginal discharge is not reflected in our study (Kjetland et al., 2008).

Our data shows that there is no significant difference between sociodemographic data and clinical signs in the Tanzanian study population. The significant difference between FGS prevalence in the referent group and study group can be explained by the higher quality of the gynaecological examination in the study group. However, this is not influencing our research focusing on the evaluation of colposcopic findings and their diagnostic value.

6.2 Comparison of the photo-colposcopic findings of the Tanzanian study population with the available data in the literature

Both, the majority of FGS-negative cases 88.1% (52/59) and FGS-positive cases, 61.7% (29/47) present normal colposcopic findings in our study group (table 8). All kinds of normal findings were diagnosed as main criteria in the FGS-positive cases. 34.0% (16/45) are characterised by normal epithelium and normal TZ, 50% (1/1) by normal vascular pattern and 36.4% (12/33) by benign miscellaneous findings (table 7). Among the FGS-negative cases 49.1% (29/59) are characterised by normal epithelium and normal TZ, 50% (1/1) by normal vascular pattern and 35.6% (21/59) by benign miscellaneous findings (table 7). This is the first data available on normal colposcopic findings and their correlation with FGS. Our result indicates that normal findings are more frequently diagnosed in FGS-negative cases, but FGS cannot be excluded.

For the sandy patch (any type) the positive predictive value is 78.6% (11/14), the specificity is excellent with 94.9% (56/59), whereas the sensitivity is low with 23.4% (11/47) in our study population (table 8b). 21.4% of the sandy patches (any type) were diagnosed in FGS-negative cases (table 7). The diagnosed sandy patches are sub-classified into 6 GSP (all FGS-positive), 5 HYSP (3 FGS-positive and 2 FGS-negative) and 3 GSP and HYSP (2 FGS-positive and 1 FGS-negative) (figure 14). Although the numbers are small our data confirm the published relevance of GSP as pathognomonic finding for FGS (Kjetland et al., 2005). The positive predictive value is as high as 100% if a GSP is diagnosed. Our evaluated low sensitivity of the sandy patch (any type) is confirmed by Helling-Giese et al. (1996b). Their published sensitivity was 27.3% (9/33) and the positive predictive value 100% (9/9) (table 11).

With our pooled abnormal/suspect classification criteria (category 2) we focused on atypical vascular pattern; disrupted status of epithelium and tumour formation;

inflammatory lesions of the cervix and sandy patch (any type). In comparison to sandy patch (any type) the sensitivity increased to 38.3% (18/47) with a nearly constant specificity of 88.1% (52/59) and a positive predictive value of 72% (18/25). Abnormal/suspect findings are diagnosed in 11.9% (7/59) of FGS-negative case. Our approach to utilise pooled criteria is unique and comparable data have not been published.

Helling-Giese et al. (1996b) did not describe a correlation between FGS and colposcopic findings such as erosion, oedema, leukoplakia, inflammation, swelling, ulceration, erythema and ectopia. Polyps and papillomatous tumours correlating with FGS were only located in vagina and vulva. Contrary to their observations, Friedberg et al. (1991) described cauliflower-like, warty growth and granulomatous ulcers as pathognomonic lesions for FGS on the cervix (cited in Kjetland et al., 1996). Neither the data presented by Helling-Giese (1996) nor our data can confirm such correlation between tumour-like lesions on the cervix and FGS. Only one FGS-negative woman of our study population presented a colposcopic finding of a tumour-like lesion on the cervix. Our evaluated images were taken from vagina and cervix. Therefore, we cannot make any statement regarding FGS on the vulva.

Abnormal vascular pattern is a rare finding in our study population. Only 1.9% (2/106) of the study population presented with this finding as main criterion. Both cases were FGS-positive. This is contrary to the observation made by Kjetland et al. (2005). Atypical neo-vascularisation appropriate to pathognomonic findings and suspect for malignant and/or pre-malignant lesions was observed in 44% (231/527) of their cases. Disregarding the figure stated for neo-vascularisation, they diagnosed a malignant-looking lesion in only 6% of the cases. These figures are inconsistent. Malignant-like lesions in 6% of the cases is already a high figure. We diagnosed 3.8% (4/106) of the women with colposcopic suspect findings of pre-malignant or malignant lesions in our study population. Our figure correlates with the 3.9% (1128/28553) of females with high grade CIN or worse lesions described by Muwonge et al. (2009). This study is the only colposcopy screening study for CIN, which has ever been performed in SSA. It is obvious that a figure of 44% for neo-vascularisation (by definition correlating with pre-malignant and/or malignant finding) is inexplicable. Kjetland et al. (2005) did not differentiate between normal vascular

pattern (annex 9.2) and atypical vascular pattern (annex 9.3). In our study group normal vascular pattern were frequently seen in addition to the diagnosed main criteria. An association between normal vascular pattern and FGS was not evident in our study group. Pre-contact bleeding and contact bleeding are clinical signs of general epithelium vulnerability and not a specific colposcopic finding. They are not mentioned in the IFCPC classification (Quaas, Petry and Heinrich, 2008). The evaluation of these clinical signs on photo-colposcopic images is not feasible.

Although pooled criteria to diagnose FGS present an opportunity to increase the sensitivity of colposcopy as diagnostic test for FGS, we have to conclude that the majority of women without any abnormal/suspect findings have FGS in the LRT. In our study population any colposcopic findings can be diagnosed in FGS-positive and FGS-negative patients and none of our considered criteria can exclude the probability of FGS.

