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CHAPTER 4

Urogenital schistosomiasis during pregnancy is associated with low birth weight delivery: Analysis of a prospective cohort of pregnant women in Gabon

Ghyslain Mombo-Ngoma, Josiane Honkpehedji, Arti Basra, Jean Rodolphe Mackanga, Rella Manego Zoleko, Jeannot Zinsou, Jean Claude Dejon Agobe, Bertrand Lell, Pierre-Blaise Matsiegui, Raquel Gonzales, Selidji T Agnandji, Maria Yazdanbakhsh, Clara Menendez , Peter Kremsner, Ayola Akim Adegnika, and Michael Ramharter.

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Abstract

Background

An estimated 40 million women of childbearing age suffer from schistosomiasis. Animal models indicate a deleterious effect of maternal schistosomiasis infection on pregnancy outcomes. However, to date there is a lack of epidemiological evidence evaluating schistosomiasis related morbidity in pregnancy. This study was designed to describe the impact of urogenital schistosomiasis on pregnancy outcomes in a highly endemic region of Central Africa.

Methods

Pregnant women attending antenatal clinics in Fougamou and Lambaréné, Gabon, were consecutively screened for the presence of *Schistosoma haematobium* eggs in diurnal urine samples. Maternal and newborn characteristics were assessed at delivery and compared between infected and uninfected mothers. The impact of maternal schistosomiasis on low birth weight and preterm delivery was assessed in logistic regression analysis.

Results

Urogenital schistosomiasis was diagnosed in 103 (9%) of 1115 pregnant women. Maternal age was inversely associated with prevalence of urogenital schistosomiasis with higher burden among nulliparous women. Low birth weight was more common among infants of *S. haematobium* infected mothers. This association was unaffected by controlling for demographic characteristics and *Plasmodium* infection status (adjusted OR 1.92; 95%CI: 1.08-3.41). Other risk factors associated with low birth weight delivery were underweight mothers (aOR 3.00; 95%CI: 1.47-6.14), peripheral or placental *P. falciparum* infection (aOR 1.83; 95%CI: 1.08-3.08) and female gender of the newborn (aOR 1.52; 95%CI: 1.04-2.20). Preterm delivery was not associated with *S. haematobium* infection (aOR 1.22 95%CI: 0.58-2.56).

Conclusions

This study indicates that pregnant women with urogenital schistosomiasis are at an increased risk for low birth weight deliveries. Further studies evaluating targeted treatment and prevention programs for urogenital schistosomiasis in pregnant women and their impact on delivery outcomes are warranted.

Keywords: schistosomiasis, pregnancy, low-birth-weight, prematurity, Gabon

Introduction

Schistosomiasis affects at least 200 million people globally and is ranking second in public health impact among human parasitic diseases [1]. Urogenital schistosomiasis is a particular public health concern in endemic countries of sub-Saharan Africa where successful and sustainable control programs are mostly lacking. Urogenital schistosomiasis disproportionally affects poor rural regions where it may lead to high prevalence particularly in children and young adults [2]. It is estimated that about 40 million women of childbearing age are suffering from schistosomiasis, yet little is known about the specific morbidities inflicted on pregnant women and their offspring [3].

Animal models provide evidence that schistosomiasis infection may lead to deleterious pregnancy outcomes [3]. A mouse model of *S. mansoni* indicates a significantly higher proportion of abortion, maternal and offspring deaths as well as a lower weight of the offspring [3,4]. These findings imply the potential for deleterious impact of schistosomiasis on pregnancy outcomes. A review by Nawal Nour summarizes our current understanding of the impact of urogenital schistosomiasis on women's health [5]. *Schistosoma haematobium* causes significant morbidity and may even lead to life threatening complications due to its predilection for the female urogenital tract. *Schistosoma haematobium* eggs form granulomatous inflammation and potential obstruction in the urinary bladder, ureter, uterus, fallopian tube, and ovaries [6]. To date there are however no high quality epidemiological surveys assessing the impact of urogenital schistosomiasis on pregnancy in humans. Published case reports indicate such an association, however causal inference is inherently limited from single patient reports [7–9]. Studies evaluating the association of *S. mansoni* with pregnancy outcomes have demonstrated an increased risk for anaemia, preterm deliveries, and low birth weight infants [10,11].

