

Malaria and anaemia : the impact on maternal and perinatal outcomes

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MALARIA AND ANAEMIA

THE IMPACT ON MATERNAL AND PERINATAL OUTCOMES

Ishag Adam

MALARIA AND ANAEMIA. THE IMPACT ON MATERNAL AND PERINATAL OUTCOMES

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MALARIA AND ANAEMIA

THE IMPACT ON MATERNAL AND PERINATAL OUTCOMES

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DISSERTATION

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***For the soul of my father, Adam, mercy be upon him,
and for my beloved mother, Khadija***

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Chapter 1

Introduction

Around 50 million pregnancies occur in malaria endemic areas every year and approximately half of them occur in sub-Saharan Africa (Steketee et al., 2001). Malaria during pregnancy poses a substantial risk to the mother, her fetus, and the neonate; the infection contributes to maternal anemia, low birth weight infants, and infant mortality (Cot and Deloron, 2003).

Malaria is the major health problem in Sudan (Malik and Khalafalla, 2004). It has been reported that, pregnant Sudanese women are more attractive to the main malaria vector (Himedian et al., 2004a). Malaria is the leading cause of maternal and perinatal mortality in Sudan (Taha et al., 1993; Dafalla et al., 2003; Adam et al., 2004a, Adam and Elbashir, 2004).

Increased susceptibility to malaria in pregnancy is well recognized, and has generally been assumed to be due to hormonal changes resulting in altered immunity (Tian et al; 1998). Just as cerebral malaria results from parasite sequestration in the brain, maternal malaria results from parasite sequestration in the placenta. Parasites adhere to the surface of trophoblastic villi, eliciting the accumulation of inflammatory leukocytes in the intervillous space, and the necrosis of adjacent placental tissue. Maternal malaria results in poor pregnancy outcomes, although the responsible mechanisms have not been defined.

In areas with stable malaria transmission both placental infection and poor outcome decrease in frequency with successive pregnancies; protection may result from control of parasite adhesion, suggesting an attractive target for new therapies/vaccine (Fried and Ouffy, 1998).

Massive chronic intervillitis is an infrequent placental lesion thought to be of immunologic origin composed mainly of monocytes and macrophages and can lead to poor fetal outcome. The villi are characteristically spared; the intervillous spaces appear to be largely obliterated. Increased fibrin deposition and prominent syncytial knots are frequently associated findings. Malaria affect predominantly primigravid women, and is associated with reduced birth weight (Menedez et al., 2001).

While *P. falciparum* commonly causes anemia in the mother (McGregor 1984; Beeson et al; 2001; Adam et al., 2005a), the frequency of other complications depends on a woman's pre-existing immunity to malaria.

Women in stable malaria transmission (and therefore high immunity) areas are typically asymptomatic (Beeson et al; 2001); among women with incomplete immunity, severe syndromes, such as cerebral malaria and pulmonary edema, frequently occur (Rasheed et al; 1995; Adam et al., 2004c; Adam and Elbashir, 2004; Adam et al., 2005a; Adam et al., 2005b).

Since the clinical, epidemiological and immunopathological features of malaria during pregnancy vary according to the level of transmission in the area, so the pattern may be different from the results obtained from areas with high transmission.

The presentation of malaria during pregnancy varies according to the pre-existing immunity of the mother. Women living in areas of low transmission have little immunity to malaria which can cause severe syndromes, such as cerebral malaria and pulmonary oedema. In contrast, those who live in areas of stable malaria transmission enjoy greater immunity and experience fewer symptoms during episodes of malaria, although they commonly develop severe anaemia (Brabin, 1983).

Understanding the epidemiology and pathogenesis of malaria during pregnancy provides important insight into relevant immunological processes and facilitates decision on control strategies. Although there are extensive studies in highly endemic African countries, there is no proper published data available for Sudan, which is the biggest African country with a forty million population and *P. falciparum* malaria transmission is unstable in the eastern region (Himedian et al., 2005a; Himedian et al., 2005b).

OUTLINE OF THIS THESIS

A longitudinal community- based study was conducted in which pregnant women and non-pregnant controls were followed for one year. In this study we investigated the susceptibility of pregnant women to *P. Falciparum* malaria in comparison to their non-pregnant counterparts (Chapter 2).

A cross sectional study was conducted, where antenatal clinical attendants were investigated for malaria and anaemia and risk factors for these conditions were assessed.. In this group of patients both the prevalence of malaria and its risk factors (Chapter 3) and the prevalence of anemia was and its risk factors (Chapter 4) were described.

In a next study, that was cross-sectional, parturient women were investigated for anaemia, peripheral and placental malaria. The prevalence and risk factors for placental malaria in eastern Sudan were described (Chapter 5), as well as the effect of malaria and anaemia on maternal and perinatal outcomes (Chapter 6).

A case control study was conducted to investigate the role of cortisol and prolactin in the pathogenesis of malaria (Chapter 7). Finally, in a community- based survey the perceptions among midwives and pregnant women of the causes of malaria, its complications, its treatment and methods of prevention were assessed (Chapter 8).

Study area

The study was performed in New Halfa area in the eastern Sudan. The New Halfa area was constructed in 1964 to settle the inhabitants of old Halfa in the northern border of Sudan who were displaced after construction of the High Dam on the Nile in Southern Egypt. The area itself is made up of similar villages constituting 400 000 inhabitants. It is an agricultural area, 500 km east from Khartoum and 450 m above sea level, located around 15° N 35° E. The average annual rainfall is 238 mm and the average annual relative humidity is 35%. Cotton, sorghum, groundnut, sugar cane and various vegetables are cultivated in about 1700 km² of the area. There is a permanent irrigation system. The area is characterized by unstable malaria transmission, with peak transmission following the rainy season, which extend usually from September to January (Himeidan et al., 2005a; Himeidan et al., 2005b). The predominant malaria parasite species is *P. falciparum*, with *P. vivax* and *P. malariae* occasionally seen. *Anopheles arabiensis* is the sole malaria vector in the area (Himeidan et al., 2004b). The incidence of malaria varies considerably from year to year depending on the rainfall (Himedean et al., 2007). There is one teaching hospital, 40 dispensaries and one single-doctor hospital. Bed nets and malaria chemoprophylaxis are not used routinely in the area.

Figure 1: The map of Sudan including the study area.



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Chapter 2

***Plasmodium falciparum* infection during pregnancy in an unstable transmission area in eastern Sudan**

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ABSTRACT

Background

While the epidemiology of malaria during pregnancy has been extensively studied in highly endemic areas, very little data are available from areas with seasonal and unstable malaria transmission.

Aims

The study was conducted to investigate the susceptibility of pregnant women to *P. falciparum* malaria in comparison to non-pregnant women controls.

Methods

A one-year prospective community-based study of malaria during pregnancy was conducted in an area of unstable malaria transmission in eastern Sudan. At a village antenatal clinic, 89 non-pregnant controls and 86 pregnant women were enrolled and followed every 2 weeks until 6 weeks after delivery.

Results

The incidence of *P. falciparum* infection was significantly higher among pregnant than control women (17.4% versus 5.6%) with no difference between primigravidae and multigravidae (22.2% versus 15.2%). There was a significant difference in the mean (SD) haemoglobin concentration between infected and uninfected mothers, 9.1(1.3) versus 9.5 (0.6) g/dL, $P = 0.001$. The mean (SD) birth weight of their babies was significantly lower in women infected with malaria, 2.72 (0.26) versus 2.95 (0.05) kg) despite prompt case management of infected women.

Conclusion

Thus in this area, pregnant women were found to be more susceptible to malaria than their non-pregnant ones. Malaria had adverse effects on pregnant women. Further studies are needed.

BACKGROUND

In Africa each year around 24 million women become pregnant in malaria-endemic areas. Pregnancy increases susceptibility to malaria and pregnant women are more likely to develop clinical attacks of malaria and serious complications than non-pregnant women of the same age. The increased susceptibility of pregnant women to malaria is thought to be, in part, the result of a certain degree of immune suppression during pregnancy required for retention of the fetal allograft (Vleugels et al., 1987; Fievet et al., 1997).

The increased risk of malaria in pregnant women is associated with serious adverse effects in pregnancy, leading to miscarriage, preterm labour (Menon, 1976), intrauterine growth restriction (Brabin, 1991), intrauterine fetal death and low birth weight (McGregor, 1984). In addition to the effect of malaria on the fetus, malaria causes maternal anaemia, which contributes significantly to maternal morbidity and may be a risk factor for maternal death by increasing the case fatality rate in postpartum haemorrhage (Brabin and Piper, 1990). Malaria infection in the mother is also a risk factor for perinatal mortality and morbidity by reducing the baby's birth weight (Brabin, 1991).

There are some distinctive features of the epidemiology of malaria during pregnancy that are important in terms of raising relevant research questions about the basic immunological processes, as well as in deciding the control strategies to be applied. First, the susceptibility to malaria infection and severity of clinical manifestations of malaria are determined by the level of pre-pregnancy immunity, which largely depends on the intensity and stability of malaria transmission (McGregor et al., 1983). Secondly, an important epidemiological aspect is the effect of parity of the pregnant woman on susceptibility to and severity of malaria infection.

In areas that are highly endemic for *P. falciparum* infection, adult women have acquired substantial protective immunity to malaria through repeated prior infections (McGregor et al., 1983). Although the prevalence and density of *P. falciparum* parasites are higher in pregnant women than in non-pregnant women, most infections remain asymptomatic (Greenwood et al., 1988; Greenwood et al., 1994; Menendez, 1995), with little clinical consequences at least among multigravidae. The only clearly established beneficial effects of malaria chemoprophylaxis during pregnancy are to reduce maternal anaemia and increase the baby's birth weight in primigravidae (Garner and Brabin, 1994). Primigravidae in particular are an exception and suffer deleterious effects of malaria (particularly during the second trimester) whereas complications are less frequent in multigravidae women, indicating that the protective immunity in pregnancy is a function of parity (Brabin, 1983). The reason for this is unclear; immune suppression is probably more marked in primigravidae but it is also possible that protective immunity may be acquired in the reproductive tract through malaria infection during the first pregnancy, reducing susceptibility in later pregnancies (Greenwood et al., 1994).