6.3 The sandy patch of the LRT: Relevance and options for colposcopy/photo-colposcopy to diagnose FGS

The sandy patch is predominantly known as pathognomonic lesion for urinary schistosomiasis in the bladder. Urinary schistosomiasis can be diagnosed by the cystoscopic finding of a sandy patch because of its characteristic presentation in the bladder (Döhring, Mand and Zimmermann, 1999). Organ-related characteristics of the urinary tract can explain the consistent appearance of this finding. A normal bladder is storing abacterial urine. The flow of urine and the local immune system prevent urinary infections (Potts, J., M., 2004, p. 185). This abacterial environment favours the development of a uniform, reliable and pathognomonic lesion like the sandy patch with a typical cystoscopic appearance. An interference of additional specific and unspecific urinary tract infections is seldom present. However, data published on sensitivity, specificity and positive and negative predictive values of the cystoscopic finding sandy patch to diagnose urinary schistosomiasis are not given. This typical environment of the urinary tract for the sandy patch is contrastive to the environment of the vagina for the sandy patch development in the LRT.

The vaginal flora is characterised by a physiological bacterial community of anaerobic and aerobic bacteria. Furthermore, the female LRT is permanently

exposed to various germs with all possible consequences of bacterial, viral and protozoan infections. The sandy patch is most often diagnosed on the cervix uteri with its organ-related specific characteristics. The cervix uteri is the border region between the lower and the upper reproductive tract and covered by two different types of epithelium, the non-keratinizing squamous and columnar epithelium. Both types of epithelium meet at the squamocolumnar junction. The columnar epithelium is partially replaced by new metaplastic squamous epithelium. This region is called transformation zone (TZ) (Sellors and Sankaranarayanan., 2003). These physiological and pathophysiological conditions are causal for the typical changes of the cervix through a woman's lifetime, hormonal status, age, pregnancy and birth trauma are additional factors (Petersen, E., E., 2003). As consequence the development of a consistent, recognisable and specific lesion is aggravated. These characteristics of the LRT are reasonable for the difficulties to attribute a colposcopic finding to a specific disease and to use it as a diagnostic test.

As consequence the sandy patch of the LRT does not have such a constant appearance as the sandy patch of the urinary tract and the diagnostic value is limited. Although colposcopists with greater experience might have superior abilities to diagnose FGS-related findings the reproducibility of the assessment of visual characteristics is limited. The evaluation of sandy patch, GSP and HYSP is additionally aggravated by the minor to moderate quality of the published picture examples. Furthermore the reproducibility and identification of the visual characteristics of the published examples are limited (examples in Kjetland et al., 2005 and Helling-Giese et al. 1996b). The pictures show only a cut-out of the cervix uteri and the image resolution is of minor quality. In addition, no standardised replicable picture documentation in a comprehensive colposcopy textbook or atlas of a sandy patch, GSP and HYSP has ever been prepared. Although cervical schistosomiasis is mentioned by Sellors and Sankaranarayanan, (2003) as differential diagnosis for uncommon necrotic cervical changes, a picture example is not given.

Kjetland et al. (2005) performed a retrospective measurement of the sandy patch grains on their photo-colposcopic slides. We were unable to apply this method – our photo-colposcopic images were taken with a 7.5x or 15x times magnification. The limited image resolution is further reduced by this

magnification. Because of this, retrospective measurement of 0.186 mm grains is not feasible in our study.

The sandy patches in our study do not have such a constant pathognomonic presentation as stated by Kjetland et al. (2005). The resemblance of sandy patches (any type) is more chronic post-infectious lesions of variant morphology and size. It seems that the varying physiological and pathophysiological conditions in the LRT have unpredictable effects on the appearance of these findings. However, the diagnosis of sandy patch (any type) by colposcope/photo-colposcope can give relevant indications for FGS. The published figures of the positive predictive values range between 100% for sandy patch (any type) (table 11) and 78.6% sandy patch (any type) (Table 8b) and 60.5% for GSP (table 9). Furthermore, the sandy patch is characterised by an excellent specificity of 94.9% in our study (Table 8b). This correlates to the data presented in the literature (table 9, 10). If a characteristic sandy patch (any type) is diagnosed by colposcopy the finding is pathognomonic for FGS but many infected women cannot be diagnosed by these findings. The explanations are: frequently the sandy patch do not have a characteristic presentation or FGS infected women do not have any abnormal/suspect findings.

6.4 Discussion of the validity of colposcopy as diagnostic test for FGS in SSA

In general, colposcopy in SSA is challenged by difficult working conditions with limited technical, financial and human resources (Muwonge et al., 2009). Various factors are influencing the validity of the diagnostic test for FGS based on colposcopic findings. Local irritants like traditionally applied herbals, intrauterine devices or mechanical traumata caused by intercourse can produce unspecific signs of infection in the LRT (Sellors and Sankaranarayanan, 2003). Furthermore, the evaluation of colposcopic findings is aggravated by numerous unspecific and specific genital infections, which result in various colposcopic findings (Kjetland et al., 2008). Likewise is vaginal and cervical discharge of different qualities and quantities limiting the diagnostic value of colposcopy (Sellors and Sankaranarayanan, 2003).

Exact prevalence figures for female STDs have not been published for SSA. Johnson, Coetzee and Dorrington (2005) stated for South Africa the highest

prevalence for Herpes simplex virus type 2 (HSV-2), trichomoniasis, candidiasis and bacterial vaginosis. Infections caused by caused by chlamydia and gonorrhoea are another persistent problem. The diagnostic is complicated by mixed genital infections not attributable to a specific pathogenic agent. In the majority colposcopic findings are not specific for a certain STD but rather characterised by a widespread inflammatory reaction of the cervical and vaginal mucosa. The epithelium of the LRT is frequently disrupted, which is leading to desquamation and ulcerations in the epithelium (Pisani et al., 1999). The value of the two key ingredients for the assessment by colposcope, acetic acid and iodine solution, is limited by the inflammatory response and cannot be used to differentiate between findings caused by STDs (Sellors and Sankaranarayanan, 2003). Pisani et al. (1999) concluded that colposcopy is not a useful tool to differentiate between the various STDs. The same statement is applicable for rare specific infectious diseases on the cervix uteri such as tuberculosis, amoebiasis and schistosomiasis. All of these cause general clinical signs like cervical necrosis and ulcerations. For any of those suspect findings Sellors and Sankaranarayanan, (2003) recommend diagnosis by biopsy and not diagnosis based on specific colposcopic findings.

