

Communications — Mededelingen

INVOLVEMENT OF HUMAN AND PRIMATE OVARIES IN SCHISTOSOMIASIS. A REVIEW OF THE LITERATURE

by

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Summary — A critical review is presented of the literature published during the last 70 years on the morphological alterations of the ovaries caused by human and primate schistosomiasis and on their functional consequences.

KEYWORDS : Schistosomiasis; Ovary Involvement; Review.

During the past seventy years several publications have appeared on the involvement of ovaries in schistosomiasis. These publications are scattered in the journals appearing in four different continents and in different languages, and, moreover, they have appeared in periodicals which are essentially other than purely parasitological journals.

The objects of this study was to collect all this information available in literature, to classify them according their subject and according to the place and date where and when they were published and to compile a critical review.

1. *Schistosomiasis of the ovaries*

1.1. Case studies

Symmers (1906a and 1906b) was the first to describe the condition of ovarian schistosomiasis in a young child. He observed a mass of fibrous tissue which involved the upper edge of broad ligament and ovary and detected presence of schistosome ova in the ovarian tissue.

The second case was published by Des Ligneris (1921) where an Indian woman developed dysmenorrhoea and oligomenorrhoea. She acquired tubal pregnancy and, on operation, the ovary was found to be the seat of schistosomiasis due to *Schistosoma haematobium*.

Subsequently, several reports appeared on ovarian schistosomiasis. Almost in half of the reported cases schistosomiasis was observed only in the ovaries and other parts of the genital tract were intact. In other cases the disease of the ovaries formed only one part of bilharziasis of the genital organs. In all the cases ovariectomy or ovarian resection was performed and the schistosomiasis was proved histologically by the presence of schistosoma ova.

Various authors have published case studies on *S. mansoni* infected individuals. Pitta and Cardeman in *Brasil* reported in 1959 one case of ovarian schistosomiasis and a review of publications up to 1957 about genital schistosomiasis, among these about schistosomiasis of the ovaries (Fernandes and Lapa, 1941a; Junqueira, 1946). Besides the publications mentioned in this review the following references could still be found in the Brazilian literature : Fernandes and Lapa (1941b), Machado (1954) and Câmara (1959) with single and Rozemberg (1950, 1951) with two cases. Iglesias (1941) and Lana (1961) from *Puerto Rico* reported on single cases and Areán (1956) on seven cases. Bahary *et al.* (1967) from *Izrael* published one case, Fortique (1943) from *Venezuela* reported on two cases. The most recent case study is that of Mahmood (1975) from the United States who found ovarian schistosomiasis and ovarian endometriosis in a west *Indian* woman.

There are few case studies on the infection of ovaries with *S. haematobium*. Gelfand (1941) published his report on one case and Gilbert (1943) on eight cases from *Rhodesia*. Camain (1953) found three cases in *Senegal*, Haspels (1967) observed one case in Northern-*Nigeria* and Renaud *et al.* (1971) reported on one case from the *Ivory Coast*.

The only publication implicating the role of *S. japonicum* in ovarian schistosomiasis is that of Carpenter *et al.* (1964) about a patient from the *Philippines*.

Some authors did not indicate the involved species of schistosome as Seif-Eldin (1958), Mouktar (1966) and El-Zeneiny (1968) from *Egypt* in single cases and Diouf *et al.* (1973) from *Senegal* in eleven cases.

1.2. Frequency of ovarian involvement in schistosomiasis

Shafeek (1958) observed schistosomiasis of ovaries in *Egypt* during the ten years period ending 1955 in 8.2 per cent of all ovarian lesions in the pathology department of the Ministry of Public Health. Badawy (1962) reported that 4.5 per cent of the ovaries were infected out of 88 cases of genital schistosomiasis while Youssef *et al.* (1970) found bilharzial lesions in the ovaries in 16 per cent out of 397 patients with genital involvement.