In areas where malaria transmission is seasonal and unstable, both the mother and her fetus can suffer the most severe consequences of the infection (Menendez, 1995). In these areas, it is believed the degree of acquired immunity of the women prior to pregnancy is likely to be low or poorly developed and the epidemiological profile and clinical pattern of disease are different from that seen in highly endemic areas (Snow et al., 1977). While the epidemiology of malaria during pregnancy has been extensively studied in highly endemic areas, very little data are available from areas with seasonal and unstable malaria (Nosten et al., 1991). The present study was conducted to investigate the pattern of malaria morbidity during pregnancy among women living in unstable malaria transmission in eastern Sudan (Himeidan et al., 2005a; Himeidan et al., 2005b).

METHODS

Study area

The study was performed in Elhara Eloula, a village in the New Halfa area in the eastern Sudan. The population in the last census in 2001 was 1841. The New Halfa town was constructed in 1964 to settle the inhabitants of old Halfa in the northern border of Sudan who were displaced after

construction of the High Dam on the Nile in Egypt. The area is characterized by unstable malaria transmission with peak transmission following the rainy season (September to January). The predominant malaria parasite species is *P. falciparum*, with *P. vivax* and *P. malariae* occasionally seen. *Anopheles arabiensis* is the sole malaria vector in the area (Himeidan et al., 2004). The incidence of malaria varies considerably from year to year depending on the rainfall (Himeidan et al., 2007). Bed nets and malaria chemoprophylaxis are not used routinely in the area.

Study design and population

This was a prospective community-based study that was timed to begin before the malaria transmission season (late June) and continue for one year. An antenatal clinic was initiated in the health centre in the village. Our aim was to enroll and follow-up all pregnant women in the village, an average of 6–10 women per day. All pregnant women were encouraged to attend the antenatal clinic. Free medical care (including free medication) was provided, so it was unlikely that the women sought medical advice elsewhere. For each pregnant woman the nearest non-pregnant woman neighbour, matched for age and socioeconomic status, was asked to participate in the study as part of a control group.

Data collection

The clinical and obstetric history of the women was recorded in detail, including last menstrual period, gravidity, parity and history of miscarriage or preterm labour.

Obstetric and physical examinations were carried out on pregnant women (blood pressure, pallor, and fundal level). The pregnancy and its duration were calculated from the last menstrual period and confirmed by ultrasound, which also used to exclude pregnancy in the controls. After enrolment, pregnant women were requested to present to the antenatal clinic once every 2 weeks until 6 weeks after delivery. Control women also attended every 2 weeks. Our team (medical officer and a microscope technician) was available daily to take care of those presenting with complaints. Initially and at every visit women were asked specifically about symptoms suggestive of malaria (fever, headache, sweating, joint pain and vomiting). Parasitological and detailed medical examinations were carried out in cases presenting to the medical staff complaining of fever or giving a recent history of fever (within the past 3 days). Due to the high rate of chloroquine resistance in the area (Adam et al., 2004), confirmed *P. falciparum* infections were treated with quinine 10 mg/kg body weight 3 times/day for 7 days.

At every visit, pregnant women were supplied with ferrous sulfate (200 mg/1 tablet per day) and folic acid (0.5 mg/1 tablet per day). Deliveries were conducted by trained midwives and the birth weight was recorded (to the near 50 g) within 24 hours of delivery. High-risk patients were advised to deliver in New Halfa hospital under the supervision of an obstetrician.

Parasitology and clinical tests

Blood was taken by finger prick from subjects complaining of fever and thick and thin blood films were prepared and stained with Giemsa (pH 7.0, diluted with phosphate buffered saline). The thick blood films were used to detect the malaria parasite and the thin films for defining the parasite species. For parasite detection, 100 fields were examined irrespective of the parasites encountered. The parasitological data were crosschecked by another technician, blind to the results and verified by the supervisor if there was any controversy. The number of asexual parasites per 200 leukocytes was counted and parasite densities (asexual parasites/ μ L) were calculated assuming a normal value of 6000 leukocytes/ μ L blood. The haemoglobin concentration was measured using a modified Sahli method (Barduagni, 2003).

A malaria episode was defined by a positive parasitology result, regardless of symptoms. An episode of symptomatic malaria was fever (oral temperature $> 37.5^{\circ}\text{C}$) or a history of fever together with parasitaemia. Anaemia was defined as a haemoglobin concentration < 11 g/dL and severe anaemia as < 7 g/dL. Miscarriage was defined as expulsion of a dead fetus before 28 weeks gestation. Premature labour was labour before completion of 37 weeks of gestation. Perinatal death was death from 28 weeks in utero until the age of 1 week. Low birth weight was defined as birth weight less than 2500 kg.

Statistical analysis

Data were entered into a computer database and were analyzed using the statistical program SPSS for Windows, version 11.5. Student's t-test, chi-squared and Fisher exact test were used as appropriate. $P < 0.05$ was regarded as significant.

Ethical considerations

Women consented to participate in the study after being given adequate information on the objectives and benefits of the project. The study was monitored and supervised by qualified medical personnel whose first responsibility was the welfare of the patients enrolled in the study. At all times, proper patient management took priority over continuation of the study. The study was carried out following WHO Guidelines for good clinical practice (WHO, 1995). To maintain the privacy of women participating in the study, patient data were treated as confidential and each woman was coded in the computer database.

RESULTS

Out of 209 women enrolled, 175 completed the study (86 pregnant and 89 control women) during 2 dry seasons and one wet season (June 2001 to May 2002). The remaining 34 were excluded because of their absence from the village for more than 4 consecutive visits or they delivered before the rainy season. As shown in Table 1, no significant differences were seen between the 2 groups of women (pregnant and non-pregnant controls) in basic characteristics. None of the women in the control group became pregnant during the study period. The mean gestational age (SD) of pregnant women at the time of enrolment was 22.2 (9.1) weeks.

Malaria during pregnancy

All infections occurred during the transmission season following the rainy season. All infections were due to *P. falciparum* and no *P. vivax* or *P. malariae* was detected. Fifteen (17.4%) out of 86 pregnant women became infected with *P. falciparum* versus 5 (5.6 %) out of 89 in the control group, $P = 0.014$. Table 1.

Malaria infections were detected in 6 (22.2%) out of the 27 primigravidae, one (8.3%) of 12 secundigravidae and 8 (17.0%) of 47 of multigravidae. $P = 0.4$. Women were infected at mean (SD) 29.9 (0.8) weeks gestational age. Eleven (73.3%) of the infected 15 cases occurred in the third trimester of pregnancy, while only 4/15 (26.7%) were in the second trimester and none in the first trimester. Most of the infections (66.6%) were symptomatic (e.g. fever, headache, joint pain) at presentation.

Table 1 comparison of variable between pregnant and control (non-pregnant) women*

Variable	Pregnant women (n = 86)		Control women (n = 89)		P
Age, years	25.4	(5.9)	24.4	(4.9)	0.2
Parity	2.1	(2.2)	2.4	(2.9)	0.4
Weight, Kg	58.5	(9.7)	56.5	(8.7)	0.08
History of miscarriage	27	(31)	21	(34.7)	0.2
Antennal visits	8.1	(3.4)	8.9	(3.8)	0.1
Incidence of malaria	15	(17.4)	5	(5.6)	0.01

* Data were shown as mean (SD) or n (%) as applicable.

Malaria and haemoglobin levels

Table 2 compares different variables among the infected (n = 15) and non-infected (n = 71) pregnant women. The mean (SD) haemoglobin levels at enrolment were not statistically different in pregnant patients who developed malaria infection compared with those who did not: 9.35 (0.80) g/dL versus 9.32 (1.10) g/dL (P = 0.8). However, at term, the mean haemoglobin levels were significantly lower among those who developed malaria during pregnancy: 9.10 (1.30) g/dL versus 9.50 (0.60) g/dL (P = 0.001 (Table 2). One of the infected pregnant women presented with severe anaemia (haemoglobin level 4.5g/dL).

Table 2 comparison of the mean (SD) of the different variables between women who developed malaria and those who did not.

Variable	Infected women (N=15)		Non- infected women (N=71)		P
Age, years	24.5	(6.2)	26.7	(6.2)	0.2
Haemoglobin at enrollment, g/dl	9.35	(0.8)	9.32	(1.1)	0.8
Haemoglobin at term, g/dl	9.1	(1.3)	9.5	(0.6)	0.001
Birth weight, Kg	2.72	(0.26)	2.95	(0.05)	0.001

Malaria and birth weight

The mean (SD) birth weight of babies born to malaria-infected women (n = 13, 2 cases not determined) was significantly lower compared with those born to non-infected women: 2.72 (0.26) kg versus 2.95 (0.05) kg, P = 0.04, Table 2. The mean (SD) birth weight of babies born to primigravidae was not statistically different from those born to multiparae, 2.73 (0.56) kg versus 2.97 (0.53) kg, P = 0.7.

Pregnancy outcome

One maternal death was reported as a complication of septicaemia following obstructed labour. Four perinatal deaths occurred, all in the non-infected group, and no clear reason was identified. One of the non-infected women aborted her fetus at 10 weeks gestational age. Four of the pregnant women (4/86) delivered prematurely (2/15 in the infected group and 2/71 in the non-infected group).

Treatment response

P. falciparum-infected patients (pregnant and controls) received prompt, adequate treatment according to the Sudanese national drug policy and response to treatment was assessed. All the infected women responded satisfactory to quinine therapy; all were symptom-free by day 3 and their blood films were negative on days 7, 14, 21 and 28.

DISCUSSION

This was a prospective study of *P. falciparum* malaria during pregnancy in an area of unstable malaria transmission in the eastern Sudan. The infection rate was significantly higher in the pregnant compared with the non-pregnant women. This finding was supported by data from areas where malaria is hyperendemic (McGregor, 1984). The incidence of infection in pregnant women during the study year was surprisingly lower than expected compared with the preceding years (Adam unpublished). This can be explained by two factors. First, the rainfall during the study period was low. The incidence of malaria in eastern Sudan varies considerably from year to year depending on the rainfall (Himedan et al., 2007). Secondly, for the first time, a vector control strategy was applied in the area and all houses in the province were sprayed with deltamethrin.