The recommendations of IFCPC emphasise that a validity of colposcopic findings in the situation of severe inflammation is not given (Walker et al., 2003). The colposcopic evaluation is additionally aggravated by hormone-dependent changes of the LRT epithelium, variable changes post pregnancy and ageing processes of the LRT (Sellors and Sankaranarayanan, 2003).
Findings caused by FGS can have polymorphous characteristics. Cauliflower-like, nodular hypertrophy, ulcerative, polypoid and sometimes malignant-like lesions are described (Poggensee and Feldmeier, 2001). In current publications the diagnosis of FGS is based mainly on pathognomonic colposcopic findings. Kjetland et al. (2005) stated evidence that the colposcopic finding of GSP has a diagnostic test quality equal to egg detection procedures. The stated test quality is based on their data on predictors for GSP and HYSP gained in their Zimbabwean study.

Table 12: Predictors for grainy sandy patches (from Kjetland et al., 2005)

Laboratory test	Grainy sandy patch/Positive laboratory test results (%)	Grainy sandy patch/Negative laboratory test results (%)	Odds ratio (95% Confidence interval)	P
S. h. in Pap smears §	18/27 (67)	130/448 (29)	4.89 (2.14-11.17)	< 0.001
S. h. in genital wet mount #	28/39 (72)	21/56 (38)	4.24 (1.76-10.26)	0.001
S. h. in genital biopsy *	6/19 (31)	1/17 (6)	7.38 (0.79-69.29)	0.80
Herpes simplex virus type 2	89/307 (30)	50/169 (30)	0.97 (0.64-1.47)	0.89
Bacterial vaginosis	5/14 (36)	115/395 (29)	1.35 (0.44-4.11)	0.60

§ S. haematobium ova in Pap smear. This was done in all consenting women; some were lost due to mistakes on form
# Done in the presence of mucosa bleeding only
* Done only when malignancy was suspected

Table 13: Predictors for genital homogeneous yellow sandy patch (from Kjetland et al., 2005)

Laboratory test	HYSP/Positive laboratory test results (%)	HYSP/Negative test results (%)	Odds ratio (95 % confidence interval)	P
S. h. ova in Pap smear §	14/27 (52)	120/448 (29)	2.94 (1.35-6.44)	0.007
S. h. ova in genital wet mounts #	33/39 (85)	32/56 (57)	4.12 (1.49-11.42)	0.0060
S. h. ova in genital biopsy *	6/19 (33)	5/17 (29)	1.12 (0.27-4.59)	0.89
Herpes simplex virus type 2 (Serology)	96/307 (31)	37/169 (22)	1.62 (1.05-2.51)	30

§ S. haematobium ova in Pap smear. This was done in all consenting women; some were lost due to mistakes on form
# Done in the presence of mucosa bleeding only
* Done in suspicion of malignancy only

Kjetland et al. (2005) and Helling-Giese et al (1996b) presented odds ratios (OR) to identify associations between colposcopic findings and FGS. In their conclusion about the test quality they put the OR on a level with sensitivity and specificity analysis. Although they fail to find a significant association on the 5% level except for the reference tests Pap smear and wet mount they concluded

that the test quality based on GSP is equivalent to egg detection procedures. They stated a FGS prevalence rate of 49% (257/527) by adding up FGS-positive cases from Pap smear, wet mounts, biopsies and all cases with colposcopic finding GSP.

Their data about GSP does not show congruent results (Table 9). The sensitivity ranges from 12.2% (18/148) [reference Pap smear] to 85.7% (6/7) [reference biopsy] and the specificity from 55.2% (16/29) [reference biopsy] to 97.2% (318/327) [reference Pap]. Furthermore, the positive predictive values are ranging from 31.6% (6/19) [reference biopsy] to 71.8% (28/39) [reference wet mount]. For the pooled egg detection procedures (Pap, wet mount, biopsy) the sensitivity is 30.5% (46/151), the specificity 91.2% (311/341), positive predictive value 60.5% (46/76) and negative predictive value 74.8% (311/414). A sensitivity of 30.5 % means that 69.5% (105/151) of the FGS-positive patients will not be diagnosed by colposcope (table 9). Although the GSP is a pathognomonic lesion the quality as diagnostic test is not sufficient.

The sensitivities for HYSP to diagnose FGS are ranging from 10.4% (14/134) [reference Pap] to 50.8% (33/65) [reference wet mount]. The positive predictive values are ranging from 31.6% (6/19) [reference biopsy] to 91.7% (33/36) [reference wet mount]. In comparison, the sensitivity of the HYSP to diagnose HSV-2 is 72.2% (96/133), the specificity 38.5% (132/343) and the positive predictive value 31.3% (96/307) [reference laboratory test] (table 10). Kjetland et al. (2005) concluded from this data HYSP is pathognomonic for HSV-2 infection and not for FGS. However the majority of women 61.5% (211/343) present a HYSP without HSV-2 infection (table 10). Although the test quality of HYSP is as good or even better for HSV-2 infection as the test quality of GSP for FGS, they are not concluding that the test validity of HYSP for HSV-2 is equal to laboratory testing. The re-evaluation of their published data confirms that odds ratios can not be put on a level with sensitivity analysis to assess the validity of a diagnostic test. This approach is misleading since OR is only offering a minute part of a complex picture with regard to the usefulness of a diagnostic test for a certain disease. The assessment of the validity of a diagnostic test has to be based on sensitivity, specificity and positive and negative predictive value calculations (Gordis, 2004, p. 71-94).

