International Journal for Parasitology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara

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

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ARTICLE INFO

Article history:
Received 20 August 2016
Received in revised form 3 November 2016
Accepted 7 November 2016
Available online xxxx

Keywords:
Schistosomiasis
Pregnancy
Low birth-weight
Prematurity
Gabon

ABSTRACT

An estimated 40 million women of childbearing age suffer from schistosomiasis. Animal models indicate a deleterious effect of maternal schistosomiasis on pregnancy outcomes. 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. 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 assessed at delivery were compared between infected and uninfected mothers. The impact of maternal schistosomiasis on low birth weight and preterm delivery was assessed using logistic regression analysis. Urogenital schistosomiasis was diagnosed in 103 (9%) of 1115 pregnant women. Maternal age was inversely associated with the prevalence of urogenital schistosomiasis, with a higher burden amongst nulliparous women. Low birth weight was more common amongst infants of *S. haematobium*-infected mothers. This association was unaffected by controlling for demographic characteristics, gestational age and *Plasmodium* infection status (adjusted Odds Ratio 1.93; 95% confidence interval: 1.08–3.42). Other risk factors associated with low birth weight delivery were underweight mothers (adjusted Odds Ratio 2.34; 95% confidence interval: 1.12–4.92), peripheral or placental *Plasmodium falciparum* infection (adjusted Odds Ratio 2.04; 95% confidence interval: 1.18–3.53) and preterm birth (adjusted Odds Ratio 3.12; 95% confidence interval: 1.97–4.96). Preterm delivery was not associated with *S. haematobium* infection (adjusted Odds Ratio 1.07 95% confidence interval: 0.57–1.98). In conclusion, 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 programmes for urogenital schistosomiasis in pregnant women and their impact on delivery outcomes are warranted.

1. Introduction

Schistosomiasis affects at least 200 million people globally and is currently ranked second in public health impact amongst human parasitic diseases (King and Dangerfield-Cha, 2008). Urogenital

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http://dx.doi.org/10.1016/j.ijpara.2016.11.001
0020-7519/

schistosomiasis is a particular public health concern in endemic countries of sub-Saharan Africa where successful and sustainable control programmes are mostly lacking. Urogenital schistosomiasis disproportionately affects poor rural regions where it may lead to high prevalence, particularly in children and young adults (Chitsulo et al., 2000). It is estimated that approximately 40 million women of childbearing age currently suffer from schistosomiasis, yet little is known about the specific morbidities inflicted on pregnant women and their offspring (Friedman et al., 2007).

Animal models provide evidence that schistosomiasis infection may lead to deleterious pregnancy outcomes (Friedman et al., 2007). A mouse model of *Schistosoma mansoni* indicates a significantly higher proportion of abortion, maternal and offspring deaths, as well as a lower weight of the offspring (el-Nahal et al., 1998; Friedman et al., 2007). These findings imply the potential for deleterious impact of schistosomiasis on pregnancy outcomes. A review by Nour (2010) summarises our current understanding of the impact of urogenital schistosomiasis on women's health. *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 (Qunhua et al., 2000). To date there are no high quality epidemiological surveys assessing the impact of urogenital schistosomiasis on pregnancy in humans. Published case reports indicate such an association (Youssef and Abdine, 1958; Bittencourt et al., 1980; McNeely, 1988), however causal inference is inherently limited in single patient reports. Studies evaluating the association of *S. mansoni* with pregnancy outcomes have demonstrated an increased risk for anaemia, preterm deliveries and low birth weight infants (Siegrist and Siegrist-Obimpeh, 1992; Ajanga et al., 2006).

Based on these data, we therefore hypothesised that urogenital schistosomiasis in human pregnancy may similarly lead to deleterious pregnancy outcomes (Friedman et al., 2005; Kanzaria et al., 2005). To further substantiate this hypothesis, we assessed 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.

2. Materials and methods

2.1. 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. The region was previously described by Ramharter et al. (2007). Fougamou is a rural municipality located in central Gabon, approximately 100 km south of Lambaréné, which is a semi-rural city situated within equatorial rainforest. This region is highly endemic for *S. haematobium* (Grogan et al., 1996; Ramharter et al., 2007; Adegnika et al., 2010).

The study population of this analysis consists of pregnant women and their offspring participating in two prospective cohort studies, the Malaria in Pregnancy Preventive Alternative Drugs trial (MiPPAD: NCT 00811421), reported elsewhere (Basra et al., 2012; González et al., 2014), and the Infectious Diseases European and African research initiative study (IDEA; www.idearesearch.eu). Pregnant women were invited to provide written informed consent when presenting at the antenatal clinic 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 1 year of age.

2.2. Detection of S. haematobium infections

Determination of *S. haematobium* infection was performed using 10 mL of midstream urine, collected during the day, which was passed through a 12 μm polyamide N-filter (Millipore, Billerica, MA, USA), followed by subsequent microscopic examination for the detection of eggs as described in more detail elsewhere (Basra et al., 2012). Women were classified as infected if at least one *S. haematobium* egg was detected in the urine. All schistosomiasis-infected women were treated with a 40 mg/kg single dose of praziquantel after delivery.

2.3. Study variables and outcomes

The 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 2500 g and was measured using calibrated digital infant scales. In cases of home deliveries or other reasons for delayed measurement of birth weight, data were imputed using a previously published regression model by Greenwood et al. (1992). 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 the 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 recorded at enrolment from birth certificates or as self-reported. Maternal age was divided into the following four categories: young adolescent girls aged $\leqslant$ 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 categorised 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; obese, BMI $\geqslant$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 a HemoCue device (www.eurotrol.com). Anaemia was defined as an haemoglobin level <11 g/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 using impression smears.

2.4. Statistical methods

Statistical analyses were performed using Stata/IC version 13.1 for Windows (StataCorp LP, College Station, TX, USA). Chi square tests were used to compare proportions between infected and uninfected mothers amongst categories of different variables. Logistic regression models were used for univariate and multivariate analyses 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 $P < 0.01$.

Please cite this article in press as: Mombo-Ngoma, G., et al. Urogenital schistosomiasis during pregnancy is associated with low birth weight delivery: analysis of a prospective cohort of pregnant women and their offspring in Gabon. Int. J. Parasitol. (2016), http://dx.doi.org/10.1016/j.ijpara.2016.11.001