In contrast to studies conducted in areas where malaria transmission is stable (McGregor, 1984; Shulman et al., 2001), this study showed that the infection rate was not different between primigravidae and multigravidae. Studies from an area with perennial malaria transmission in Africa showed a higher prevalence of infection in all pregnant women but highest in primigravidae (McGregor, 1984; Shulman et al., 2001), with both gravidity influencing susceptibility to malaria infection (Mutabingwa et al., 1993; Cot et al., 1995; Bouvier et al., 1997). In addition, there was no significant difference in age between infected and non-infected pregnant women. Giha et al. observed that in eastern Sudan the incidence of malaria was significantly higher in individuals aged 5 to 19 years compared with older age groups (> 20 years); however, pregnant women were not included in that study (Giha, 2000). Bouyou-Akotet et al. (2003) showed that primigravidae and young pregnant women are most susceptible to malaria infection.

In this study, there was strong tendency for a lower mean haemoglobin concentration near delivery in those pregnant women who developed malaria. Data from an area of unstable malaria transmission in Thailand (Nosten et al., 1991) showed significantly lower haemoglobin concentrations in pregnant women who became infected despite prompt diagnosis and antimalarial treatment, and the study was further confirmed by another study from areas of unstable malaria transmission in Ethiopia (Newman et al., 2003).

The mean birth weight of babies in our study was significantly lower in the mothers who became infected during pregnancy. The finding is consistent with the observation by Nosten et al., where the birth weight was significantly lower in the pregnant women who developed malaria despite early diagnosis and treatment (Nosten et al., 1991). Studies from areas of stable malaria transmission (Mutabingwa et al., 1994), including areas of Ethiopia (Newman et al., 2003), also found a significant association between malaria and reduced birth weights. However, in areas of unstable malaria in Ethiopia (Newman et al., 2003), Newman found no significant association between malaria and decreased birth weight and this contrasts with our own observation and Nosten's (Nosten et al., 1991). Malaria was a known cause of low birth weight in the central Sudan, as well as in the other African countries (Taha et al., 1993; Guyatt and Snow, 2001).

In our study the reduction in the birth weight of babies born to pregnant women who became infected occurred in spite of active diagnosis and effective therapy with the standard quinine regime. Low birth weight has been closely linked with 'placental' rather than 'peripheral' parasitaemia (Galbraith et al., 1989). The parasite sequestration in the placenta is considered to be the main pathological mechanism (Shulman and Dorman, 2003) and the placenta is often heavily infected with *P. falciparum* (Diagne et al., 1997). Placental infection leads to thickening of the syncytiotrophoblasts, abnormal utero/placental blood flow and placental insufficiency. As low birth weight is the leading cause of infant mortality (Menendez et al., 2000), prevention of this should be a major goal.

In areas of moderate or high malaria transmission, including large parts of Africa, malaria in pregnancy is a common cause of severe maternal anaemia and reduced birth weight of babies, these complications being more common in primigravidae than multigravidae (Fried and Duffy, 1996). In our study, there was no significant difference between the birth weight of babies born to primigravidae or multigravidae.

Pregnancy is known to induce a state of immune suppression. Timing of peak suppression and increased susceptibility to infection is of importance for timing of possible intervention to reduce severe adverse effects of malaria on both the mother and the baby. In our study, over 70% of the infections were in the third trimester and no infections were reported during the first trimester. This may be because pregnant women presented to the antenatal care clinic for the first time during the second trimester, as the mean gestational at enrolment was 22 weeks. A peak incidence rate of malaria attacks during the second trimester was observed in areas with perennial transmission (Luxemburger et al., 2001). In this study, all infections occurred during the narrow transmission season following the rainy season. Almost two-thirds of infections were symptomatic which may suggest that the level of immunity is low and inadequate. This is in contrast to data from

areas where malaria is stable and hyper-endemic, malaria is still frequently asymptomatic, and may go unsuspected and undetectable, but may be associated with placental parasitization (Shulman et al., 2001). In spite of the fact that most of the infections were detected actively after development of clinical malaria, no mortality was associated with malaria.

Thus, in these areas, the prevention of low birth weight could be possible by measurements such as reduction of exposure to the vector, and effective preventive treatment with sulphadoxine/pyrimethamine provided in 2 single doses during and at the end of the transmission season to all pregnant women (during the second and third trimester) irrespective of parity. In addition, routine hospital data such as birth weight and number of malaria cases can provide information on the level of malaria transmission useful for the health services to target appropriate malaria interventions and allocate resources to control outbreaks of malaria epidemics.

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Chapter 3

Prevalence and risk factors for *Plasmodium falciparum* malaria in pregnant women of eastern Sudan

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ABSTRACT

Background

The presentation of malaria during pregnancy varies according to the level of transmission in the area. While much data available form areas of stable malaria transmission, few data are available from areas characterized by unstable malaria transmission.

Aim

The study aimed to demonstrate the prevalence and risk factors for malaria (age, parity and gestational age) among pregnant women of eastern Sudan, which is characterized by unstable malaria transmission.

Methods

A cross sectional study was conducted in the antenatal clinic of New Halfa Teaching Hospital, eastern Sudan, during October 2003-April 2004.

Results

A total 102 (13.7%) of 744 women had *P. falciparum* malaria, 18 (17.6%) of these were severe cases (jaundice and severe anaemia). Univariate and multivariate analysis showed that, age and parity were not associated with malaria. Women who attended the antenatal clinic in the third trimester were at highest risk for malaria (OR = 1.58, 95% CI = 1.02-2.4; $P < 0.05$).

Women with malaria had significantly lower mean haemoglobin (9.4 g/dl, 95% CI 9.1-9.7 versus 10.7, CI 10.6-10.8, $P < 0.05$). A significantly lower haemoglobin was observed in those with severe *P. falciparum* malaria compared to those with non-severe form (8.3 g/dl, 95% CI 7.6-9.1 versus 9.4, 95% CI 9.1-9.7, $P < 0.05$).

Conclusion

The results suggest that *P. falciparum* malaria is common in pregnant women attending antenatal care and that anaemia is an important complication. Preventive measures (chemoprophylaxis and insecticide-treated bednets) may be beneficial in this area for all women irrespective of age or parity.

BACKGROUND

Pregnant women are more susceptible to malaria, which causes serious adverse effects including miscarriage, low birth weight and maternal anaemia (Brabin, 1983; McGregor, 1984; Nosten et al., 1991; Menendez, 1995; Newman et al., 2003). It is the leading cause maternal mortality in Sudan (Dafallah et al., 2003; Adam and Elbashir, 2004).

The presentation of malaria during pregnancy varies according to the pre-existing immunity of the mother. Women living in areas of unstable malaria transmission have little immunity to malaria which can cause severe syndromes, such as cerebral malaria and pulmonary oedema (Adam et al., 2004). In contrast, those who live in areas of stable malaria transmission enjoy greater immunity and experience fewer symptoms during episodes of malaria, although they commonly develop severe anaemia as consequence of the infection (Brabin, 1983; McGregor, 1984; Nosten et al., 1991; Menendez, 1995; Okoko et al., 2003; Shulman and Dorman, 2003).

Understanding the epidemiology of malaria during pregnancy provides important insight into relevant immunological processes and facilitates decision on control strategies. Although there are extensive studies in highly endemic African countries (Brabin, 1983; McGregor, 1984; Rogerson et al., 2000; Bouyou-Akotet et al., 2003; Dicko et al., 2003; Newman et al., 2003), there is little published data available for Sudan, an African country where *P. falciparum* malaria transmission is unstable in the eastern region (Himiedan et al., 2005). This study was conducted to investigate the prevalence and associated risk factors for *P. falciparum* malaria in pregnant women from eastern Sudan.

PATIENTS AND METHODS

Data collection

Pregnant women attending antenatal clinic (booking visit) of the New Halfa Teaching Hospital, eastern Sudan, during the period October 2003-April 2004 were approached to participate in the study. After consent, questionnaires were administered requesting demographic information on age, parity, gestational age and history of maternal illness. Gestational age was calculated from the last menstrual period and confirmed by ultrasound, when clinically indicated. Physical examination was completed to identify signs of severe malaria (WHO, 2000) and also obstetrical examination (blood pressure, pallor, fundal level and foetal heart sound).

Laboratory methods

Thick and thin blood films were prepared from capillary blood, stained with Giemsa and 100 oil immersion fields were examined. Parasite density was determined by counting parasites and 200 leucocytes, assuming each woman has 6,000 leucocytes/ μ l. All the slides were double-checked blindly.

The haemoglobin concentration was estimated by the haematic acid method (Sahli, 1984) in the first two months and, subsequently, using Haemocue haemoglobinometer (HemCue AB, Angelholm, Sweden). Ferrous sulfate (200mg/day) and folic acid tablets (0.25 mg/day) were supplied.

Ethical clearance

The study received ethical clearance from the Research Board of the Faculty of Medicine, University of Khartoum.

Statistical analysis

Data were entered in a computer using SPSS for windows. Comparisons between means and percentages were done by Students' t-test, ANOVA, X² and Fisher's exact tests as appropriate. $P < 0.05$ was regarded as significant. Multivariate logistic regression was performed with malaria as the dependent variable, using age, parity and gestation as independent variables. These variables were

categorized and used as follows: median age, < 25 years versus >25 years); gravidae as primigravidae, secundigravidae, multigravidae (3-5) or grandmultigravidae >5; gestation as first (< 14 weeks), second (14-28 weeks) and third (> 28 weeks) trimester.

RESULTS

Malaria and pregnancy

A total of 744 pregnant women attended the antenatal clinic of New Halfa Teaching Hospital during the study, 29.5% were primigravidae.

Table 1 summarizes patient characteristics for all sub-groups. 102 (13.7%) of women were infected with *P. falciparum*, 18(17.6%) of these were severe cases (jaundice and severe anaemia). Malaria prevalence and intensity (parasite count) were not significantly different amongst the different gravidity sub-groups ($P > 0.05$). The highest prevalence (18.3%) occurred in grandmultigravidae and the highest intensity (11,511 parasites/ μ l) was observed in primigravidae, Table 1.

Mean (SD) age, 26.2 (5.7) versus 25.9 (5.3) years, $P > 0.05$ and parity, 2.4 (2.4) versus 2.1 (2.1), $P > 0.05$ were not significantly different between infected and non-infected women. Two of 18 (11.1%), 29 of 290 (10%) and 71 of 436 (16.3%) women were infected in the first, second and third trimester respectively ($P = 0.05$).