Loubière *et al.* (1976) reported on eight ovarian cases in genital schistosomiasis of 92 women in the Republic of *Ivory Coast*.

Edington (1967) detected presence of ova in the ovary in 1 instance in 19,826 surgical biopsies from different organs in Ibadan, *Nigeria*. Nirodi (1974) saw three cases of ovarian schistosomiasis in Zaria, Northern *Nigeria*, out of 8,379 biopsies.

Prates (1948) found 27 instances of ovarian involvement with schistosomiasis in *Mozambique* at the autopsy of several hundred females who had schistosomiasis.

In *South Africa* Charlewood *et al.* (1949) found seven ovaries infected with *S. haematobium* out of 34 African women (21 per cent) who had schistosomiasis of the genital tract. Out of 140 histological sections showing schistosomiasis of the female genital tract, Berry (1966) found that 14 per cent of these involved ovaries due to *S. haematobium* infection.

According to Boulle and Notelovitz (1964) the frequency of ovarian involvement in genital schistosomiasis was 2.2 per cent and according to Friedberg and Schneider (1967) it was almost the same : 2.5 per cent.

Areán (1956) reported seven ovarian cases affected with *S. mansoni* infection out of 18 gynecological lesions (39 per cent) in *Puerto Rico*.

In Bahia, *Brazil* Cheever and Andrade (1967) found by autopsy 6 per cent of the ovaries infected with *S. mansoni* among individuals suffering from Symmers hepatic fibrosis and 5 per cent among the cases with « asymptomatic » hepatic involvement.

More precise information was available from autopsies where the ovaries had been digested with potassium hydroxide.

Gelfand (1949) using this digestion method found ova of *S. haematobium* in the ovaries in 24 of 30 cases (80 per cent) where the bladder and the rectum were affected. In a subsequent publication appearing in 1950, Gelfand reported to have found 34 ovaries infected with *S. haematobium* in 45 African women (76 per cent) from *South Central Africa* (at present Rhodesia, Zambia, Mozambique and Malawi), where the bladder was infected with *S. mansoni* in 42 cases and with both *S. haematobium* and *S. mansoni* in three cases. Gelfand and Ross (1953), using the same method found *S. haematobium* infection of the ovaries in 16 out of 24 African women (67 per cent) who were infected with bilharziasis. Gelfand *et al.* (1971), using digestion technique alone or together with histology, demonstrated ovarian schistosomiasis due to *S. haematobium* in seven out of 64 African women (11 per cent) who died due to various causes. The digestion and histological procedures carried out by Bland and Gelfand (1970) on tissue material removed at operation from patients suffering from genital schistosomiasis revealed that the frequency of ovarian involvement was 7 per cent.

Edington *et al.* (1975) in *Nigeria*, using digestion method, found 31 per cent of the ovaries harboured *S. haematobium* in 37 females who had bladder schistosomiasis. It is noteworthy that they could not find ova in any of the cases using histological techniques only.

1.3. Pathology of ovarian schistosomiasis

The schistosome ova and even the worms themselves can reach the ovaries through porto-caval anastomoses. (Schistosome worms were found in the capillaries of the ovaries by Koppisch, 1941; Areán, 1956 and Renaud *et al.*, 1971.) A good summary about these anastomoses can be found in the publications of Pitta and Cardeman (1959) and Bahary *et al.* (1967).

The ovaries are sometimes enlarged, cystic and seeded with yellow patches (Nosny, 1963; Haspels, 1967). Adhesions could not be found in the majority of cases of isolated ovarian schistosomiasis.

Berry (1966) could not find any tissue reaction around *S. haematobium* ova in the ovaries of all the ten cases examined by her. Gelfand *et al.* (1971) wrote that from their studies « ... it appears unlikely that deposition of eggs in these organs evokes tissue response ».

