Genital Manifestations of Schistosomiasis mansoni in Women: Important but Neglected

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Egg-induced lesions in the upper and the lower female reproductive tract are important complications of the infection with Schistosoma mansoni. *The understanding of the pathophysiology and pathology of genital lesions is only rudimentary, simple and reliable diagnostic tools are not at hand, epidemiological data do not exist and how to treat best the women affected, is not known. In view of recent advances in the understanding of genital lesions induced by* S. haematobium *the existing literature is critically analysized and possible consequences of female genital schistosomiasis are outlined. We estimate that 6 to 27 % girls and women with intestinal schistosomiasis, at least temporarily, suffer from pathology induced by eggs sequestered somewhere in their genital organs. This is a mattern of concern and warrants more research into the epidemiology, pathology, diagnosis and therapy of this disease entity.*

Key words: schistosomiasis - female genital schistosomiasis - ectopic localization - *Schistosoma mansoni* - disease complication

Vaginal schistosomiasis was reported for the first time in Egypt, in 1899 (Madden 1899). Since then involvement of female organs, from the vulva to the ovaries, has been observed by pathologists from almost every country where schistosomiasis is endemic (for review see Feldmeier et al. 1995b). Clinically apparent vulval, vaginal and cervical schistosomiasis is a common gynecological finding in areas where infection with *Schistosoma haematobium* prevails (Friedberg et al. 1991). However, as a disease entity, female genital schistosomiasis (FGS) has been neglected during a period when considerable progress has been achieved in almost any other field of schistosomiasis research. Very recently, this has been acknowledged also by the World Health Organization: in 1997 the Gender Task Force of WHO's Tropical Diseases Programme has included FGS into a list of scientific areas which deserve a high research priority (Vlassoff 1997).

Whereas there is convincing evidence that infections with *S. haematobium* cause genital lesions in 50 to 80% of girls and women parasitized by this species (Renaud et al. 1989, Kjetland et al. 1996, Leutscher et al. 1997), the relevance of genital manifestations as a consequence of the infection with intestinal schistosomes is not precisely known. Previous reviews of the existing literature indicate that *S. japonicum* and *S. intercalatum* infrequently induce genital lesions and rarely cause significant pathology in the affected women (Sakamoto 1951, Carpenter et al. 1964, Richard-Lenoble et al. 1993). As to *S. mansoni* the picture is less clear: in Africa the geographic distribution of *S. haematobium* and *S. mansoni* widely overlaps, and the differentiation in histological specimen between *S. haematobium* and *S. mansoni* is not easily achieved. Nonetheless, there are several reports indicating that genital lesions in *S. mansoni* infection are not uncommon (Arean 1956, Renaud et al. 1971, Berry 1976, Chen & Mott 1989).

The objective of this paper is to examine excess pathology of the genital tract associated with *S. mansoni*. For this purpose the existing literature is critically reviewed and the findings are analyzed in the context of emerging knowledge of genital schistosomiasis in *S. haematobium* infection.

PARASITOLOGICAL AND PATHOPHYSIOLOGICAL BASIS

After maturation in the liver *S. mansoni* worms leave the portal vein circulation against the blood stream to eventually reach the superior, middle and inferior hemorrhoidal veins. As these vessels have numerous anastomoses with the veins draining the