Table 1 characteristics of pregnant women in the study subjects *

Characteristics	Total (N=744)	Primi- gravidae (N= 220)	Secundi- gravidae (N= 131)	Multi- gravidae (N =322)	Grand- multigravidae (N =71)	P Value
Age, years	26.6 (9.9)	21.2 (2.9)	25.7 (2.3)	28.2 (3.8)	34.9 (3.2)	<0.001
Gestation, weeks	27.7 (7.7)	27.3 (8.09)	28.1 (6.9)	27.6 (7.6)	28.3 (28.3)	0.18
Haemoglobin (g/dl)	10.5 (1.4)	10.5 (1.3)	10.3 (1.6)	10.6 (1.3)	10.3 (1.2)	0.2
Malaria (total)	102 (13.7)	32 (14.5)	14 (10.7)	43 (13.4)	13 (18.3)	0.4
Non-severe	84 (11.3)	28 (12.7)	9 (6.9)	34 (10.6)	13 (18.3)	0.08
Severe	18 (2.4)	4 (1.8)	5 (3.8)	9 (2.8)	0	0.3
Parasite count (parasites/ μ l)	6.5 (19.6)	11.5 (3.2)	6.8 (14.3)	3.5 (7.7)	4.4 (7.7)	0.4

*Data as mean (SD) or number (%) as appropriate

Factors associated with malaria infection

Univariate and multivariate analysis indicated that, age and parity were not significantly associated with malaria infection. The third trimester was significantly associated with malaria infection (OR = 1.58, 95% CI = 1.02-2.4; $P < 0.05$), Table 2.

Malaria and haemoglobin

Mean haemoglobin was significantly lower in infected women (9.4 g/dl, 95% CI 9.1-9.7 versus 10.7, CI 10.6-10.8, $P < 0.05$). A lower haemoglobin also occurred in women with severe malaria (9.4 g/dl, 95% CI 9.1-9.7 versus 8.3, 95% CI 7.6-9.1, $P < 0.05$).

Table 2 risk factor analysis

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age \leq 25 years	1.03	0.68-1.5	0.40	0.90	0.52-1.6	0.74
Parity						
Primigravidae	1.10	0.70-1.7	0.60	0.76	0.32-1.8	0.55
Secundigravidae	0.72	0.39-1.3	0.20	0.50	0.21-1.4	0.22
Multigravidae	0.96	0.62-1.4	0.80	0.74	0.37-1.4	0.41
Grandmultigravidae	1.40	0.77-2.7	0.20	3.20	0.27-46.2	0.30
Gestational age						
First trimester	0.61	0.27-1.3	0.15	0.51	0.22-1.1	0.11
Second Trimester	0.71	0.45-1.3	0.09	0.67	0.41-1.08	0.10
Third trimester	1.50	1.02-2.4	0.02	1.58	1.02-2.4	0.03

OR: odds ratio

DISCUSSION

This study investigated the morbidity pattern of *P. falciparum* malaria during pregnancy in an area of New Halfa, which is characterized by unstable transmission (Himeidan et al., 2005). The malaria prevalence was 13.7% and 18 women (17.6%) were severe cases. With the exception of the neighboring country Ethiopia (Newman et al., 2003), malaria prevalence was much lower than in other African countries characterized by intense malaria transmission (Rogerson et al., 2000; Bouyou-Akotet et al., 2003; Dicko et al., 2003). Several severe cases occurred in areas of unstable transmission, pregnant women are more susceptible to severe *falciparum* malaria than their non-pregnant peers (Luxemburger, 1997) and different manifestations of severe *falciparum* malaria including cerebral malaria have been reported among pregnant women of central Sudan (Adam et al., 2004).

The study showed no significant association between malaria and parity, which is also reported from other areas and locations with intense malaria transmission (Rogerson et al., 2000; Lander et al., 2002; Dicko et al., 2003). In areas where transmission is high and the level of acquired pregnancy immunity against malaria is expected to be significant, primigravidae will be more affected (Brabin, 1983; McGregor, 1984; Bouyou-Akotet et al., 2003).

In contrast to the previous observations (Rogerson et al., 2000; Bouyou-Akotet et al., 2003; Dicko et al., 2003), age was not significantly associated with malaria in the present study. Lander et al., have also reported no significant association between malaria infection and maternal age (Lander et al., 2002).

Women who attended the antenatal clinic in the third trimester had about a 1.5-fold higher risk of malaria parasitaemia. This is in line with some observations, although several studies report the second and early third trimesters as the time of peak prevalence (Brabin, 1983; Nosten et al., 1991; Menendez, 1995; Rogerson et al., 2000; Bouyou-Akotet et al., 2003; Dicko et al., 2003). Dicko et al., reported the first trimester as the main risk period (Adam and Elbashir, 2005).

The mean haemoglobin was significantly lower in women with malaria infection and significantly lower in severe cases. Reduction of haemoglobin has been reported in areas of unstable transmission in Thailand and in Ethiopia, as well as in areas with stable transmission (Nosten et al., 1991; Newman et al., 2003). Regardless of transmission level and pre-pregnancy level of malaria immunity, maternal anaemia remains the most frequent consequence of malaria during pregnancy (Menendez, 1995).

CONCLUSION

The results suggest that prevalence of *P. falciparum* malaria is considerable in pregnant women in this part of Sudan and severe cases do occur. Preventive measures (chemoprophylaxis and

insecticide-treated bednets) may be beneficial in this area for all women irrespective of their age or parity.

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Chapter 4

Prevalence and risk factors for anaemia in pregnant women of eastern Sudan

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ABSTRACT

Background

Pregnant women are more susceptible to anaemia, which is associated with adverse effects on pregnancy and poor maternal health. There is no published data concerning anaemia and pregnancy in Sudan.

Aims

The prevalence and possible risk factors for anaemia were investigated in 744 pregnant Sudanese women attending antenatal clinic of New Halfa teaching hospital, eastern Sudan between October 2003 and April 2004.

Results

466 (62.6%) had anaemia (haemoglobin [Hb]: <11 gm/dl). 52.4% had mild anaemia (Hb: 9.0-10.9 gm/dl), 8.1% had moderate anemia (Hb: 7.0-8.9 gm/dl), and 2.2 % had severe anaemia (Hb: < 7gm/dl), respectively. The prevalence of anaemia (73.2%) was significantly high in grandmultigravidae. Univariate and multivariate analysis showed that age and parity, were not significantly associated with anaemia. Malaria (OR = 4.5, 95% CI = 2.5-8.1; P < 0.0001) and pica (OR = 1.6, 95% CI = 1.05-2.6; P = 0.03) were the risk factors for anaemia.

Conclusions

Thus, preventive measures against malaria (chemoprophylaxis and insecticide-treated bednets) may be needed for all pregnant women irrespective to their age or parity.

BACKGROUND

Over half of all women in the world experience anaemia during pregnancy with 95 % occurring in the developing countries (DeMaeyer and Adiels-Tegman, 1985). Pregnant women are more susceptible to anaemia, which is associated with adverse effects on pregnancy and it has been reported as the risk factor for poor maternal health (Brabin, 1991; Brabin, 1992; Campbell and Abu Sham, 1995; Brabin and Piper, 1997; Santiso, 1997; Hagaz et al., 2003; Lone et al., 2004). The control of anaemia in women of reproductive age is one of the Safe Motherhood Initiatives (WHO, 1989).

Epidemiology of anaemia during pregnancy is important for deciding the control strategies. While this has been extensively studied in other African countries (Ndyomugenyi and Magnussen, 1999; Rogerson et al., 2000; Bouyou-Akotet et al., 2003; Dicko et al., 2003; Newman et al., 2003) hardly any proper published data is available for Sudan, an African country with 40 million individuals and *P. falciparum* malaria with unstable transmission dominates its most parts including the eastern (Himeidan et al., 2005). The present study was conducted to investigate the prevalence and the risk factors for anaemia in pregnant women of eastern Sudan.

METHODS

The study was conducted between October 2003 and April 2004 at antenatal clinic (booking visit) of New Halfa teaching hospital, eastern Sudan. After taking the consent, a questionnaire form was used to gather relevant general informations and particularly on possible risk factors for anaemia: age, parity, pica (eating clay) and tonics use (ferrous /folic acid). Obstetrical examinations were performed and findings recorded (blood pressure, pallor, fundal level and fetal heart sound). The gestational age was calculated from the last menstrual period and confirmed by ultrasound in case of discrepancies.

Haematology

Thick and thin blood films were stained with Giemsa, examined using 100 oil immersion fields and double-checked blindly. The haemoglobin concentration was estimated by the haematic acid method (Sahli, 1894) in the first two months and by Hemocue haemoglobinometer (HemoCue AB, Angelhom, Sweden) in the rest.

Ethical clearance

The study received ethical clearance from the Research Board at the Faculty of Medicine, University of Khartoum.

Statistics

Data were entered in computer using SPSS for windows and double-checked before analysis. Means and percentages were compared by Students' t-test, ANOVA, X² and Fisher's exact tests as appropriate. $P < 0.05$ was regarded as significant. Multivariate logistic regressions were performed with the presence of anaemia as a dependent variable and age, parity, pica, lack of tonics and malaria as possible influencing factors. The age and parity were categorized as follows: median age (≤ 25 and >25 years), gravidity was categorized as primigravidae, secundigravidae, multigravidae (3-5) and grandmultigravidae (>5 pregnancies).

RESULTS

Anaemia and pregnancy

A total of 744 pregnant women were investigated, 220 (29.5%) were primigravidae, 144 (19.4%) gave history of taking tonics, 108 (14.5%) were practicing pica and 102 (13.7%) had *P. falciparum* malaria.

Table (1) demonstrates the patients' presenting characteristics.

A total 466 (62.6%) had anaemia ([haemoglobin] (Hb): <11 gm/dl; 52.4%, 8.1% and 2.2 % had mild (Hb: 9-10.9 gm/dl), moderate (7-8.9 gm/dl and severe anaemia (Hb: < 7gm/dl), respectively. The prevalence (73.2%) of anaemia was significantly high in grandmultigravidae and that of severe anaemia (6.1%) was significantly high in secundigravidae, Table 1. There were no significant differences in the mean (SD) age [26.2 (5.6) vs. 25.6 (4.8), $P > 0.05$] and parity [2.3 (2.3) vs. 2.07 (1.9), $P > 0.05$] in the anaemic vs. non- anaemic women. 8 (44.4%) of 18, 163 (56.2%) of 290 and 295 (67.7%) of 436 women had anaemia in the first, second and third trimester, respectively, $P = 0.002$.