Nevertheless, several case reports mentioned at the beginning of the present publication proved the contrary. Generally different stages of the evolution of pseudo-tubercles (so-called bilharziomas) can be seen with schistosome ova in their centre, sometimes included in foreign body giant cells. This ovarian alteration can be described as « granulomatous oophoritis » (Mahmood, 1975). Areán (1956) and Bahary *et al.* (1967) described acute bilharzial lesions in the ovaries including necrosis and acute inflammation.

The ovarian involvement is mainly at the hilum (Abdallah and Mousa, 1974) and « In some cases the ovary may contain hard fibrotic masses which are occasionally so large as to replace the ovary » (Gilbert, 1943). Camain *et al.* (1951) and Camain (1953) wrote about an « évolution sclérokystique » of the ovaries and Nosny (1963) reported on the same pathological changes in three out of seven histological preparations of ovarian schistosomiasis. In the small, fibrosed ovaries « no Graafian follicles were found » (El-Zeiney *et al.*, 1968).

According to Girges (1934) « The ovaries are scarred and fibrous, containing large number of ova in their parenchyma. They may be covered with a thick fibrous coating, which makes ovulation an impossibility, and sterility is the result ». We find the same opinion in the publications of Camain (1953) and Gaudefroy *et al.* (1972) and even in the earlier publications of Gelfand (1949, 1950) where he writes that « ... where the local deposition is severe..., effects from the fibrosis may ensue, resulting in sequelae such as sterility... ».

Ferguson (1917) was the first to lay emphasis on the sterility as an outcome of schistosomiasis. Now the same views are being expressed in the books dealing with tropical diseases (Abdallah and Mousa, 1974), with gynaecology in the tropics (Magdi, 1970) or with bilharziasis (Payet and Camain, 1967).

Bullough (1976) found that the frequency of bilharziasis in Malawi was significantly higher among the infertile than in the fertile women.

Charlewood *et al.* (1949), Machado (1954) and Shafeek (1958) found theca cell luteinization. Nosny (1963) reported on ovarian cysts where the granulosa cells showed an important luteinization in two out of seven histological preparations with ovarian schistosomiasis. Foda *et al.* (1961), Friedberg and Schneider (1967) found theca-cell proliferation. According to Haspels (1967) atrophy of the Graafian follicles and increase of the stroma are remarkable pathological changes around the foci containing ova of *S. haematobium*.

Rozemberg (1951) observed microcystic transformation. Fernandes and Lapa (1941a and 1941b) demonstrated multiple hemorrhagic follicular cysts around large number of bilharzial granulomas associated with glandular cystic hyperplasia of the endometrium which was confirmed by endometrial biopsy.

1.4. Clinical signs and symptoms of ovarian schistosomiasis

The clinical signs and symptoms are different according to the localisation. If not only the ovaries but also other internal genital organs are involved, the clinical signs and symptoms of the disease of those organs (Fallopian tube, uterus) are prevalent.

An isolated bilharziasis of the ovary can be « a silent condition » (El-Zeiney *et al.*, 1968), but sometimes an increased, cystic ovary causes pain and discomfort in the lower abdomen (Areán, 1956; Renaud *et al.*, 1971).

Menstrual disturbances are attributed to ovarian schistosomiasis. Dysmenorrhoea was described by Fernandes and Lapa (1941b), Charlewood *et al.* (1949) and Areán (1956) who found dysmenorrhoea in two out of six cases. Oligomenorrhoea (Girges, 1934) can also occur. Diouf *et al.*

(1973) mentioned the case of a 20 years old woman where the indication of the exploration was primary amenorrhoea with genital infantilism. They found ovarian schistosomiasis.

Normal cycle could be restored subsequent to adequate antiparasitic therapy of ovarian schistosomiasis (Ribeiro, 1936; Charlewood *et al.*, 1949) or subsequent to removal of the ovary which contained bilharzia granulomes (Fernandes and Lapa, 1941b) or following oophorectomy and antiparasitic therapy (Pitta and Cardeman, 1959).