Based on these data, we therefore hypothesised that urogenital schistosomiasis in pregnancy may similarly lead to deleterious pregnancy outcomes [12,13]. To further substantiate this hypothesis, we assessed the clinical evidence for an adverse impact of urogenital schistosomiasis on delivery outcomes in a cohort of pregnant women in a rural region of Central African Gabon.

Materials and methods

Study settings and population

This study was carried out from September 2009 to November 2013 at the Centre de Recherches Médicales de Lambaréné (CERMEL) in the Albert Schweitzer hospital in Lambaréné, and the Ngounié Medical Research Centre in Fougamou, Gabon [14]. Fougamou is a rural municipality located in Central Gabon about 100 km south of Lambaréné, which is a semi-rural city situated within the equatorial rainforest. This region is highly endemic for *S. hematobium* [15–17].

The study population of this analysis consists of pregnant women and their offspring participating in two prospective cohort studies, the MIPPAD trial (Malaria in Pregnancy Preventive Alternative Drugs, NCT 00811421) [18,19], and the IDEA study (www.idearesearch.eu). Pregnant women were invited to provide written informed consent when presenting until the 28th week of gestation and were screened for urogenital schistosomiasis on three consecutive days. Participants were followed up until delivery and further follow-up of the child was performed until one year of age.

Detection of S. haematobium infections

Determination of *S. haematobium* infection was performed using 10 mL of midstream urine collected during the day, which urine was passed through a 12-µm polyamide N-filter (Millipore, Billerica) followed by subsequent microscopic examination for the detection of eggs as described in more detail elsewhere [19]. Women were classified as infected if at least one *S. haematobium* egg was detected in the urine. All schistosomiasis infected women were treated with praziquantel 40mg/kg after delivery.

Study variables and outcomes

Main study endpoints for pregnancy outcomes were defined as the proportion of low birth weight infants and preterm delivery. Low birth weight was defined as birth weight less than 2500g and was measured using calibrated digital infant scales. In case of home deliveries or other reasons for delayed measurement of birth weight, data were imputed using a previously published regression model [20]. Preterm delivery was defined as delivery before 37 weeks of gestation. Gestational age was determined at recruitment and during gestation by measuring symphysis-fundus height by bimanual palpation and date of last menses, and by Ballard Score assessment of newborns after delivery.

Participants' baseline information was recorded at recruitment including maternal age calculated based on the date of birth at enrolment or as self-reported. Maternal age was divided into the following four categories: young adolescent girls aged $\leq$16 years, older adolescents aged 17-19 years, adults

aged 20-30 years and adults > 30 years of age. Weight and height were assessed to calculate body mass index (BMI) which was categorized for further statistical analysis using predefined threshold levels according to World Health Organisation recommendations (underweight: BMI<18.5; normal weight: BMI 18.5-24.9; overweight: BMI 25.0-29.9; obesity: BMI>=30.0).
Gestational age, birth outcome and delivery characteristics were recorded at delivery and haemoglobin levels were assessed from finger-prick or venous blood using the HemoCue device (www.eurotrol.com). Anaemia was defined as haemoglobin level <11g/dL. *Plasmodium* infection was defined as the detection of malaria parasites in peripheral blood or placenta samples collected at delivery. Parasitological assessments were performed from peripheral and cord blood by thick and thin smears. Placental malaria assessments were performed by impression smears.

Statistical methods

Statistical analyses were performed using Stata/IC version 13.1 for Windows (StataCorp Lp, College station TX). Chi square tests were used to compare proportions between infected and uninfected mothers among categories of different variables. Logistic regression models were used for univariate and multivariate analysis of risk factors associated with adverse pregnancy outcomes. The multivariate model included variables that were associated in the univariate analysis with the outcome of interest but also included forced variables that comprised the known risk factors parity, maternal haemoglobin, maternal age, and infant's gender. Likelihood ratio test p-values were computed and statistical significance was interpreted as weak evidence if $p<0.1$, good quality evidence if $p<0.05$ and strong evidence if $p<0.01$.