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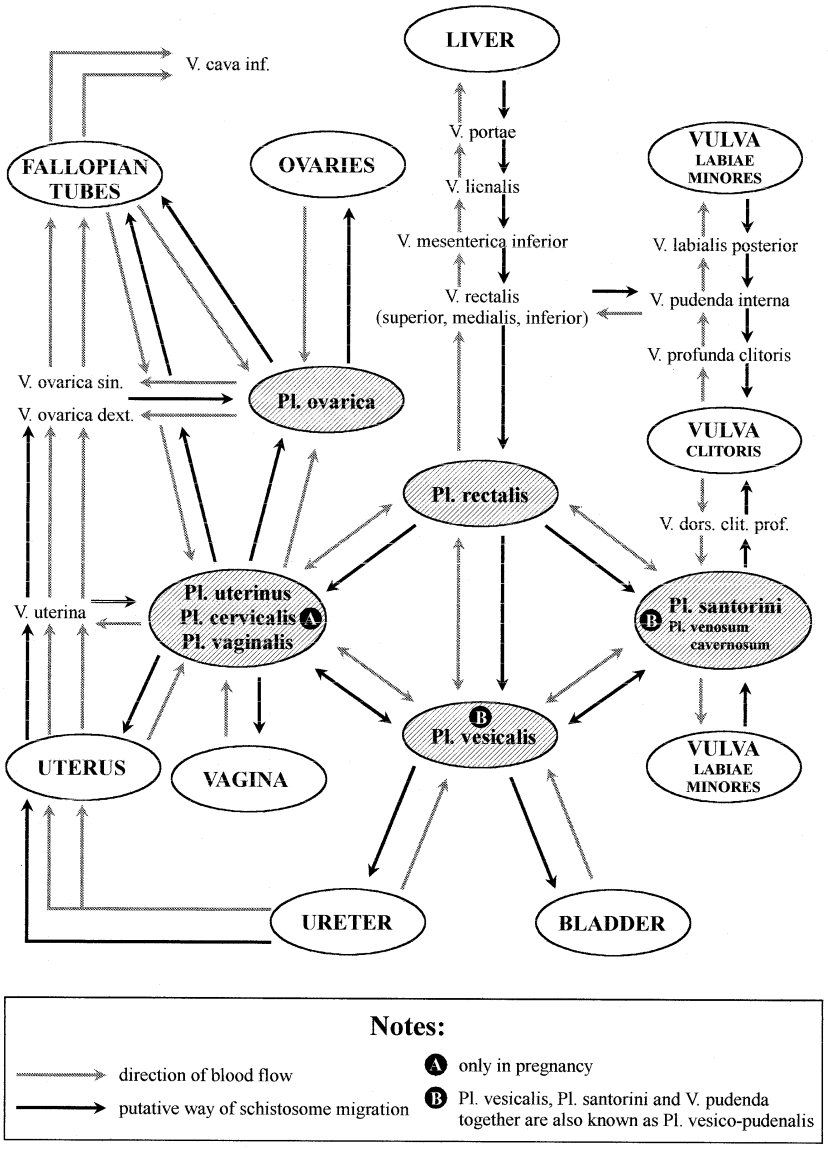
internal genital organs and the vulval area towards the vena cava inferior, and because the valves of the veins in question being rather imperfectly developed, there is no major obstacle which could impede the migration of adult *S. mansoni* worms from the territory of the portal vein to that of the vena cava inferior (Figure).

Arean (1956) pointed out that there also communications between the right and left spermatic veins with the superior and inferior mesenteric veins. As in females the ovarian veins are the counterparts of the spermatic veins, another channel is offered to migrating schistosomes to invade internal genital organs. Finally, as the ovarian and the uterine plexus are linked through anastomosises this explains why *S. mansoni* eggs can be found in the cervix and the vagina as well (Arian 1956, da Costa Froes 1957, Camara 1959).

Whereas the specific vasculature of the female pelvis is the essential prerequisite allowing worms to migrate, the anatomical situation is by no means fixed. In fact, it is modulated by host and by parasite-derived factors. Firstly, adaptive changes in pelvic vascularization occur during puberty, and especially during pregnancy. Such physiological changes increase the chances that *S. mansoni* worms can reach ectopic localizations. Secondly, there is a tendency of schistosomes to shift their intravascular positions late in chronic infection. As von Lichtenberg (1987) has pointed out, in patients



Vascular anatomy of the female pelvis and putative migration routes of schistosome worms.

with liver fibrosis *S. mansoni* worms frequently lodge in the superior mesenteric rather than in the hemorrhoidal veins. Since in those patients very few worms remain in the plexus rectalis - resulting e.g. in falsely negative rectal biopsies - infestation of genital organs through rectal-genital anastomosises could be less frequent in advanced stages of hepatosplenic disease. Thirdly, abnormal migration patterns of adult worms might be triggered by crowding. Indeed, Feldmeier et al. (1982) showed that in mixed *S. mansoni-S. haematobium* infected children the number of *S. mansoni* eggs in the urine was directly related to the number of *S. mansoni* eggs excreted in the stool. If one assumes that the number of eggs excreted per unit of stool or urine roughly corresponds to the worm pairs dwelling in the respective organs, this finding implicates that, if many *S. mansoni* worms are located in the hemorrhoidal veins, a proportional number tends to migrate through the recto-vesical anastomosises to eventually reach the plexus vesicalis. In analogy, a similar phenomenon may trigger the migration of *S. mansoni* worms to genital organs.