Gaiao and Gueiros (1945) published a case of a woman who had high chorionic gonadotropin level and this was associated with severe schistosomal oophoritis.

Due to the pathological alterations the ovulation can be inhibited causing sterility and the dysfunction of the ovaries creating unfavourable conditions for a good nidation, can lead to abortions and premature births (Charlewood *et al.*, 1949).

The presence of urinary or rectal schistosomiasis, schistosomiasis of other genital organs (proved by cytological examination of the vaginal smear or by biopsy) or laboratory tests (eosinophily, positive complement-fixation test) with the clinical picture above mentioned can give rise to suspicion of ovarian schistosomiasis.

1.5. Ovarian tumours and schistosomiasis

Werneck and Junqueira (1941) were the first to describe the association of ovarian schistosomiasis with ovarian neoplasm, in their case with bilateral cystadenocarcinoma. Foda *et al.* (1961) observed the association with arrhenoblastoma and made a mention of ten cases of ovarian tumours associated with schistosomiasis of the ovary which were reported until 1961 (Schmitt, 1954; Zajac and Gaafar, 1959; Foda and Shafeek, 1960). Foda *et al.* (*loc. cit.*) supposed that schistosomiasis of the ovary, in some way, predisposes to tumour formations which arise from ovarian mesenchyme.

Paradinas (1972) reported on schistosomiasis in a cystic teratoma of the ovary and compiled a review of old and more recent references (Berry, 1966; Iskander and Kamel, 1968) on ovarian tumours containing schistosome ova.

Besides the references of the two reviews above mentioned some other publications on this subject can be still found. Malter (1950) in Brazil, Ali *et al.* (1956) in Surinam and Abu Zikry and Fahmy (1967) in Kuwait wrote about schistosome ova in ovarian *cystomas*, Stigliani (1949), Maltez (1951), Abu Zikry and Fahmy (1963) and Sunder-Raj (1976) reported on schistosomiasis in ovarian *cystic teratomas* and Lemos *et al.* (1960) found an association between *arrhenoblastoma* and Manson's schistosomiasis.

1.6. Involvement of primate ovaries in schistosomiasis

There is only one publication in the literature about the occurrence of ovarian schistosomiasis in experimental animals. Webbe *et al.* (1974) found *S. haematobium* ova in the ovary or the Fallopian tubes in nine out of ten female baboons and « ... in 2 animals there was replacement of most of the glandular tissue producing parasitic castration... ». They suggested that « ... more attention should be given to the effect of the infection on the genital system and/or fertility ».

2. Endocrine changes with involvement of the ovaries in schistosomiasis

The direct ovarian affection with schistosomes is probably not the only way which could influence the morphology and the function of the human ovaries.

Puberty and menstruation among girls suffering from schistosomiasis could be delayed up to the age of 20 or 22 years. The period of menstruation cycle may be suspended for two, four, five or even eight months and menopause could take place quite early in life at the age of 30 to 40 years. In the patients infected with *S. haematobium* growth is retarded to the extent that they look considerably younger than their real age (Afifi, 1928; Girges, 1934).

It would appear that in the cases where puberty is delayed or the onset of menopause is unusually early there must be considerable ovarian involvement, but the literature reveals a lack of direct observation in such cases (Gilbert, 1943).

Bassily (1954-1955) analysed in his thesis 33 cases of infantilism with advanced bilharzial cirrhosis in *Egypt* suggesting that panhypopituitarism was the most likely cause of infantilism in these cases. Ghalioungui and Shawarby (1962) thought that undernutrition was the most important factor responsible for the endocrine disturbances in adult bilharziasis. Aboul Dahab *et al.* (1973) commenting on male and female children suffering from schistosomiasis, stated that « ... none of the 7 cases above 12 years showed signs of sexual maturation ». They found evidence of mild ACTH deficiency. (However the levels of gonadal hormones or gonadotropins were not studied.)