Likewise to our study approach Helling-Giese et al., (1996) compared their colposcopic findings with QCTB. They stated for sandy patch (not sub-classified) a positive predictive value of 100% (9/9), sensitivity of 27.3% (9/33) and specificity of 100% (21/21). For papillomatous/polypous tumour the sensitivity and positive predictive value was 60.6% (20/33), (Table 11). Although the sandy patch has a positive predictive value of 100% in their study only 9 out of 33 FGS-positive women presented this pathognomonic finding (table 11).

The wide range of diagnosed sandy patch in FGS-endemic areas is another problem of the sandy patch. Kjetland et al. (2005) published figures of 46% diagnosed sandy patches (any type), 30% GSP and 29% HYSP in their study population. This is controversial to the figure of 16.6% sandy patch (not sub-classified) presented by Helling-Giese et al. (1996) and the 13.2% sandy patch (any type) diagnosed in our research (Table 8b). Our figures of the sub-classified sandy patches (Figure 14) are too small for a separated calculation of the test validity. For the pooled sandy patches the sensitivity is 23.4% (11/47), the specificity 94.9% (56/59) and the positive predictive value 78.6% (11/14). However the sandy patch (criteria 2.5) is the only criteria of our classification criteria with a significant association diagnosed FGS using chi-square test (table 7). Evaluation by pooled category 2 (Table 2) increased the sensitivity to 38.3% (18/47) with a minor decrease of the specificity to 88.1% (52/59). The positive predictive value of 72.0% (18/25) remained almost unchanged. The pooled category 2 with additional abnormal/suspect criteria enhances the diagnostic validity minimally.

The published relevance of the diagnostic value of colposcopic findings like GSP and HYSO is inconsistent. Kjetland et al. (2005) stated in 2005, GSP is pathogonomonic for FGS and HYSP is pathognomonic for STDs (primarily HSV-2). This conclusion is based on data from the same Zimbabwean study population they published in 2006 about FGS and the association with HIV. In their 2006 study HIV was significant associated with HYSP (pathogonomonic for HSV-2), but not with GSP (pathogonomonic for FGS) (Kjetland et al., 2006b). They concluded that FGS is the main risk factor for HIV transmission and not HSV-2, regardless of their previously stated evidence that HYSP is pathognomonic for HSV-2 and the result that HIV is correlating with HYSP (Kjetland et al., 2006b).

Unlike limited research activity about colposcopy for FGS, research activity about colposcopy for cervical intraepithelial neoplasia (CIN) is comprehensive. Furthermore, there is an existing standardised nomenclature for the assessment of lesions suspect for dysplasia. Although colposcopy for CIN is an accepted diagnostic technique there is compelling evidence that the validity of colposcopic impressions for CIN is limited (Zahm et al., 1998; Jeronimo and Schiffman, 2006). This limitation is evident, although additional diagnostic criteria (application of acetic acid and iodine solution) are available for the assessment of lesions suspect for CIN. Zahm et al. (1998) analysed the significance of colposcopic findings for the diagnosis of CIN. In patients with trivial colposcopic changes (37/116, 32%) had almost as often CIN was almost as often confirmed by histology as in patients (43/99, 43%) with colposcopic findings suspect for CIN. The diagnostic validity of colposcopic findings for CIN is not sufficient (Dexeus, S., Cararach and Dexeus, D., 2002, Jernimo and Schiffman, 2006). The colposcopic guided biopsy remains essential for the diagnosis to maximise the sensitivity considering a good specificity and the task of colposcopy for CIM is to state whether and were to biopsy (Jeronimo and Schiffman, 2006).

Kejtland et al. (2008) defined genital schistosomiasis as “having sandy patches and/or microscopically proven S. haematobium ova in genital tissue.” Under consideration of the calculated sensitivity, specificity and positive and negative predictive value from their data (Table 9 and 10) this conclusion is doubtful.

6.5 Comparison of the published criteria to diagnose FGS by colposcope with the pre-existing nomenclature by IFCPC

Consistent criteria of colposcopic findings indicating FGS are no existing. A problem of colposcopy for FGS is that the colposcopy has been developed for the diagnosis and evaluation of CIN (Sellors and Sankaranarayanan, 2003). The globally practised IFCPC-colposcopic classification and its nomenclature (Barcelona 2002) are primarily used for the screening context of intraepithelial neoplasia in the LRT. The region of most interest is the cervix uteri with its squamocolumnar junction of the transformation zone (TZ). The IFCPC classification is based on 5 categories: I normal colposcopic findings, II abnormal colposcopic findings, III colposcopic features suggestive of invasive

cancer, IV unsatisfactory colposcopy, V miscellaneous findings. The colposcopic observation after the application of acetic acid and iodine solution of Lugol application is a major element of this classification (Quaas, Petry and Heinrich, 2008). The characteristics of acetowhite changes after acetic acid and the colour change of the epithelium are essential for the assessment of suspect colposcopic impressions. Basic requirement for the investigation are a visible cervix uteri and its squamocolumnar junction, the absence of serve inflammation of the LRT and absence of epithelium atrophia and trauma (Sellors and Sankaranarayanan, 2003). The primarily scope of colposcopy is not the diagnostic and differentiation of infectious diseases. As consequence, criteria to diagnose specific infectious diseases have never been established by IFCPC.