That migrating worms are actually responsible for the deposition of eggs in ectopic organs rather than a mere embolization of passively transported eggs to aberrant sites is clearly evidenced by the identification of copulating adult worms in histological sections of internal genital organs (da Costa Froes 1957).

PATHOLOGICAL AND GYNECOLOGICAL FINDINGS

From the clinical point of view, ectopic localizations of adult worms and the deposition of eggs in adjacent tissues are of considerable importance. Eggs deposited at the wrong site find themselves in a anatomical impasse, are sequestered and induce the formation of perioval granulomas that eventually lead to destruction of soft tissue, fibrosis and formation of scars.

However, the histopathological picture of genital schistosomiasis is only imperfectly understood and systematic observations so far are limited to infections with *S. haematobium*. Nosny (1963) based on the examination of histological sections from surgical specimen concluded that sequestered eggs are always surrounded by granulomatious tissue, but that the type of tissue reaction essentially depends on the topographic site affected. In contrast, in a comprehensive study in *S. haematobium* infected women in whom a colposcopic examination was combined with histological sectioning of cervix biopsies Helling-Giese et al. (1996b) observed a spectrum of inflammatory responses with two opponing poles. The first pole was characterized by a diffuse infiltration of plasma cells, lymphocytes, eosinophils and macrophages. This reaction type mainly occurred in the proximity of viable eggs, and macroscopically corresponded to polypoid/polypous tumors. The second pole was portrayed by a minimal cellular infiltrate best described as scar tissue. This pattern was predominatly observed around non-viable eggs or calcified egg fragments. Macroscopically, it coincided with sandy patches-like lesions. Surprisingly, the different types of histology may be simultaneously present in the same patient (Balasch et al. 1995, Helling-Giese et al. 1996b).

Da Costa Froes (1957) when examining histological specimen of ovaries, tubes and the cervix of Brazilian patients also reported a wide range of tissue reaction patterns. It is important to underline, though, that genital tissue reaction types around *S. mansoni* as well as *S. haematobium* eggs described so far clearly differed from the typical perioval granuloma as seen in the liver, the rectum or the bladder (von Lichtenberg 1987).

Taken together, it seems safe to assume that reaction patterns of genital tissue are complex and are modulated by host (topographic site, stage of disease, immunological competence, etc.) as well as by parasite-derived factors. This makes it difficult to elucidate the pathology through cross-sectional investigations of histological specimens alone. Serial investigations using an appropriate animal model (which still is not at hand) seem to warranted.

It is conceivable that host reactions against sequestered ova in the internal genital organs translate clinically into lower abdominal pain, dyspareunia, bloody cervical discharge, dysmenorrhea, or abdominal/pelvic tumors, frequent findings mentioned by gynecologists from *S. mansoni* endemic areas (Arean 1956, da Costa Froes 1957, Camara 1959). Explorative laparotomy revealed ovarial cysts, parietal tubal thickening and pelvic masses of tubal origin in these patients (da Costa Froes 1957, Camara 1959). This indicates that, if schistosome eggs are sequestered in internal genital organs the clinical picture, and presumably also the underlying pathology are similar, irrespective whether *S. mansoni* or *S. haematobium* are the responsible parasites (Helling-Giese 1996a).

There are experimental and clinical hints for a causal relationship between genital schistosomiasis and impaired fertility (da Costa Froes 1957, Bullough 1976, Tiboldi 1979, Tiboldi et al. 1979, Amano 1990, Krolikowski et al. 1995). Indeed, there are several ways in which schistosomiasis may influence fertility. If granulomas are situated in the fallopian tubes they induce a sterile salpingitis followed by local fibrosis eventually leading to fibrotic scars and tubal occlusion, the consequence of which would be infertility or ectopic pregnancy through altered peristalsis.

If granulomatous reactions develop near the hilus, hilar obstruction and parovarian adhesions may also be responsible for anovulation (Helling-Giese et al. 1996a). Hormonal disturbances in women with genital schistosomiasis may also explain infertility and subfecundity (Bindseil et al. 1991). In experimental schistosomiasis mansoni low concentrations of progesterone have been consistently observed (Tiboldi et al. 1979, Tiboldi 1979), probably provide another explanation for infertility observed in women with FGS. The authors suggest that low progesterone levels can be explained by atrophy of corpora lutea and discontinuance of their development as observed in mice.