Table 1 characteristics of the study subjects and the prevalence of malaria and anaemia*

Variable	The total (N=744)	Primi- gravidae (N=220)	Secundi- gravidae (N= 131)	Multi- gravidae (N=322)	Grand- multigravidae (N=71)	P. Value
Age, years	26.6 (9.9)	21.2 (2.9)	25.7 (2.3)	28.2 (3.8)	34.9 (3.2)	< 0.001
Gestation, weeks	27.7 (7.7)	27.3 (8.09)	28.06 (6.9)	27.6 (7.6)	28.3 (28.3)	0.18
Haemoglobin, /dl	10.5 (1.4)	10.5 (1.3)	10.3 (1.6)	10.6 (1.3)	10.3 (1.2)	0.2
Malaria	102 (13.7)	32 (14.5)	14 (10.7)	43 (13.4)	13 (18.3)	0.4
Anaemia	466 (62.6)	141 (64.1)	88 (67.2)	185 (57.5)	52 (73.2)	0.03
Mild	390 (52.4)	122 (55.5)	66 (50.4)	157 (48.8)	45 (63.4)	0.6
Moderate	60 (8.1)	17 (7.7)	14 (10.7)	23 (7.1)	6 (8.5)	0.2
Severe	16 (2.2)	2 (0.9)	8 (6.1)	5 (1.6)	1 (1.4)	0.01

*Data as mean (SD) or number (%) as appropriate.

Risk factors for anaemia

Univariate and multivariate analysis indicated that, age, parity, and lack of tonics were not significantly associated with anaemia. Grandmultigravidae was significantly associated with anaemia in univariate analysis, but this did not persist in multivariate analysis after removing the confounding factors.

Malaria (OR = 4.5, 95% CI = 2.5- 8.1; $P < 0.0001$) and pica (OR = 1.6, 95% CI = 1.05-2.6; $P = 0.03$) were the risk factors for anaemia. The odds ratios and 95% CI of factors associated with anaemia using univariate and multivariate analysis were shown in Table2.

Table 2 factors associated with anaemia in pregnant women of eastern Sudan using univariate or multivariate analysis.

The variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age ≤ 25 years	1.38	0.75 - 2.5	0.18	0.32	0.67 - 2.6	0.4
Parity						
Primigravidae	1.09	0.79 - 1.52	0.3	0.61	0.10 - 3.6	0.59
Secundigravidae	1.02	0.85 - 1.8	0.14	0.76	0.13 - 4.5	0.77
Multigravidae	0.48	0.08 - 2.7	0.41	0.74	0.37 - 1.4	0.41
Grandmultigravidae	1.73	1.002 - 2.9	0.03	1.01	0.17 - 6.06	0.9
Pica	1.5	1.02 - 2.4	0.02	1.65	1.05 - 2.6	0.03
Lack of tonics	1.09	0.74 - 1.58	0.3	1.02	0.69 - 1.5	0.9
Malaria	4.47	2.4 - 7.9	0.0001	4.5	2.5 - 8.1	0.001

DISCUSSION

The prevalence of anaemia in this study was 62.6% and 2.2% were severe cases; it might be less than this if the dry months were investigated as higher prevalence of anaemia was reported during wet seasons (Ndyomugenyi and Magnussen, 1999; Rogerson et al., 2000; Dicko et al., 2003; Anya, 2004). With exception of the neighbor -Ethiopia- with its high altitude (Giles et al., 2003; Newman et al., 2003), the prevalence of anaemia in this study is comparable with that in other African countries (Ndyomugenyi and Magnussen, 1999; Rogerson et al., 2000; Bouyou-Akotet et al., 2003; Dicko et al., 2003).

In this study there was no significant association between anaemia: age and gravidity; this goes with Dicko et al., 2003 findings. Grandmultigravidae was risk factor for anaemia in univariate analysis, but this did not persist in multivariate analysis after removing the confounding factors. Grandmultigravidae are expected to be older and repeated pregnancies/lactation would exhaust their iron storage. Interestingly, the prevalence of malaria in these women was not significantly different between the gravidity subgroups; this might be another explanation for the susceptibility of multigravidae to anaemia. This was not a community-based survey; and it is possible that women with problems (grandmultigravidae) were over represented in the antenatal clinic than their actual representation in the community. However, in other African countries with intense malaria transmission, primigravidae and secundigravidae were the risk factors for anaemia (Ndyomugenyi and Magnussen, 1999; Rogerson et al., 2000; Bouyou-Akotet et al., 2003).

The study showed that, pica was significantly associated with anaemia, (OR = 1.6, 95% CI = 1.05-2.6; P = 0.03). Soil eating (pica) was reported as risk factor for maternal anaemia in the community of eastern Sudan (Adam et al., 2004a), African pregnant women practice pica widely, however; its effects on pregnancy outcomes were questioned (Geissler et al., 1998; Geissler et al., 1999; Rainville, 1998).

In this study women infected with *P. falciparum* malaria had 4.5-fold higher risk for anaemia. Several studies have reported malaria as primary reason for anaemia in pregnant women in other countries with unstable or stable malaria transmission (Nosten et al., 1991; Menendez, 1995; Ndyomugenyi and Magnussen, 1999; Bouyou-Akotet et al., 2003; Dicko et al., 2003; Giles et al., 2003; Newman et al., 2003; Anya, 2004). In this study anaemia presented (co-exited) with malaria simultaneously. Interestingly, reduction of haemoglobin level followed malaria infection during pregnancy after sometime even if the malaria was effectively treated (Elghazali et al., 2004b), the explanation for this was unclear, although persistent placental parasitaemia after the clearance of peripheral one was a possibility (Sartelet et al., 1997).

Malaria and pica were the major risk factors for anaemia; other possible risk factors for anaemia (education and income) were not investigated, if these were considered they might have influenced the results directly or as confounding factors.

Thus, preventive measures such as intermittent preventive therapy and insecticide treated nets may be needed in the area for all women irrespective to their age or parity especially during the rainy season

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Chapter 5

ABO blood group system and placental malaria in an area of unstable malaria transmission in eastern Sudan

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ABSTRACT

Background

Understanding the pathogenesis of malaria in pregnancy and its consequences for both the mother and the baby is fundamental for improving malaria control in pregnant women.

Aims

The study aimed to investigate the role of ABO blood groups on pregnancy outcomes in an area of unstable malaria transmission in eastern Sudan.

Methods

A total of 293 women delivering in New Half teaching hospital, eastern Sudan during the period October 2006-March 2007 have been analyzed. ABO blood groups were determined and placental histopathology examinations for malaria were performed. Birth and placental weight were recorded and maternal haemoglobin was measured.

Results

114 (39.7%), 61 (22.1%) and 118 (38.2%) women were primiparae, secundiparae and multiparae, respectively. The ABO blood group distribution was 82(A), 59 (B), 24 (AB) and 128 (O). Placental histopathology showed acute placental malaria infections in 6 (2%), chronic infections in 6 (2%), 82 (28.0%) of the placentae showed past infection and 199 (68.0%) showed no infection. There was no association between the age (OR =1.02, 95% CI = 0.45-2.2; P = 0.9), parity (OR =0.6, 95% CI = 0.3-1.2; P = 0.1) and placental malaria infections. In all parity blood group O was associated with a higher risk of past (OR =1.9, 95% CI = 1.1-3.2; P = 0.01) placental malaria infection. This was also true when primiparae were considered separately (OR = 2.6, 95% CI = 1.05-6.5, P = 0.03).

Among women with all placental infections / past placental infection, the mean haemoglobin was higher in women with the blood group O, but the mean birth weight, feto-placental weight ratio was not different between these groups and the non-O group.

Conclusion

These results indicate that women of eastern Sudan are at risk for placental malaria infection irrespective to their age or parity. Those women with blood group O were at higher risk of past placental malaria infection.

BACKGROUND

It has been estimated that 90% of the global malaria burden occurs in sub-Saharan Africa, where 40% women are exposed to malaria infections during pregnancy (Steketee et al., 2001). Malaria during pregnancy poses a substantial risk to the mother, her foetus and the neonate (Cot et al., 2003): it is a major health problem in Sudan, where it has been reported to be associated with maternal anaemia, low birth weight infants and a major cause of maternal mortality (Taha et al., 1993; Dafallah et al., 2003; Adam et al., 2005a; Adam et al., 2005b).

Host genetic factors modulate the risk and severity of infection via specific mediators, which can be different in various epidemiological settings. Cell adhesion plays a fundamental role in placental malaria pathophysiology (Costa et al., 2003). Cell surface glycans, such as the ABO and related antigens could modulate some of those specific cell interactions (Cserti et al., 2007). A century since the discovery of the ABO blood groups, numerous associations between ABO groups and disease have been reported. Interestingly, some strains of *Plasmodium falciparum* preferentially trigger rosette formation depending on the red blood cell blood group (Barragan et al., 2000). However, the rosette formation is not a feature of *P. falciparum* infections during pregnancy (Maubert et al., 1998).

Recently, ABO blood groups have been reported to be one of the host risk factors for placental malaria infections and also to be associated with other materno-foetal outcomes (Loscertales and Brabin, 2006). The current study was conducted in eastern Sudan, an area that is characterized by unstable malaria transmission (Himeidan et al., 2005) and where malaria is a substantial burden affecting pregnant women irrespective to their age or parity (Adam et al., 2005a). The study aimed to investigate the epidemio-pathological characteristics of placental malaria infections with special attention to blood groups and their association with materno-fetal outcomes and to add to the ongoing data on the pathogenesis of malaria during pregnancy in the area (Adam et al., 2007).

METHODS

Patients

The study was conducted between October 2006 and March 2007, at the labour ward of New Halfa Teaching Hospital, eastern Sudan. After informed consent, women with a singleton baby were approached to participate in the study. Those with antepartum haemorrhage, hypertensive disorder of pregnancy (diastolic blood pressure > 90 mm Hg) and diabetes mellitus were excluded. A structured questionnaire was administered to collect information about socio-demographic characteristics, mode of delivery and birth outcome. Obstetrical examinations were performed and the findings recorded (blood pressure, pallor, fundal level and foetal heart sound). The babies were weighted immediately following birth on a Salter scale to the nearest 10 g; scales were checked for accuracy on a weekly basis.