Helling-Giese et al. (1996) documented the colposcopic findings according to a modified WHO protocol (WHO, 1995). This manual for colposcopy is used for the evaluation of epithelial changes caused by the application of vaginal products like spermicidal creams for contraception. The main criteria are the status of the epithelium (intact, disrupted superficial or deep) and the status of the blood vessels (intact or disrupted) (WHO and CONRAD, 2004). Helling-Giese et al. (1996) evaluated the frequency of colposcopic findings (sandy patch, papillomatous/polypous tumour, swelling, inflammation and leukoplakia) in FGS-positive and FGS-negative cases. Their published definition of the sandy patch is based on their own observations. Swelling is a clinical sign of general infection not mentioned in the IFCPC classification (Quaas, Petry and Heinrich, 2008). Polyp, leukoplakia the equivalent for hyperkeratosis and inflammation are classed as miscellaneous findings of the category V by the IFCPC-classification (annex 9.4) (Quaas, Petry and Heinrich, 2008). Miscellaneous findings are generally unspecific findings for typical diseases. The sandy patch is not mentioned in the IFCPC classification. There is no definition of sandy patch and the sub-classified GSP and HYSP internationally agreed on.

Kjetland et al. (2005) focused on the colposcopic findings of GSP and HYSP, signs of neo-vascularisation, contact bleeding and pre-contact bleeding. Furthermore, they evaluated clinical findings of the mucosa like oedema, erosion, leukoplakia, but there was no correlation with FGS. The evaluation criteria used by Kjetland et al., (2005) are a combination of established

nomenclature by IFCPC and clinical signs like contact bleeding and pre-contact bleeding. A consistent and standardised approach is missing. Neo-vascularisation, ulcerations and erosions are included in the IFCPC-classification category III (annex 9.4), classified as colposcopic features suggestive of invasive cancer (Quaas, Petry and Heinrich, 2008). Contact bleeding and pre-contact bleeding are unspecific signs of epithelium vulnerability and not characteristic colposcopic findings (Sellors and Sankaranarayanan, 2003).

The data published about colposcopy for FGS do not mention criteria of unsatisfactory colposcopy and conditions of insufficient investigations (in Kjetland et al., 2005 and Helling-Giese et al. 1996). Conditions for sufficient investigations are an essential requirement for the evaluation of colposcopic findings. Furthermore, no consistent terminology for the main colposcopic findings indicating FGS has been established. It is obvious that there is an urgent need for standardised criteria and a consistent methodology as these are essentials for scientific research with reliable data in the area of colposcopy for FGS.

6.6 Present relevance and future prospects of colposcopy for FGS in the LRT

The present scope of colposcopy is risk screening based on pathognomonic findings (sandy patch, GSP). In doing so sandy patch and GSP can pinpoint the group of females with an extremely high risk of FGS. Pooled criteria can improve the test quality for this risk screening (table 8a). However, any pathognomonic finding indicating FGS is characterised by poor sensitivity. Evidence gained in our study indicates that FGS can be diagnosed by QCBT without any abnormal/suspect colposcopic findings (table 7, 9, 10, 11). A prevalence assessment for FGS based on colposcopic findings like sandy patch and or GSP is not feasible. The definitive diagnosis and reliable prevalence data need a biopsy for confirmation.

Furthermore, colposcopy is a useful tool to follow-up regression and healing of confirmed lesions under therapy (Kjetland et al., 2006). This policy helps to optimise the therapy strategies. In future prospects colposcopy should be integrated into the training scheme for Sub-Saharan African gynaecologists. A

standardised and a continuing education programme have to be established. As stated it is sensible that the performance of colposcopy is related to daily practise and the experience gained (Muwonge et al., 2009). Exchange programmes should be developed with international societies for colposcopy (Van Niekerk et al., 1998). Beside colposcopy for CIN to prevent invasive cancer the pathognomonic findings of FGS should be an integral part of the mediated skills of colposcopy. Telecolposcopy and colpophotographs can open up distance learning through the worldwide web and will transfer knowledge about FGS and colposcopy. New technologies in digital imaging might provide further steps for the application of colposcopy (Schädel et al., 2004).

6.7 Research methodology

6.7.1 Limitations and strengths of photo-colposcopic evaluation

The images of this study have been obtained under challenging conditions in rural SSA, thus less then optimal quality of the images is occasionally limiting the assessment. Furthermore, the images have not been obtained by a standardized approach; the magnification (7.5 or 15x times) used is not documented. The image assessment can be aggravated by discharge, bloodiness, contamination by hair, decentralised position of the cervix and limited visibility caused by speculum or prolapse of the vaginal walls. There is no certainty that the accessible part of the cervix is representing the important colposcopic findings. Additional information and options of a real-time colposcopy examination are missing (revision of the set-up considering the area of most interest, discharge removal, palpation of the finding). Reference standard images of the colposcopic findings sandy patch, GSP and HYSP do not exist, thus our evaluation is based on the limited picture examples available in the literature. Furthermore, there is evidence stated that the diagnostic value of colposcopy based on static images is limited and that the inter-observer variations are causing poor reproducibility (Jeronimo et al., 2007). Although our image evaluation was performed by a specialist for gynaecology and an expert colposcopist, another second independent evaluator would have been favourable regarding the inter-observer variations. Our image assessment was done in a single-time procedure, thus a statement regarding the intra-observer variation cannot be presented. As a result of this, an obvious degree of subjectivity has to be accepted and the aspect of intra-observer and inter-observer incongruence is not reflected in our results.