Ethical considerations and Informed Consent

The MiPPAD study protocol and study materials received ethical approvals from the University Hospital of Barcelona Institutional Review Board and from the national ethics committee of Gabon. The IDEA protocol received the ethical approval of the national ethics committee of Gabon. All participating women signed a written informed consent form before any study related procedure was performed. The studies were conducted according to the ICH-GCP principles and the declaration of Helsinki.

Results

A total of 1115 pregnant women were screened for urogenital schistosomiasis in the two prospective cohorts (674 and 441 women in MiPPAD and IDEA, respectively). Delivery data were available from 1031 mothers and 44 pregnancies resulted in stillbirth or miscarriage. Among 987 live births, 28 deliveries were multiple gestations, leaving 959 singleton live births for the analysis of pregnancy outcomes. Details of study participants flow are shown in Figure 1.

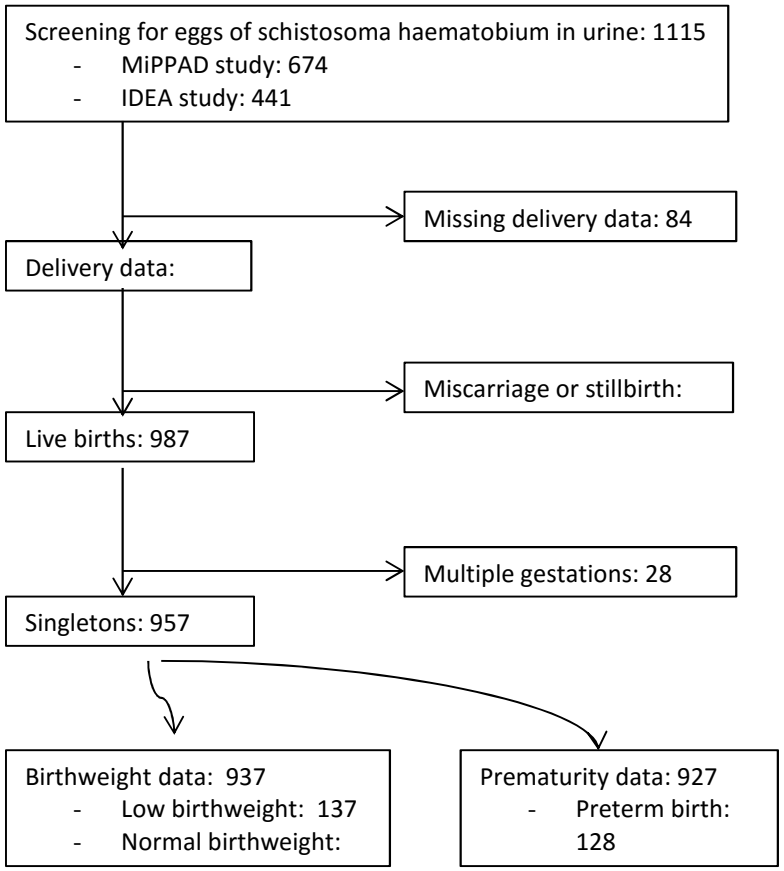

Figure 1: **Participants' flow diagram**
MiPPAD: Malaria in Pregnancy Preventive Alternative Drug; IDEA: Infectious Diseases European and African research initiatives

Among 1115 pregnant women screened for urogenital schistosomiasis, 103 (9%) were positive for *S. haematobium* eggs in urine. Increasing maternal age was inversely associated with schistosomiasis as younger women were more commonly infected than older participants, with five times the odds of *S. haematobium* infection in young adolescents, Odds Ratio (OR) 5.03 (95% CI: 1.93-13.10) and more than twice the odds in the 17-19 years, OR: 2.66 (95% CI: 1.17-6.04) and the 20-30 years OR: 2.86 (95% CI: 1.34-6.09) compared to women above 30 years (Table 1). Similarly, urogenital schistosomiasis was more prevalent in primigravide women, OR: 1.64 (95%CI: 1.06-2.55), than in multigravidae (Table 1). At the same time the incidence of placental malaria infection was higher among *S. haematobium* infected, OR 3.36 (95%CI: 1.73-6.52), than in uninfected mothers (Table 2).