Haematology

Maternal, placental and cord blood films were prepared, the slides were Giemsa-stained and the number of asexual *P. falciparum* parasites per 200 white blood cells was counted and double-checked blindly by an expert microscopist. Maternal haemoglobin concentrations were estimated by HemoCue haemoglobinometer (HemoCue AB, Angelholm, Sweden). Maternal blood groups were investigated by the agglutination method.

Histopathology

Full thickness placental blocks of around 2-3 cm were taken from the placenta, kept in neutral buffer formalin for histopathology examinations. Placental malaria infections were characterized based on the classification of Bulmer et al., (1994): uninfected (no parasites or pigment), acute (parasites in intervillous spaces), chronic (parasites in maternal erythrocytes and pigment in fibrin

or cells within fibrin and/or chorionic villous syncytiotrophoblast or stroma), past (no parasites and pigment confined to fibrin or cells within fibrin).

Statistics

Data were entered in computer using SPSS for windows and double-checked before analysis. Means and percentages were compared either by Students' t-test, ANOVA (if data were normally distributed) or by the Mann-Whitney test (if the data were not normally distributed). χ^2 and Fisher's exact tests as appropriate. Multiple linear regressions were used to analyze placental malaria infections as a dependent variable and age < 19 years, parity (primiparae, secundiparae and multiparae) and maternal blood group (O versus non O) as possible influencing factors. The others factors included in the analyses were: maternal blood group (O versus non O), parity, placental infection, maternal haemoglobin, birth weight and foeto-placental ration. $P \leq 0.05$ was regarded as significant.

Ethics

The study received ethical clearance from the Research Board at the Faculty of Medicine, University of Khartoum.

RESULTS

During the study period, there were 578 deliveries. Of these, 24 were twins and four were triplets, 550 singleton deliveries. The data of placental histopathology, maternal haemoglobin, placental and birth weight were complete in 293 women; these data were included in the final analyses. Out of these 293 women, there were 114 (39.7%), 61 (22.1%) and 118 (38.2%) primiparae, secundiparae and multiparae, respectively. The mean (SD) age was 25.6 (6.4) years and 57(19.4%) of the women were teenagers (age \leq 19 years). Of the 293 women, 82 (28.0%), 59 (20.1%), 24 (8.2%) and 128 (43.7%) had blood group A, B, AB and O, respectively. The mean (SD) haemoglobin was 11.4 (2.1) gm/dl. The mean (SD) birthweight was 3,063.4 (545.4) gm, while the mean foeto/placental ratio was 5.6 (1.2). Maternal and placental blood films were positive in four cases and the blood films for malaria were positive in one maternal, placental and cord setting.

Six (2%), 6 (2%) and 82 (28.0%) of the placentae showed acute, chronic, past infection on histopathology examination respectively, while 199 (68.0%) of them showed no infection. There were no associations between the age (OR =1.02, 95 CI=0.45-2.2; $P = 0.9$), parity (OR =0.6, 95 CI=0.3-1.2; $P = 0.1$) and placental infections (all or in subgroups).

Women who have blood group O were at higher risk for past placental infections (OR =1.9, 95 CI=1.1-3.2; $P =0.01$). This was also true when primiparae were considered separately (OR= 2.6, 95% CI = 1.05-6.5, $P = 0.03$, Table 1.

Past placental malaria infections were observed in 45 (35.2%) of 128 women with blood group O versus 37 (22.4%) of 165 with non- O group, $P = 0.01$. This was also true when primiparae were considered separately, 16 (31.4%) of 51 primiparae women with group O versus 10 (15.9%) of 63 with non- group O, $P = 0.05$, (Table 2).

The mean birth weight and foeto-placental ratio were not significantly different between those with and without placental malaria infections or those women with blood group O and non-O group, (Table 2).

Maternal haemoglobin concentration was significantly higher in O type mothers with all placental /past placental malaria (11.8 g/dl, versus 10.9 g/dl, $P = 0.02$), this difference was statistically significant even when primiparae were considered separately (12.0 g/dl, versus 10.4 g/dl, $P = 0.05$), (Table 2).

Table 1 ABO phenotype by placental malaria category and parity group

Parity	Placental malaria Type	number	Blood group Phenotype							
			A		B		AB		O	
Total	Acute	6	5	(6.1)	1	(1.7)	0	(0)	0	(0)
	Chronic	6	2	(2.4)	1	(1.7)	1	(4.2)	2	(1.6)
	Past	82	19	(23.2)	13	(22.0)	5	(20.8)	45	(35.2)*
	None	199	56	(68.3)	44	(74.6)	18	(75)	81	(63.3)
	Total	293	82		59		24		128	
Primi- parae	Acute	2	2	(6.5)	0	(0)	0	(0)	0	(0)
	Chronic	1	0	(0)	0	(0)	1	(12.5)	0	(0)
	Past	26	5	(16.1)	3	(12.5)	2	(25.0)	16	(31.4)*
	None	85	24	(77.4)	21	(87.5)	5	(62.5)	35	(68.6)
	Total	114	31		24		8		51	
Secundi- parae	Acute	2	1	(4.2)	1	(12.5)	0	(0)	0	(0)
	Chronic	0	0	(0)	0	(0)	0	(0)	0	(0)
	Past	18	8	(33.3)	0	(0)	0	(0)	10	(38.5)
	None	41	15	(62.5)	7	(87.5)	3	(100)	16	(61.5)
	Total	61	24		8		3		26	
Multi- parae	Acute	2	2	(7.4)	0		0		0	
	Chronic	5	2	(7.4)	1	(3.7)	0		2	(3.9)
	Past	38	6	(22.2)	10	(37)	3	(23.1)	19	(37.3)
	None	73	17	(63.0)	16	(59.3)	10	(76.9)	30	(58.8)
	Total	118	27		27		13		51	

* Significant difference

Table 2 mean (SD) maternal and birth outcomes by parity and maternal blood group phenotype

Parity	Placental malaria type	Maternal and foetal parameters				
		Blood group	number	Maternal Hb	Birth weight	Foeto-placental ratio
All parity	Infection	Group O	47	11.8 (2.1)*	3060.1 (370.0)	5.4 (1.0)
		Non- O	47	10.9 (1.9)	310.9 (575.4)	5.6 (1.0)
	No infection	Group O	81	11.5 (2.1)	3098.3 (561.6)	5.7 (1.1)
		Non- O	118	11.6 (2.2)	3037.2 (554.2)	5.6 (1.4)
Primi- parae	Infection	Group O	16	12.0 (2.0)*	2946.4 (367.2)	5.6 (0.8)
		Non- O	13	10.4 (2.3)	2898.3 (409.7)	5.7 (0.9)
	No infection	Group O	35	11.1 (2.1)	3065.4 (462.4)	5.8 (1.0)
		Non- O	50	11.7 (2.3)	3019.8 (593.9)	5.8 (1.8)
Secundi- parae	Infection	Group O	10	11.1 (2.5)	3150.1 (348.4)	5.7 (0.3)
		Non- O	10	11.0 (1.2)	3298.6 (655.0)	5.5 (1.3)
	No infection	Group O	16	11.5 (1.9)	3251.2 (570.5)	6.0 (1.2)
		Non- O	25	12.1 (2.1)	2947.4 (529.9)	5.4 (1.0)
Multi- parae	Infection	Group O	21	12.0 (2.0)	3098.5 (379.2)	5.1 (0.98)
		Non- O	24	11.1 (2.0)	3038.0 (604.4)	5.5 (1.3)
	No infection	Group O	30	11.9 (2.1)	3055.6 (656.9)	5.4 (1.1)
		Non- O	43	11.2 (2.0)	3109.524.8)	5.3 (0.9)

* Significant difference

DISCUSSION

As in previous findings on the peripheral microscopically- and submicroscopically-detected parasitaemia and the pathogenesis of malaria during pregnancy in the same hospital (Adam et al., 2005a; Adam et al., 2005c; Adam et al., 2007), the histopathological placental malaria infections were not associated with age or parity in the current study. The explanation for this may be the low immunity in the area, which is characterized by unstable malaria transmission (Himeidan et al., 2005).

In this study around 32% of the placentae had been observed to have some degree of infections, few of these infections were acute while the vast majority was past infections. Women (even primiparae) with blood group O were at higher risk for past placental malaria infections. While significantly higher haemoglobin was observed in women with past placental malaria and blood group O, the other parameters (birth weight and foeto-placental ration) were not different between the two groups. Surprisingly, in this study the birthweight was not associated with histopathological placental malaria infections and the explanation for this remains unclear. These women had very low prevalence of peripheral, placental and cord microscopically detected parasitaemia, hence the role of submicroscopic parasitaemia on low birthweight cannot be excluded. Previously, a large burden of submicroscopically-detected parasitaemia was observed to be associated with morbidity and mortality among pregnant and non-pregnant individuals in the same geographical area (Adam et al., 2005c; Giha et al., 2005).

Recently, Loscertales and Brabin (2006) have observed that; in primiparae, blood group O was associated with a higher risk of acute infection and a lower risk of past infection, in contrary to multiparae in whom O phenotype was associated with reduced prevalence of acute or past placental infection. However, findings from other studies suggested that individuals of blood group O are relatively resistant to severe disease caused by *P. falciparum* infection. It was established that parasitized erythrocytes form rosettes more readily with red blood cells (RBCs) of A, B, or AB groups than with blood group O and this parasite-triggered RBC rosette formation is associated with the severity of clinical disease and with the development of cerebral malaria (Pathirana et al., 2005; Uneke, 2007). Pregnant women are more attractive for the vector (Himiedan et al., 2004) – and a differential affinity of blood group O for the vector has also been reported before (Wood, 1974). Furthermore, an antigen sharing between ABO phenotypes and *P. falciparum* leading to changes in immune response (Athreya and Coriell L, 1976) or facilitating entry of the parasite into the red cell has been described recently (Podbielska et al., 2004).

In the current study, women with past placental infection had higher mean haemoglobin when they were of O blood group. This correlates with the previous findings where non- pregnant patients with severe *P. falciparum* malaria and non-O blood group had significantly lower haemoglobin levels compared with patients with group O blood (Fischer and Boone 1998). The higher Hb level associated with the O phenotype could relate to the development of improved malaria immunity in this particular group of women, following on from a preceding increased risk of malaria infection in this phenotype. Recently, Loscertales and Brabin (2006) have also reported higher (although, not statistically significant) haemoglobin in women with blood group O.