Women, who consented to a gynaecological examination might, have been motivated by discomfort caused by additional diseases of the genital tract such as STDs, CIN, menstrual disorders, discharge problems and primary or secondary infertility. These circumstances can cause a selection bias and reduce the explanatory power of our research. Present STD co-infections have not been diagnosed by laboratory testing. STD can cause multiple and varying colposcopic findings. In a Zimbabwean study population 65% of females had a positive serology for Herpes simplex type 2 (HSV-) and 29% for an HIV-infection (Kjetland et al. 2006). In our Tanzanian study population this kind of testing was not part of the study protocol.

A major strength of our study is the fact that the diagnosis of FGS is exclusively based on QCBT. The diagnostic test quality of colposcopic findings can be consistently compared with the gold standard. Furthermore, the approach of a routine cervix biopsy irrespective of abnormal/suspect or normal colposcopic findings offers the opportunity to present correlations to any of the colposcopic findings. Because of the restriction to perform QCBT a data set comparable to ours will no longer be available in the setting of SAA.

The classification criteria, based on international accepted nomenclature and diagnostic criteria, used by us allows a systematic assessment. The evaluation criteria are adapted to the international recommended nomenclature and its recommended use. Furthermore, the systematic evaluation of photo-colposcopic findings and their relevance for FGS has never been conducted before in a study population from SSA.

6.7.2 Limitations and strengths of the literature review

Although the WHO Gender Task Force has recognised the urgent need to support research for FGS since the mid-90s, only three studies with primary data research and focus on FGS have been conducted in SSA. The studies have been conducted in Malawi (Kjetland et al., 1996; Helling-Giese et al., 1996), Tanzania (Poggensee et al., 2001) and Zimbabwe (Kjetland et al., 2005) between 1994 and 1999. Kjetland et al. (1996) were the first to publish data on the value of colposcopic findings to diagnose FGS. Furthermore, they used the established QCBT developed for intestinal schistosomiasis to diagnose FGS from cervix biopsies. This exclusive diagnostic approach by QCBT has been used only at one other time in the Tanzanian study (Poggensee at a., 2001).

Ethical approval was no longer granted for QCBT as reference test in the latest study conducted in Zimbabwe. Because of the fear to favour HIV-transmission by superficial lacerations, cervix biopsies without suspicion of malignancy were not performed (Kjetland et al., 2005). As consequence the data on QCBT-diagnosed FGS and corresponding colposcopic findings is limited. Kjetland et al., (2005) had to use various tests like Pap smear, genital wet mount and only in selected cases biopsies with QCTB as reference procedures. Because of this, the test quality of their colposcopic findings cannot be compared to consistent reference tests and the review of their data is complicated by this condition. In addition, only one clinician (E., F., Kjetland) performed the gynaecological and colposcopic examination. Although Kjetland et al. (2005) presented photo-colposcopic cases with doubtful findings to a self-announced expert committee no data on intra-observer and/or inter-observer variability of colposcopic findings are available. The poor reproducibility of findings is a major and persistent problem of photo-colposcopy and vital colposcopy (Jeronimo et al., 2007). Since Kjetland et al. (2005) inaugurated the sub-classification of the HYSP and superficial and/or deep GSP no further study evaluated critically these findings. Furthermore, the test quality of these findings has never been challenged by comparative studies.

To date colposcopy is rarely practised in SSA and almost no additional information about colposcopy in SSA is available (Muwonge et al., 2009). In European countries, where colposcopy is established, diseases like schistosomiasis are not present. Through these conditions our review is limited to three studies and the resulting publications.

7. Conclusions and recommendations

7.1 Conclusion

Currently FGS is in the global focus of interest because of the stated evidence that lesions caused by FGS in the LRT are causal for an accelerated HIV transmission rate with tremendous consequences for SSA (Hotez, Fenwick and Kjetland, 2009; Erikstrup et al., 2008). Diagnosis, treatment and prevention of schistosomiasis and FGS might have a major impact on future HIV/AIDS prevention strategies. To date no profound data exists on the impact of FGS on women's health. Since 2000 no actual study focussing on FGS has been conducted in SSA.

A remaining problem is the diagnostic of FGS. QCBT is problematic in SSA regions and other direct or indirect diagnostic procedures are not applicable in low resource settings or are invalid and unreliable (Poggensee et al., 1996, Poggensee et al., 2001, Midzi et al., 2003). In recent publications the diagnosis is based on specific colposcopic findings presented as an elegant solution for this diagnostic dilemma (Kjetland et al., 2005, Kjetland et al., 2006). Although photo-colposcopic/colposcopic findings like sandy patch of any type or pooled criteria of abnormal/suspect findings provide important indications for FGS, is the diagnostic test quality low. Evidence gained from our study indicates that the test quality to diagnose FGS by the findings sandy patch, GSP and HYSP based on the low sensitivity is not sufficient. The majority of FGS-positive cases do not present characteristic findings like sandy patch and GSP (table 8b, table 9, table 10, and table 11). As consequence the diagnosis of FGS by colposcope has still to be based on biopsy to maximise the sensitivity and not on colposcopic findings like sandy patch and GSP. The quality of a diagnostic test remains too low without biopsy. Because of the limitations to perform biopsies other diagnostic tests should be developed suitable for the setting of SSA. Prevalence data based on colposcopic findings are not valid and conclusions considering these data are questionable.

7.2 Recommendations

A risk assessment for FGS can be done by photo-colposcopy/colposcopy. Colposcopy enables to follow-up the regression of pathognomonic findings (favourably verified by biopsy) under therapy (Kjetland et al., 2006, Richter et al., 1996).