Meira (1951), Ferreira (1957) and later Parthermore *et al.* (1967) described retarded growth and retarded sexual development with hepatosplenic schistosomiasis *Mansoni* in *Brazil*. Ferreira (loc. cit.) found low levels of gonadotropins in the urine of these infantile children with biological method and he observed an improvement after splenectomy. He considered that spleen might have had an inactivating effect on the circulating gonadotropins. Macedo de Carvalho and Horwith (1972) contemplated, on the base of hormonal examinations, that pituitary gland played a role in such an endocrine disorder.

Huang *et al.* (1957) in *China* reported on patients of both the sexes whose infection with *S. japonicum* was associated with dwarfism and sexual infantilism. They called this endocrine disturbance « schistosomiasis dwarfism » and believed that the gonadal deficiency was a result of failure of stimulation from the pituitary gland. Kuo and Chiang (1958) affirmed the observations of Huang *et al.* (loc. cit.) and agreed with their aetiopathogenetic interpretation. Ko (1957) and Ch'eng and Tiao (1958) performed autopsies and found morphologic changes in the pituitary gland, adrenals and thyroid among patients who had the clinical signs and symptoms as mentioned above. Ko (loc. cit.) found infantile ovaries and Ch'eng and Tiao (loc. cit.) observed underdevelopment of sexual organs like those of preadolescent children. Cheng *et al.* (1959) called this pathological state caused by schistosomiasis « selective hypopituitarism » with a reduction in gonadotropin and corticotropin production. Hsüeh and Wu

(1963) and Chu *et al.* (1963) suggested that the endocrine disorders observed in late stages of schistosomiasis signify a polyglandular defect where the gonads are the most vulnerable.

Hsüeh and Wu (*loc. cit.*) emphasised that many patients with advanced schistosomiasis who had primary amenorrhoea, disturbed menstruation or sterility, had recovered after appropriate antimony treatment. According to these authors the endocrine disturbance is a functional and reversible hypopituitarism.

3. Comments

The *first part* of this study was dealing with the different aspects of ovarian schistosomiasis where the ovarian involvement was proved by the presence of schistosome ova.

It is evident that big differences can be found in the frequency of ovarian involvement among different countries, however the frequencies are sometimes different also in the same country. For example in Egypt the ovaries were involved in 4.5 per cent by genital schistosomiasis according to Badawy (1962) and in 16 per cent according to Youssef *et al.* (1970). In South Africa the percentages varied between 2.2 and 21.0. These differences could exist due to the possibility that the patients came to the hospitals from different parts of the country where the frequency of the disease was different, that the number of pieces of ovaries cut off for pathological examination was different, that the number of the histological preparations and the accuracy of their examination were not the same in the different laboratories of pathology. The most reliable data are those of Gelfand (1949, 1950), Gelfand and Ross (1953), Gelfand *et al.* (1971) and Bland and Gelfand (1970) in Rhodesia because the examination occurred with digestion method and in the same laboratory.

The extended examinations about the frequency of schistosomiasis in different organs demonstrated that bilharzial affection can exist in the ovaries in several instances although clinical manifestations are probably infrequent.

Perhaps the results of animal experiments could lead to better understanding of the pathomechanism of the theca-cell luteinization and theca-cell proliferation observed by several investigators (Charlewood *et al.*, 1949; Machado, 1954; Shafeek, 1958; Foda *et al.*, 1961; Nosny, 1963; Friedberg and Schneider, 1967).

Collip *et al.* (1933) observed a marked over-development and the appearance of luteinization of the theca-cells in hypophysectomised immature rats after treatment with the anterior pituitary-like hormone of the human placenta and Greep *et al.* (1942) reported on similar observations after a combined treatment of FSH and LH hormones. « There seems little doubt that the thecal proliferations in human... arise as a direct or indirect result of pituitary (ICSH) stimulation » (Culiner, 1945).