Table 1: **Maternal characteristics and urogenital schistosomisis during pregnancy**

Variables		**N**	***S. hematobium* positive, n (%)**	**OR (95% CI)**	***P* value***
overall prevalence of S. haematobium		1115	103 (9.2)		
Maternal age (years)	*14-16*	66	11 (16.7)	5.03 (1.93-13.10)	0.004
	17-19	251	24 (9.6)	2.66 (1.17-6.04)	
	20-30	587	60 (10.2)	2.86 (1.10-6.09)	
	≥ 31	209	8 (3.8)	1	
BMI	*Underweight*	52	6 (11.5)	1.29 (0.53-3.13)	0.84
	Normal	695	64 (9.2)	1	
	Overweight /Obese	367	33 (9.0)	0.97 (0.63-1.51)	
Gravidity	*Primigravida*	263	33 (12.6)	1.62 (1.04-2.52)	0.04
	Multigravida	848	69 (8.1)	1	
Parity	*Nulliparous*	293	39 (13.3)	3.17 (1.77-5.67)	0.0001
	Primiparous	429	46 (10.7)	2.48 (1.41-4.36)	
	Multiparous	390	18 (4.6)	1	
Any previous abortion	*Yes*	235	17 (7.2)	0.71 (0.42-1.23)	0.21
	No	873	86 (9.8)	1	

Footnote: N/n=number of participants; OR=odds ratio; 95%CI= 95% Confidence Interval; BMI=Body Mass Index;
*Likelihood Ratio Test;

Table 2: **Maternal urogenital schistosomiasis and pregnancy outcomes**

Variables		**N**	***S. hematobium* positive, n (%)**	**OR (95% CI)**	**P value ǂ**
Maternal Schistosomiasis		1031	92 (8.9)		
Term at delivery	*Normal*	828	73 (84.9)	1	0.84
	Preterm (<37 weeks)	139	13 (15.1)	1.07 (0.57-1.98)	
Type of delivery	*Vaginal*	877	74 (94.9)	1	0.62
	Caesarean	37	4 (5.1)	1.32 (0.45-3.81)	
Delivery outcome	*Live birth*	987	88 (94.6)	1	0.59
	Stillbirth or miscarriage	44	5 (5.4)	1.31 (0.50-3.41)	
Maternal haemoglobin (g/dl)	*Normal (≥ 11g/dl)*	500	45 (49.4)	1	0.976
	Anaemia (<11g/dl)	498	46 (50.6)	1.03 (0.67-1.58)	
Placental malaria infection	*No*	897	71 (84.5)	1	**0.001**
	Yes	58	13 (15.5)	3.36 (1.73-6.52)	
Peripheral malaria infection	*No*	908	77 (88.5)	1	0.31
	Yes	84	10 (11.5)	1.46 (0.72-2.94)	
*Birth weight**	*Normal*	816	67 (74.4)	1	**0.04**
	Low (<2500g)	174	23 (25.6)	1.70 (1.03-2.82)	
*Infant Sex***	*Male*	511	53 (57.6)	1	0.15
	Female	500	39 (42.4)	0.73 (0.47-1.13)	
*Infant Haemoglobin level***	*Normal (≥ 11g/dl)*	796	68 (93.2)	1	0.73
	Anaemia (<11g/dl)	50	5 (6.8)	1.19 (0.46-3.10)	

Footnote: *including multiple gestation and non-live birth; **including twins and stillbirths; N=number of participants; OR=odds ratio; 95%CI= 95% Confidence Interval; ǂLikelihood Ratio Test.