Lesions caused by FGS are an important differential diagnosis for any colposcopic finding in regions with schistosomiasis and for any women who have been in countries where schistosomiasis is present. Colposcopy for FGS beside colposcopy for CIN should be an essential part of the mediated skills of colposcopy in SSA. This requires a standardised and continuing education programme to be established (Muwonge et al., 2009). The performance of colposcopy is related to daily practise favourably under supervision (Jeronimo and Schiffman, 2006). A manual for colposcopy of FGS-induced lesions adapted to the “Manual For The Standardization Of Colposcopy For The Evaluation Of Vaginal Products” should be developed. An integral part of this

manual has to be guidelines for obtaining, recording and analysing static images for colposcopic diagnosis. Standard images of high quality as references with all important findings indicating FGS should be established and used for training and evaluating. National colposcopy societies should be launched and exchange programmes with international societies for colposcopy established (Van Niekerk et al., 1998; Muwonge et al., 2009).

7.3 Suggested areas for future research

A basic requirement for future research is the development of standardised guidelines based on a consistent terminology and coherent colposcopic criteria indicating FGS. Rigorous, formal studies to compare the colposcopic findings and FGS will provide further evidence about the validity of colposcopic findings to diagnose FGS. Evidence should be gained regarding the benefit of pooled criteria indicating FGS. The diagnostic quality of colposcopic findings has to be compared with a uniform, standardised diagnostic procedure, favourably the QCTB. The question regarding the reproducibility (inter-observer and intra-observer variations) of colposcopic findings indicating FGS have to be answered (Jeronimo et al., 2007).

Finally, there is an urgent need to solve the persistent diagnostic dilemma of FGS. The solution of this task is a major prerequisite for the most urgent research question to answer: What impact has FGS on HIV transmission in SSA?

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9. Annexes

9.1 Reproductive Health Questionnaire

Are you pregnant?	1 = no 2 = yes	**Exclusion criterion** for gynaecol. examination
Number of pregnancies?	1 = no 2 = yes	
Pregnancy complications Premature labor	1 = no 2 = yes	
Stillbirth	1 = no 2 = yes	
Abortion	1 = no 2 = yes	
Delivery complications	1 = no 2 = yes	
Number of children alive		
Age of the oldest child (years)		
Age of the youngest child (years)		
Do you wish another child?	1 = no 2 = yes	
Do you have difficulties to conceive?	1 = no 2 = yes	

Did you ever had the following problems?
(**more than one symptom can be named**)

painful mensis	
prolonged mensis	
heavy bleeding	
Intermenstrual bleeding	
irregular mensis	

When did you have your first sexual intercourse (age in years) |

Have you had the following symptoms in the last two weeks?

Headache	1 = no 2 = yes	
Cough	1 = no 2 = yes	
Backache	1 = no 2 = yes	
Lower abdo. Pain	1 = no 2 = yes	
Dysuria	1 = no 2 = yes	
Bloody urine	1 = no 2 = yes	
fever	1 = no 2 = yes	
Vaginal discharge	1 = no 2 = yes	

Since when (19..)

Have you had your menstruations in the last three months?
1 = no
2 = yes

If no, why not?
1 = pregnancy
2 = breast-feeding
3 = family planning
4 = menopause
5 = other

When did your last menstruation start (date)?

Usual duration of the menstruation (days)

Do you have actually menstrual disorders?
1 = no
2 = yes

What problems do you have? (**more than one symptom can be named**)
1 = no
2 = yes

painful mensis

prolonged mensis

heavy bleeding

Intermenstrual bleeding

Intermenstrual bleeding

irregular mensis

Intermenstrual Bleeding	1 = no 2 = yes	
post-coital bleeding	1 = no 2 = yes	
Vaginal Discharge	1 = no 2 = yes	
if yes	1 = whitish 2 = yellowish 3 = greenish 4 = bloody discharge 5 = bad smelling	
Genital itching	1 = no 2 = yes	

Have you ever had the following problems?

Lower abdo. Pain	1 = no 2 = yes
Fatigue (not able to work in fields)	1 = no 2 = yes
Loss of appetite	1 = no 2 = yes
Bloody urine	1 = no 2 = yes
Dysuria	1 = no 2 = yes
Vaginal discharge	1 = no 2 = yes
If yes	1 = whitish 2 = yellowish 3 = greenish 4 = bloody discharge 5 = bad smelling

Genital ulcer	1 = no 2 = yes	
Vaginal growth	1 = no 2 = yes	
Intermenstrual Bleeding	1 = no 2 = yes	
Post-coital Bleeding	1 = no 2 = yes	
Genital itching	1 = no 2 = yes	

3. Health seeking behaviour

Have you ever been in a hospital because of problems of the reproductive tract? Where? For what reasons?

How do you think diseases like schistosomiasis can affect the reproductive tract? How?

Have you ever been examined gynaecologically

1 = no
2 = yes

Are you willing to be examined gynaecologically? (Ask for reasons, if willing and if not willing!)

_____

_____

4. Water contact

From where do you fetch water

To drink?

1 = river
2 = well
3 = lake

To wash

1 = river
2 = well
3 = lake

Who is helping you to fetch water?

1 = daughter
2 = son
3 = husband
4 = other

Who is helping you to wash?

1 = daughter
2 = son
3 = other

Where do children swim?

_____

Do girls usually swim usually?