CONCLUSIONS

These results indicate that women of eastern Sudan are at risk for placental malaria infection irrespective to their age or parity. Those with blood group O were at higher risk of past –chronic placental malaria infection. Among women with past- chronic placental infection, the mean haemoglobin was higher in women with the O blood group, but the mean birthweight and foeto-placental weight ratio were not significantly different between these groups.

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Chapter 6

Low body mass index, anaemia and poor perinatal outcome in a rural hospital in eastern Sudan

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ABSTRACT

Background

Though there is an extensive literature on the perinatal outcome from several African countries, yet few reports have been published from the Sudan.

Aims

The study was conducted during October 2006-March 2007 at New Halfa teaching hospital, eastern Sudan to investigate the prevalence and possible risk factors for a poor perinatal outcome, defined as low birth weight (LBW), APGAR score <5 at 1 min, fetal anaemia and perinatal mortality.

Results

LBW occurred in 15.3%, the perinatal death occurred in 9.2%.

Maternal low body mass index (BMI) was significantly associated with LBW (OR= 2.3, 95% CI= 1.0-5.1; $P= 0.02$), which was a risk factor for APGAR score <5 at 1 min (OR = 6.9, 95% CI = 2.8- 16.8; $P < 0.000$) and perinatal mortality (OR= 309, 95% CI = 29.2-3271.1, $P < 0.00001$). Maternal anaemia was a risk factor for fetal anaemia (OR = 2.2, 95% CI = 1.2-3.9; $P = 0.006$) and APGAR score <5 at 1 min (OR = 0.48, 95% CI = 0.23-0.99; $P = 0.04$).

Conclusion

More attention to maternal nutrition in an attempt to prevent anaemia may lead to improvement in the perinatal outcome.

INTRODUCTION

Perinatal outcome is an important indicator of overall level of obstetric care, health status and socio-economic development. It is estimated that annually four million infants die during the first month of life worldwide (SNL, 2001). The vast majority of these neonatal deaths occur in poor countries where standards of both maternal and neonatal care are low. One of the Millennium Development Goals is to reduce the number of childhood deaths under the age of five years by two thirds from 95 per 1000 to 31 per 1000 by 2015 (UN, 2001). If the Millennium Development Goal of significantly reducing childhood deaths is to be achieved, a substantial reduction in early neonatal deaths will be required, especially in poor countries. The first steps in improving early neonatal survival are to document the number and rate of deaths during the first week, identify the common causes and look for modifiable factors. These factors usually intermingle with each other and hence can influence perinatal outcome directly or indirectly (Verhoeff, et al., 2004; le Cessie et al., 2002; Brabin and Piper, 1997).

Addressing maternal and newborn health in rural parts of Africa offers particular challenges because of the inadequate public health infrastructure and the distance of communities from facilities providing skilled care. Also, program managers lack access to local data for basic indicators such as low birth weight (LBW), fetal anaemia and perinatal deaths. A local surveillance database to more accurately assess perinatal outcome would enhance our epidemiologic knowledge and could help health care managers to understand more fully the causes of poor pregnancy outcomes as well as identify areas to which interventions should be targeted, and monitor the effectiveness of these interventions over time. In addition it would provide indicators of underlying causes and suggests the types of prevention and interventions that should be implemented. An obvious example is preventing deaths of LBW babies which requires the use of technologically advanced treatment methods associated with neonatal intensive care. This level of care is clearly not feasible for such a population. Interventions therefore could focus on decreasing LBW preemptively by e.g. improving maternal nutrition and preventing malaria and anaemia.

The prevalence of perinatal outcomes (LBW, Low AGPAR score, fetal anaemia and perinatal death) and their risk factors are not well known in Sudan in general and in the eastern part of the country in particular. The aim of the current study was to identify and quantify risk factors for poor perinatal outcome in a rural hospital in eastern Sudan and to assess the role of socio-demographic factors and maternal illnesses such as malaria and anaemia.

MATERIALS AND METHODS

Patients

The study was conducted between October 2006 through March 2007 at the labour ward of New Halfa teaching hospital, eastern Sudan. After an informed consent, women with a singleton baby had been approached to participate in the study; those with antepartum hemorrhage, hypertensive disorder (diastolic blood pressure > 90 mm HG) and diabetes mellitus were excluded.

A structured questionnaire was administered to each woman to collect information on socio-demographic markers like residence, educational, age, parity, antenatal attendance, mode of delivery, birth outcome and condition of her baby. Maternal weight and height (in bare feet and with no head cover), were measured to the nearest centimeter after delivery and expressed as body mass index (BMI – weight (kg)/ height (m)²).

Babies were weighed immediately after birth on a Salter scale to the nearest 10 g; scales were checked for accuracy on weekly basis. The APGAR score at 1 min was also recorded. In order to estimate the perinatal mortality, babies were followed until day seven postpartum.

Haematology

Maternal, placental and cord thick blood films were prepared. The slides were Giemsa stained and read counting the number of asexual *Plasmodium falciparum* parasites per 200 white blood cells

and double checked blindly by an expert microscopist. Maternal and cord haemoglobin concentrations were estimated by Hemocue haemoglobinometer (HemoCue AB, Angelhom, Sweden).

Histopathology

Full thickness placental blocks of around 2-3 cm were taken from the placentae, kept in neutral buffer formalin for histopathology examinations. Placental malaria infections was based on the pathological classification of Bulmer et al (1997): uninfected (no parasites or pigment), acute (parasites in intervillous spaces), chronic (parasites in maternal erythrocytes and pigment in fibrin or cells within fibrin and/or chorionic villous syncytiotrophoblast or stroma), past (no parasites and pigment confined to fibrin or cells within fibrin).

Definitions

Maternal anaemia was defined as a haemoglobin concentration < 11 gm/dl and severe anaemia as a haemoglobin concentration < 7 gm /dl. Fetal anaemia was defined as cord haemoglobin < 12.5 gm/dl. LBW was defined as birth weight less than 2500 gm. Perinatal mortality was defined as death from 28-week gestational age (in-utero or outside) till 7 days after birth.

Statistics

Data were entered in computer using SPSS for windows and double-checked before analysis. Means and percentages were calculated. $P < 0.05$ was regarded as significant. The main outcome variables were LBW, APGAR score <5 at 1 min, fetal anaemia and perinatal mortality. For each of these variables the odds ratio for maternal (and fetal) risk factors was estimated at 95 per cent confidence interval and multiple logistic regression analysis using the perinatal outcome as independent and the maternal factors as described above as independent variables were performed. In case of incomplete data, analyses were performed on patients with complete datasets, as reported.

Ethics

The study received ethical clearance from the Research Board at the Faculty of Medicine, University of Khartoum.

RESULTS

During the study period, there were 578 deliveries. Out of these, 24 were twins and 4 were triplets; hence 550 singleton deliveries were available for analysis.

Demographic and clinical characteristics of the women

The mean (SD) age of the mothers was 25.6 (6.4) years, 76 (14.6) % of 522 women, had their age less than 20 years. The mean (SD) parity was 2.7(2.3) and 234 (44.1%) of 531 women were primiparae. Around one fifth, 113 (21.4) of 529 women resided in the town and the remainder 416 (78.6) resided out side the town in the villages. Of the women, 186 (35.9%), 183 (35.3%) and 149 (28.8%) were illiterate, had elementary and secondary or higher education respectively. The majority, 423 (82.0%) of 516 women attended an antenatal care clinic for two or more occasion.

The mean (SD) of the BMI was 23.0 (4.6), 253 (55.5%) of 456 women had their BMI below this mean.

The mean (SD) maternal haemoglobin was 11.5 (2.1) g/dl, 174 (34.5%) of 505 women were anaemic; eight of these women had severe anaemia.

Perinatal outcomes

The mean (SD) of the cord haemoglobin was 13.9 (2.7) g/dl, 147 (29.0%) of 507 babies had fetal anaemia. Three (1.4%) positive *P. falciparum* malaria had been detected in the maternal peripheral placental and cord blood.

Eighty (15.3) of 524 babies who were weighed had LBW, mean (SD) of the birth weight was 3053.6 (559.3) gm. One hundred –thirty four babies (%) had APGAR score <5 at 1 min. There were 46 (9.2%) perinatal deaths.

Risk factors for poor perinatal outcome

Level of education, residence, antenatal care attendance had no association with any the perinatal outcome (data not shown). Maternal LBMI was significantly associated with LBW (OR= 2.3, 95% CI= 1.0-5.1; $P= 0.02$), which was a risk factor for APGAR score <5 at 1 min (OR = 6.9, 95% CI = 2.8- 16.8; $P < 0.000$) and perinatal mortality (OR= 309, 95% CI = 29.2-3271.1, $P < 0.00001$). Table 1 and table 2.

Maternal anaemia was a risk factor for fetal anaemia (OR = 2.2, 95% CI = 1.2-3.9; $P = 0.006$) and APGAR score <5 at 1 min (OR = 0.48, 95% CI = 0.23-0.99; $P = 0.04$). Table 1 and table 2.

Table 1 factors associated with low birth weight and fetal anaemia in parturient women of eastern Sudan using multivariate analysis.

Variable	Low birth weight			Fetal anaemia		
	OR	95% CI	P	OR	95% CI	P
Teenager	1.3	0.47 - 3.7	0.5	0.45	0.16 - 1.2	0.1
Primiparae	0.8	0.35 - 1.8	0.6	1.1	0.64 - 2.0	0.6
Anaemia	0.7	0.37 - 1.6	0.5	2.2	1.2 - 3.9	0.006
Malaria	0.6	0.28 - 1.3	0.2	1.0	0.56 - 1.8	0.94
Low BMI	2.3	1.0 - 5.1	0.02	1.7	0.98 - 3.1	0.05
Low birth weight	-	-	-	0.8	0.34 - 1.9	0.6

Table 2 factors associated with low APGAR score and perinatal death in parturient women of eastern Sudan using multivariate analysis.