Low birth weight and preterm delivery were very common in this study population with incidences of 16.1% (155/963; 95%CI: 13.8% – 18.5%) and 13.8% (132/951; 95%CI: 11.7% – 16.2%), respectively, among all live births and 14.6% (137/937; 95%CI: 12.4% – 17.0%) and 13.8% (128/927; 95%CI: 11.6% – 16.2%), respectively, if restricted to only singleton live births. Low birth weight was more common among infants from *S. haematobium* infected women, OR: 1.70 (95% CI: 1.03-2.82; p=0.039), compared to those without evidence for infection (Table 2). Concordantly, mean birth weight was lower in women suffering from urogenital schistosomiasis during pregnancy (mean birth weight: 2875.9 g, 95%CI: 2747.4 – 3004.4) than in uninfected participants (mean birth weight: 2956.6 g; 95%CI: 2923.0 – 2990.2)

Maternal urogenital schistosomiasis was demonstrated to constitute an independent risk factor for low birth weight delivery after controlling for maternal age, parity, body mass index, *P. falciparum* infection, haemoglobin, and infant gender (adjusted OR: 1.92; 95%CI: 1.08-3.41; Table 3). Other risk factors associated with low birth weight delivery were underweight mothers (aOR 3.00; 95%CI: 1.47-6.14), peripheral or placental *P. falciparum* infection (aOR 1.83; 95%CI: 1.08-3.08) and female gender of the newborn (aOR 1.52;

95%CI: 1.04-2.20; Table 3). Analysis for preterm delivery demonstrated no increased risk for pregnant women infected with *S. haematobium* infection (OR 1.06; 95% CI: 0.54-2.07) in univariate and multivariate analysis (aOR 1.22 95% CI: 0.58-2.56, n=894).

Table 3: **Univariate and multivariate analysis of risk factors for low birth weight**

Low birth weight (N=912)		**crude OR (95%CI)**	**P value***	**adjusted OR (95%CI)**	**P value***
Schistosoma haematobium infection	*Negative*	1	0.04	1	0.04
	Positive	1.80 (1.04-3.11)		1.92 (1.08-3.41)	
Maternal age (years)	*14-16*	1.18 (0.55-2.52)	0.44	1.64 (0.66-4.06)	0.24
	17-19	1.42 (0.92-2.19)		1.72 (1.04-2.84)	
	20-30	1		1	
	≥ 31	1.03 (0.63-1.68)		1.14 (0.64-2.03)	
BMI	*Underweight*	3.00 (1.51-5.98)	0.007	3.00 (1.47-6.14)	0.006
	Normal	1		1	
	Overweight /Obese	0.88 (0.59-1.32)		0.84 (0.54-1.28)	
Parity	*Nulliparous*	0.96 (0.59-1.56)	0.16	0.59 (0.30-1.16)	0.04
	Primiparous	1.40 (0.93-2.12)		1.17 (0.70-1.97)	
	Multiparous	1		1	
any malaria infection (placenta or peripheral)	*No*	1	0.007	1	0.02
	Yes	2.04 (1.24-3.34)		1.83 (1.08-3.08)	
Maternal haemoglobin at delivery	*Normal (≥ 11g/dl)*	1	0.68	1	0.31
	Anaemia (<11g/dl)	0.93 (0.65-1.32)		0.82 (0.57-1.20)	
Infant sex	*Male*	1	0.04	1	0.03
	Female	1.46 (1.02-2.09)		1.52 (1.04-2.20)	
Study	*MIPPAD*	1	0.09	1	0.10
	IDEA	1.37 (0.95-1.96)		1.38 (0.94-2.02)	

Footnote: N=number of participants; OR=odds ratio; 95%CI= 95% Confidence Interval; BMI=Body Mass Index;
*Likelihood Ratio Test

Discussion

This study shows that urogenital schistosomiasis infection is common among pregnant women in this rural Central African region, in line with previous reports [15]. It may be speculated that the microscopic diagnostic assay employed in this study may have had suboptimal sensitivity compared to molecular diagnostic techniques and that the burden of urogenital schistosomiasis in pregnancy may have been underestimated. Thus the prevalence of schistosomiasis might be higher than 9% in our study population of pregnant women.