1 = no
2 = yes

(Poggensee, 2002)

9.2 Normal vascular pattern

Network capillaries

'Hairpin' capillaries

'Stanghorn' – like vessels

Long, parallel blood vessels

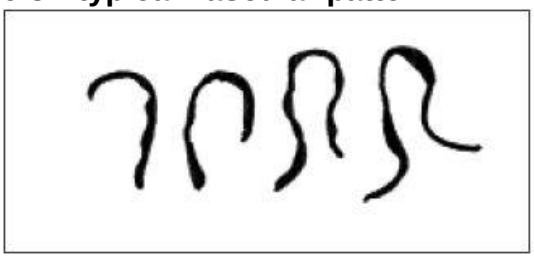
Long, regular branching vascular tree with gradual decrease in calibre

Regular vascular network

Blood vessels showing regular branching

Sellors, J. W., Sankaranarayanan, R., 2003

9.3 Atypical vascular pattern

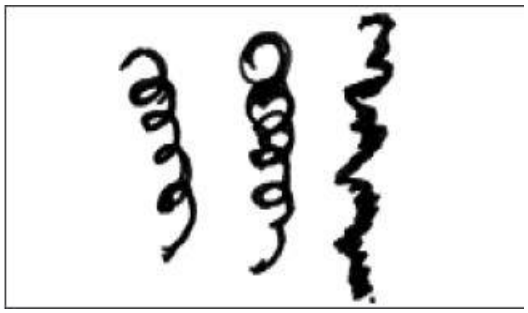


(a): Wide hair pin–like vessels

(b): Waste thread vessels

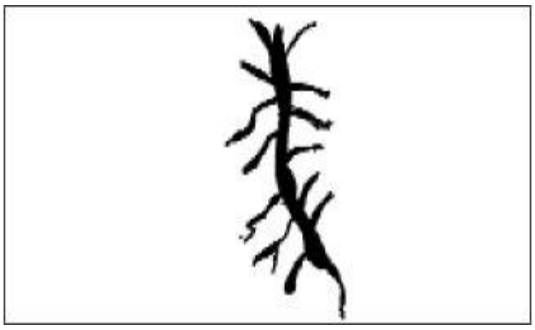
(c): Tendril–like vessels

(d): Bizarre branching waste thread vessels

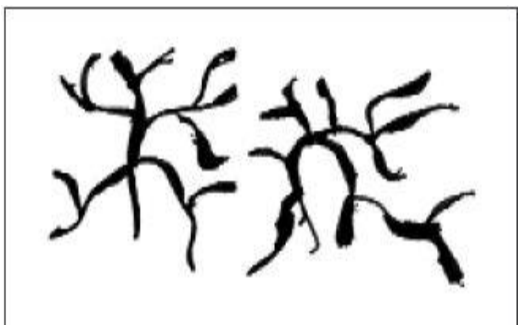


(e): Corkscrew vessels

(f): Irregular root–like vessels



(g): Tree–like vessels



(h): Irregular branching vessels

(i): Comma–shaped or tadpole-like vessels

Sellors, J. W., Sankaranarayanan, R., 2003

9.4 Barcelona Score, 2002

Übersicht über die aktuelle Nomenklatur

Englisch	Deutsch
I. normal colposcopic findings	**I. normale kolposkopische Befunde**
– original squamous epithelium	– originäres Plattenepithel
– columnar epithelium	– Zylinderepithel
– transformation zone	– Transformationszone
II. abnormal colposcopic findings	**II. abnorme kolposkopische Befunde**
a. minor changes	a. leichte Veränderungen
– flat acetowhite epithelium	– semitransparentes essigweißes Epithel
– fine mosaic	– zartes Mosaik
– fine punctation	– zarte Punktierung
– iodine partial positivity	– jodgelbe Reaktion
b. major changes	b. schwere Veränderungen
– dense acetowhite epithelium	– nicht transparentes essigweißes Epithel (intensive Essigreaktion)
– coarse mosaic	– grobes Mosaik
– coarse punctation	– grobe Punktierung
– iodine negativity	– jodnegative Reaktion
– atypical vessels	– atypische Gefäße
III. colposcopic features suggestive of invasive cancer	**III. kolposkopische Befunde bei Verdacht auf ein invasives Karzinom**
– irregular surface, erosion, or ulceration	– irreguläre Oberfläche, Erosion, oder Ulzeration
– dense acetowhite change, wide irregular punctation and mosaic, atypical vessels	– intensiv essigweiße Veränderungen, irreguläre Punktierung und Mosaik, atypische Gefäße
IV. unsatisfactory colposcopy	**IV. unzureichende Kolposkopie**
– squamocolumnar junction not visible	– Plattenepithel-Zylinderepithel-Grenze nicht einsehbar
– severe inflamation, severe atrophy, trauma	– schwere Entzündung, ausgeprägte Atrophie, Verletzung
– cervix not visible	– Zervix nicht einstellbar
V. miscellaneous findings	**V. verschiedene Befunde**
– condylomata	– Kondylome
– keratosis	– Keratose
– erosion	– Erosion
– inflammation	– Entzündung
– atrophy	– Atrophie
– deciduosis	– deziduale Umwandlung
– polyps	– Polypen

Quaas, J., Petry, K.-U. and Heinrich, H., 2008

10. Declaration of originality of work

This thesis is the result of independent investigation. Where my work is indebted to the work of others, I have made appropriate acknowledgements. I declare that this study has not already been accepted for any other degree nor is it currently being submitted in candidature for any other degree.

Hannover, February 25 th 2010 Dr. med. Dirk Grothuesmann

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Work experience

At least 15 years of postgraduate work experience. Hereby for 11 years consultant for Gynaecology and Obstetrics. Supervisor of the operating theatre responsible for quality assurance and monitoring of surgical procedures. Trainer of trainers with focus on the implementation of surgical techniques (major focus pelvic surgery). Specialist for re-constructive pelvic surgery (female genital tract, urinary and bowl system) . Specialist for obstetrics and perinatal medicine and consultant for perinatal care. Quality management and guideline establishment for emergency obstetric care. Lecture activities for medical students and PhD thesis supervision during the employment as consultant at the University Hannover, Lower Saxony.

International work experience

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- Namibia
- South Africa
- Ukraine
- Bhutan
- Bangladesh

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