It is possible that destruction of the ovarian tissue due to schistosomiasis in human subjects may result in some cases in a decreased hormone production. The low level of the ovarian hormones may trigger a hyperproduction of FSH and LH hormones in the anterior pituitary through a negative feed-back and the result would be theca-cell proliferation and theca-cell luteinization in the ovaries.

Charlewood *et al.* (loc. cit.) attributed the irregularities in the menstrual cycle presented by the patients with ovarian schistosomiasis to the theca-cell luteinization. According to the observations of Culiner (loc. cit.) on human subjects and on baboons « In the presence of extensive thecal luteinization with follicular atresia, disturbances of menstrual rhythm and bleeding may ensue ».

The clinical symptoms of isolated ovarian schistosomiasis: menstrual disorders and pain in the lower abdomen due to a palpable ovarian mass are the signs of a serious pathological alteration in the ovarian tissue. Sterility as a possible outcome of ovarian schistosomiasis is to-day generally accepted in the literature.

There were 15 publications in the literature until now dealing with the association between ovarian tumours and schistosomiasis. The supposition of Foda *et al.* (1961) that schistosomiasis of the ovary could predispose to the formation of mesenchymal tumours did not become generally accepted and the point of view to-day is that schistosomiasis in ovarian tumours is probably not more than a coincidence.

In the *second part* of this study the main point was the infantilism in schistosomiasis observed in the last two decades in Egypt, in Brazil and in China by many investigators. This infantilism is not restricted to females and Nabawy *et al.* (1961), Abdel-Kader *et al.* (1972) in Egypt and Sucupira and Pupo (1976) in Brazil reported on the same clinical manifestations of schistosomiasis in males.

The great majority of the authors suggest a pituitary origin, but some others (Charlewood *et al.*, 1949; Ghalioungui and Shawarby, 1962; Sucupira and Pupo, loc. cit.) think that undernutrition may be the major factor in the infantilism. Nabawy *et al.* (loc. cit.) could not find any correlation between delayed genital development and hepatic involvement.

However the clinical observations missed the number of subjects sufficient for an exact statistical analysis or the use of modern methods of endocrinology.

The cause of the retarded development of children with schistosomiasis is not ascertained yet. Nutritional or hepatic factors may play a role in the evolution of this syndrome, but the hypofunction of the pituitary gland seems to be the important link in the pathogenesis of this endocrine disorder.

Walker *et al.* (1970) in South Africa, Cook *et al.* (1974) in St. Lucia (Lesser Antilles) and Lehman *et al.* (1976) in Brazil, found no differences in height between infected and not infected school age children, in contradiction with the observations of Jordan and Randall (1962) in Tanganyika (to-day Tanzania) who suggested that *S. mansoni* and *S. haematobium* infections are associated with retarded growth. There are no data in the publications of these authors about the sexual development of these children.

Apparently, the survey of literature presented above reveals that the aspects of schistosomiasis with special reference to morphological and functional changes of the ovary should be scrupulously studied, not only by systematic clinical and epidemiological investigations but also by employing a model experimental host.

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Complications ovariennes et surrénales dans la schistosomiase. I. Atteinte ovarienne dans la schistosomiase de l'homme et des primates. Revue de la littérature.

Résumé — Une revue critique de la littérature publiée durant ces 70 dernières années est consacrée aux altérations morphologiques provoquées par la schistosomiase dans les ovaires chez des humains et les primates, ainsi qu'aux conséquences fonctionnelles de ces altérations.

Ovariële en adrenale verwikkelingen bij schistosomiasis. I. Ovariële aantasting bij menselijke en primaten-schistosomiasis. Overzicht van de literatuur.

Samenvatting — Een kritisch overzicht wordt voorgelegd over de literatuur der 70 laatste jaren aangaande de morfologische veranderingen die optreden aan de eierstokken van mensen en primaten, veroorzaakt door schistosomiasis, en hun functionele consequenties.

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