The main finding of this study is the observation of a significantly higher risk for delivering low birth weight infants in *S. haematobium* infected than in uninfected pregnant women. This finding was further substantiated by multivariate logistic regression analysis indicating that urogenital schistosomiasis is an independent risk factor for low birth weight delivery. Several case reports of pregnant women infected with schistosomiasis are published in literature indicating adverse birth outcomes as summarized in a review by Friedman et al.[3]. Whereas these reports provide anecdotal evidence, no causal inference could be drawn from these data due to inherent limitations of retrospective case reports.

A similar analysis has been published for intestinal schistosomiasis caused by *S. japonicum.* In this study an increased prevalence of low birth weight was observed in infected pregnant women in China [6]. Similarly, a study conducted in Ghana indicated a higher prevalence of preterm deliveries among *Schistosoma* infected compared to uninfected women [11]. In this study differences in birth weight were observed only in the small subgroup of preterm neonates. However, this study was limited by a small sample size, a lack of adjustment for potential confounders and may have suffered from selection bias. Experimental evidence from animal models indicates that both acute and chronic infections may result in decreased birth weight in urogenital schistosomiasis (3,18,19).

Schistosomiasis haematobium causes pathology in the urinary and genital tracts as a result of trapped eggs. Histology studies of urogenital schistosomiasis have shown that the tissue around both viable and inactivated eggs has increased vascularity and high density of inflammatory cells [22,23]. Concordantly clinical findings such as sandy patches and papules have been reported [24].

In order to determine the potential mechanistic link between maternal schistosomiasis and poor birth outcomes, some data have indicated that maternal schistosomiasis results in pro-inflammatory signature that is detectable in maternal and foetal compartments of the placenta and a subset

of these responses are associated with decreased birth weight [25]. Other proposed mechanisms of schistosomiasis-mediated adverse birth outcomes include hypoxia due to pro-inflammatory cytokines, placental inflammation, and maternal iron deficiency due to chronic bleeding [12,26]. This is supported by epidemiological evidence indicating that urogenital schistosomiasis causes anaemia, which is in itself a risk factor for adverse pregnancy outcome including low birth weight delivery [12]. In this study approximately half of participants were anaemic; however anaemia was not directly associated with urogenital schistosomiasis or low birth weight delivery. This observation may find an explanation in the multiplicity of causes of anaemia in this geographical setting including malaria, soil transmitted helminths, nutritional deficiencies, and pregnancy by itself.

Urogenital schistosomiasis was strongly associated with placental malaria infection in this study population. Placental malaria is an established risk factor for low birth weight in malaria endemic regions and was concordantly independently associated with low birth weight in multivariate analysis. As schistosomiasis and malaria affect both disproportionally the “rural poor”, these two major parasitic infections are likely to have a combined deleterious effect on pregnant women in regions of co-endemicity.

These raise the question of appropriate screening and treatment programs in pregnant women. Two trials investigating the impact of treatment for schistosomiasis during pregnancy on birth outcomes have shown no significant effect. A trial evaluating praziquantel treatment for *S. japonicum* in the Philippines demonstrated no significant effect on birthweight or the prevalence of low birth weight and small for gestational age [27]. Another trial from Uganda evaluated treatment of pregnant women infected with *S. mansoni* later in gestation (mean gestational age at enrolment 26.6 weeks) and showed no effect on maternal anaemia or proportion of low birth weights [28]. These results may argue that prevention of schistosomiasis before pregnancy may be more efficacious than treatment during pregnancy highlighting the importance of preconception care for schistosomiasis.

In summary, urogenital schistosomiasis was highly prevalent among pregnant women in this rural Central African region and was particularly common in younger and nulliparous women. This study provides evidence that *S. haematobium* infection is an important risk factor associated with the delivery of low birth weight infants. Contrary to previous reports, no increased risk for preterm delivery was observed in this study population. The development and evaluation of integrated public health programs for the prevention and treatment of urogenital schistosomiasis in pregnant women residing in endemic regions therefore seem highly warranted. Integration of such programs into existing health policies such as for the prevention of malaria in pregnancy seems particularly appealing.

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Conflict of interest
Authors declare no conflict of interest

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