It can also be assumed that genital schistosomiasis can complicate pregnancy. In this context two problems are expected to arise: ectopic pregnancy and pathological complications of normal pregnancy. Indeed, ectopic pregnancy leading to life-threatening peritoneal bleeding and death have been reported from Brazil (da Costa Froes 1957, Camara 1959, McNeely & Magu 1988). Secondly, infestation of the placenta may cause still birth, abortion, premature onset of labor or low birthweight (Bittencourt et al. 1980). In a prospective controlled trial Siegrist and Siegrist-Obimpeh (1992) in women infected with *S. haematobium* observed that women with urinary schistosomiasis, without necessarily presenting evidence of genital involvement, showed a significantly higher proportion of preterm deliveries and that the birthweight of their children was lower than that of non-infected women.

Histopathological and clinical data demonstrate that in addition to the upper reproductive tract the lower reproductive tract may also be affected by *S. mansoni* (Arean 1956, da Costa Froes 1957, Camara 1959, Coelho et al. 1979). Since *S. haematobium* egg-induced lesions in the vulva, the vagina and the cervix are considered to facilitate the infection with and the propagation of agents of sexually transmitted diseases, especially HIV (Feldmeier et al. 1994, Feldmeier 1995a), and because clinically the lesions are similar in *S. haematobium* and *S. mansoni* infection, the same may pertain to genital lesions caused by *S. mansoni*. Moreover, recently it has been pointed out that schistosomiasis of the cervix, together with or without concomittant human papilloma virus infection, has to be considered a risk factor for the development of cancer of the cervix (Feldmeier et al. 1996). In this context it is important to call attention to the fact that in Brazil the incidence of cancer of the cervix is highest in the northeast, i.e., in an area with a high prevalence of intestinal, and presumably also of genital schistosomiasis (de Abreu et al. 1995).

FREQUENCY AND TOPOGRAPHIC SITES AFFECTED

Already in 1957, da Costa Froes stated that "o número de casos publicados em relação com a especialidade, aumenta dia a dia" (the number of cases published by gynecologists increases from day to day). Two years later Camara (1959) underlined this statement by saying "a genitália femina, vem, cada dia, mais aparecendo no cartaz da parasitose" (manifestations of the female genitals become more apparent every day in the clinical picture of this parasitic infection). Unfortunately, this assumption has never been substantiated by appropriate clinical or epidemilogical studies. A total of 92 cases of genital manifestations have been reported from Brazil, the majority of which has been published between 1940 and 1960 (cited in da Costa Froes 1957, Camara 1959, Coelho et al. 1979). These publications are case reports or retrospective analysises of hospital records and, therefore, do not allow a definite conclusion on the true prevalence of this disease manifestation in the female population. Coelho et al. (1979), in a gynecological screening programme, found four cases of cervical schistosomiasis among 1,250 women (0.3%) with *S. mansoni* infection. However, vulval and vaginal lesions were not looked for and the examination of internal genital organs was not included in the study. Besides, even the diagnosis of cervical schistosomiasis was carried out with a rather insentive diagnostic technique. Thus, the true prevalence of cervical schistosomiasis should be considerably higher than 0.3%.

Histopathological data in Madagascar, where *S. mansoni* and *S. haematobium* occur in separate geographical areas, indicate that 74% of genital manifestations could be attributed to *S. haematobium* and 26% to *S. mansoni* (Brygoo 1968). More recent data from the same institution shows a relation of 88% for *S. haematobium* and 12% for *S. mansoni* (P. Leutscher, pers. commun. March 1997). Similarly, figures of 84 and 16%, respectively were calculated in a recent community-based study in Tanzania (G. Poggensee, pers. commun. August 1997). Based on these findings, one can estimate the ratio between the occurance of *S. haematobium* and *S. mansoni*-induced genital lesions to range between 1:0.3 to 1:0.1. If 50 to 80% of *S. haematobium* infected women present genital lesions (at least in the lower genital tract), it may be assumed that as many as 5 to 27% of women with an *S. mansoni* infection simultaneously have egg-related lesions somewhere in their genital tract.

As to the anatomical distribution of *S. mansoni* induced lesions the findings are more precise. Data from 83 cases in whom the topographic site was detailed (including publications from outside Bra-

zil) reveal that the ovaries are the organ mainly affected, followed by the cervix, the tubes and the uterus. Interestingly, vulval lesions account for 6% of all case reports. However, we doubt that this represents the true frequency in relation to other genital organs. By its very nature vulval lesions are easily detectable - by the patient as well as by the doctor - and thereby their relative importance is easily overestimated (Table).

TABLE

Relative frequency of genital lesions according to the topographic site

Organ affected	n	(%)
Vulva	5	6
Vagina	1	1
Cervix	20	25
Uterus	15	18
Fallopian tubes	14	17
Ovaries	28	33
Total	83	100

NATURAL HISTORY

Theoretically, the natural history of egg-induced lesions of the female genital tract should be of chronic nature. In experimental *S. mansoni* infection the typical egg granuloma (in the liver) reaches its maximum size by 4 to 8 days. However, total removal of residual egg-shells requires at least three months and, if the egg calcifies, probably years (von Lichtenberg 1987). Accordingly, the anatomical and/or functional abnormalities engended by granuloma and subsequent scar formation should extend over a similar period of time. In fact, data from case reports confirms this notion (da Costa Froes 1957, Camara 1959, Sedlis 1960, Mahmood 1975).

In practice, though, the natural evolution of egg-induced lesions is almost unknown. In patients whose records have been published, the natural history has been interrupted by surgical intervention, which in the case of impressively sized pelvic tumors of putative malignant origin seems to be justified. However, whether in young women with cervical schistosomiasis hysterectomy is the appropriate therapeutical means - as reported by Camara (1959) - is highly questionable. In the light of successful treatment of women with *S. haematobium*-induced genital lesions with a single dose of praziquantel, a more conservative approach in the treatment of *S. mansoni*-induced genital lesions seems to be warranted (Richter et al. 1996). Interestingly, in 1956 Arean has pointed out that unnecessary surgical treatment may be avoided if this condition is correctly diagnosed, although at that time no truely effective antischistosomal compound was available.

DISCUSSION

Genital manifestations of *S. mansoni* infections have been neglected as a disease entity during a period when considerable progress has been achieved in the diagnosis and management of other disease complications such as liver fibrosis. Our understanding of pathophysiology and pathology, especially in internal genital organs, is only rudimentary, simple and reliable diagnostic tools are not at hand, community-based epidemiological studies have never been performed, the natural history of genital lesions is not well known and controlled chemotherapeutic studies are lacking.

In contrast to infections with *S. haematobium* there are few data concerning *S. mansoni*-induced genital lesions. In Brazil, the literature abounds with case reports in the fourties and fifties, i.e., during a period when schistosomiasis received considerable scientific and public health attention for the first time. We have no explanation why thereafter the scientific literature is almost silent as far as genital schistosomiasis is concerned. It may be that the interest of the scientific community has simply waned, it may also be that the frequency of this disease entity has decreased along with a reduction in the overall prevalence of *S. mansoni* infection in this country. The former hypothesis is supported by findings from China, where - similar to the situation in Brazil - genital manifestations were frequently noted in elder publications, but not in the recent literature. A community-based study performed in the Sichuan Province (Qunha et al. 1997), though, showed considerable genital pathology in women with *S. japonicum* infection. Another explanations for the lack of recent observations on *S. mansoni*-induced genital schistosomiasis is the assumption that, at least if the lower genital tract is affected, egg-induced lesions are frequently misdiagnosed and, because women confound their complaints with symptoms with sexually transmitted diseases, they may not like to consult their gynecologist (Feldmeier et al. 1995b).

If our estimate is correct that at least 5% of girls and women with intestinal schistosomiasis also have genital lesions at an age when sexual activity peaks this should be of considerable concern. Since there is clinical, epidemiological and immunological evidence of genital lesions facilitating the transmission and propagation of HIV, FGS has to be regarded not only as an individual, but also as a public health thread. In the context of very high incidence rates of cervical cancer in Brazil in ar-

eas where *S. mansoni* is endemic the possible association between FGS, human papilloma virus infection and the development of cervical cancer deserves more attention. What is now needed are community-based or prospective clinical studies on a sound epidemiological basis.

Although the incidence of gynecological lesions in Manson's schistosomiasis presumably is much lower as compared to urinary schistosomiasis this disease entity surely is - as Arean (1956) has already pointed out - "of more than academic interest".

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