Variable	low APGAR			Perinatal death		
	OR	95% CI	P	OR	95% CI	P
Teenager	0.56	0.21 - 1.5	0.25	0.9	0.18-4.4	0.9
Primiparae	2.1	1.0 - 4.1	0.03	1.1	0.36-3.7	0.8
Anaemia	0.48	0.23 - 0.99	0.04	1.0	0.35-2.9	0.9
Malaria	0.88	0.46 - 1.6	0.7	1.0	0.34-2.9	0.9
Low BMI	1.0	0.55 - 1.8	0.9	2.0	0.64-6.7	0.2
Low birth weight	6.9	2.8 - 16.8	0.000	4.8	1.6-14.2	0.005
Fetal anaemia	0.96	0.45 - 2.0	0.9	0.6	0.19-2.4	0.5
Low APGAR	-	-	-	1.2	0.41-4.0	0.6

DISCUSSION

This hospital-based study in rural eastern Sudan has shown that low BMI had a very strong effect on LBW, which has a significant association on perinatal mortality. Maternal anaemia was a risk factor for fetal anaemia and low APGAR score. Maternal socio-demographic (with exception of primiparae) factors and placental malaria on the other hand, were not associated with any of the perinatal outcomes in this study. Actually we planned to conduct this study based on our previous observations on malaria and anemia among pregnant women and we aimed to explore their influence on perinatal outcome. Surprisingly no association between malaria and perinatal outcome was detected and this remain to be investigated in the future. The prevalence of malaria among these parturient women was unexpectedly low in comparison with our previous records (Adam et al., 2005) among the antenatal attendants in the same hospital; this could be one of the explanations. The other possibility is that, the epidemiology of the malaria and its related anaemia might have been interrupted by the recent vigorous – and hopefully sustainable- implementation of the preventive measures (bed nets and prophylactic sulphadoxine-pyremethamine) in the area (Adam et al., 2007).

Malaria during pregnancy can have serious consequences for the newborn baby- regardless of the level of malaria transmission - and constant association between placental infection and low birth weight had been reported in central Sudan and in the neighboring Ethiopia (Taha et al., 1993; Newman et al., 2003). Furthermore, *P. falciparum* malaria had been reported to be association with poor perinatal outcome (especially the severe form) in eastern central Sudan (Adam et al., 2004). However, few studies have revealed no association between malaria and LBW (Sule-Odu et al., 2002; Weiner et al., 2003). The study was conducted at the labour ward in the main hospital. The sample was not representative to whole community and allows the analysis in relation to specific risk factors for those delivering in the hospital only.

In this study the maternal anaemia was associated with poor perinatal outcome mainly low APGAR score and fetal anaemia. This goes with the previous observations from other African countries (Brabin and Piper, 1997; Malhotra et al., 2002). Levy and others had reported an association between anaemia, LBW and preterm labour (Levy et al., 2005). Comparison between these two studies should be taken cautiously because unlike our current study the other one considered the level of 10 gm/dl as a cut off point for maternal anaemia. Recently it had been reported that, maternal anemia was the main risk factor for fetal anaemia (Brabin, et al., 2004). The iron status of babies born to iron-deficient mothers is compromised and fetal iron stores are reduced in LBW and preterm infants (Ahmad et al., 1983; Siimes et al., 1985).

In the current study, around half of the women had low BMI (< the mean) and these women were at double risk of delivering LBW infant. Low BMI was associated with poor perinatal outcome in other setting (Osman et al., 2001; Lasker et al., 2005). We feel that, the issue low BMI together with other anthropometric measures and nutrition and their influence on maternal and perinatal outcome needs to be investigated in this area in more depth in the near future.

An important point in this study is that, primiparae were at higher risk for low APGAR score infants (OR, 2.1, 95% CI= 1.0-4.1). This might be a signal to another important but different public health issue, the labour and its management in the area and the association between labour and the perinatal outcome. The current study was designed to explore the influence of malaria and anaemia on perinatal outcome mainly, hence could not investigate the influence on labour management on perinatal outcome. In neighboring Kenya, where the management of labor was addressed directly, the association with perinatal outcome was significant to an extent of masking other important confounding factors such as malaria and HIV (Weiner et al., 2003).

Importantly, HIV which has a significant impact on maternal and perinatal outcome in Africa was not investigated in the current study. According to our previous records, HIV has a low prevalence (1%) among pregnant Sudanese and Sudanese women had low intake of HIV counseling and testing (Gasmelseed et al., 2006; Mahmoud et al., 2007). These points need to be mentioned when comparing these data with that data from other African countries.

CONCLUSION

Thus, more work is needed in the area of nutritional status, anthropometrics measures, labour and its management in the area. Malaria, anaemia perinatal outcome need to be explored in more depth.

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Chapter 7

Malaria susceptibility and cortisol levels in pregnant women of eastern Sudan

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ABSTRACT

Background

While much data exists on pathogenesis of malaria during pregnancy in areas of intense malaria transmission, probably no or little data are available in the areas of unstable malaria transmission.

Aims

The study was conducted to investigate the role of cortisol and prolactin in the pathogenesis of *P. falciparum* malaria during pregnancy.

Methods

The concentrations of both cortisol and prolactin were measured in sera from two groups of pregnant women in eastern Sudan. One group consisted of 50 pregnant women (18 primigravidae and 32 multigravidae) presenting with uncomplicated *P. falciparum* malaria and the other group comprised 49 healthy volunteer pregnant women (13 primigravidae and 36 multigravidae).

Results

There was no significant difference in concentration of total cortisol in pregnant women with malaria in comparison with the control group, and this is true for both primigravidae and multigravidae. In women with uncomplicated malaria cortisol concentration did not differ significantly between primigravidae and multigravidae. Cortisol was not correlated with the gravidity, gestational age or initial temperature, but positive correlation was observed in cortisol and parasite count. The total serum prolactin was not significantly different between the infected and non-infected group for both primigravidae and multigravidae.

Conclusion

Although, this was small sample sized study, cortisol and prolactin levels were not significantly different between the infected and non-infected women, even in primigravidae and multigravidae.

BACKGROUND

It has been estimated that, 40% of the pregnant women are exposed to malaria infection during pregnancy and most of this burden is in Sub Saharan Africa where 90% of the global malaria burden occurs (Steketee et al., 2001). Malaria during pregnancy poses a substantial risk to the mother, her fetus, and the neonate; the infection contributes to maternal anemia, low birth weight infants, and infant mortality (Cot and Deloron, 2003). Malaria is the major health problem in the Sudan and it has been reported that, pregnant Sudanese women are more attractive to the main malaria vector and more susceptible to malaria than their non-pregnant counterparts (Elghazali et al., 2003; Himeidan et al., 2004; Malik and Khalafalla, 2004). It is associated with maternal anaemia, low birth weight infants and it is the main cause of maternal mortality (Dafallah, et al., 2003; Adam et al., 2005a; Adam et al., 2005b).

Understanding the pathogenesis of malaria during pregnancy is fundamental- yet not completely understood- for the understanding of the disease as whole and may be essential for the development of the future vaccine for these vulnerable groups. There are many hypotheses that could explain susceptibility of pregnant women to the malaria. Indications were obtained that higher cortisol levels cause loss of malaria immunity during pregnancy (Vleugels et al., 1987; Vleugels et al., 1989; Bouyou-Akotet et al., 2005). These reports are compatible with recent findings of interactions between natural killer cells, cortisol and prolactin in malaria during pregnancy (Mavoungou, 2006). The present work was conducted to investigate the serum cortisol and prolactin among pregnant women of eastern Sudan. The area is characterized by unstable malaria (Himeidan et al., 2005a; Himeidan et al., 2005b). Malaria during pregnancy is big burden in the area and pregnant women are more susceptible to falciparum malaria irrespective to their age and parity (Adam et al., 2005a).

MATERIALS AND METHODS

The study was conducted in New Half, eastern Sudan during the period of September-November 2006, where consecutive pregnant women presented (before the midday) with uncomplicated *P. falciparum* malaria were approached to participate in the study. Healthy pregnant volunteers that matched for age, parity and gestational age were taken as control. After an informed consent was taken, pre-tested questionnaires were filled to gather the socio-demographic charters, the basic medical and obstetrical history (including the parity and gestational age). The women were examined clinically, where their temperature was taken and the fundal level was determined. Blood films were prepared, stained with Giemsa and 100x oil immersion fields were examined. The parasite density was counted against 200 leucocytes, assuming 6000 leucocytes/ μ l. All the slides were double-checked blindly and only considered negative if no parasites were detected in 100 oil immersion fields. Then 5 ml of blood was taken—after haemoglobin level was determined - centrifuged immediately and kept at -20 OC till analyzed by radioimmunoassay gamma counter (Riostad, Germany). IRMA KIT (RK-780MACE040501) and RIA KIT (RK-240MACED040501) of IZOTOP (Budapest) were used for analysis of prolactin and cortisol levels respectively. The entire samples were analyzed by the same person, who is blind about the clinical findings of the patients.

Ethical clearance

The study received ethical clearance from the Research Board at the Faculty of Medicine, University of Khartoum, Sudan.

Statistical analysis

Data were entered into a computer database and SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The means (age, weight, temperature, and hemoglobin) were calculated for all the patients and were compared between the patients in the two arms of the study subgroups using student t-test, when the data was normally distributed and by Mann-

Whitney test if the data was not normally distributed. The mean (SD) of cortisol and prolactin levels were calculated and compared between the patients in the two arm of the study groups and subgroups using student t-test. Correlations between parasitemia, temperature, gestational age, gravidity and cortisol levels (and prolactin) were determined. A P -value ≤ 0.05 was considered to be significant.

RESULTS

During the study period, 50 pregnant women presented with uncomplicated *P. falciparum* malaria. Forty-nine healthy pregnant women were taken as control. With exception of haemoglobin, the two groups were well matched and there was no difference between them, table 1.

Table 1 comparison of different variable between the pregnant women with uncomplicated falciparum malaria and the controls.

Variable	Infected women		control		PValue
Age in years	26.0	(7.1)	26.1	(6.7)	0.925
Gravidity	3.5	(2.5)	2.8	(2.0)	0.18
Weight, Kg	58.7	(12.0)	57.5	(12.2)	0.632
Gestational age, weeks	24.6	(8.5)	26.6	(6.2)	0.185
Haemoglobin, g/dl	9.1	(1.3)	9.9	(.8)	0.001

The mean (SD) of the total cortisol level was not significantly different between women with uncomplicated *P. falciparum* malaria and the control; 646.3 (1512.9) ng/ml vs. 434.7(173.08) ng/ml, $P = 0.333$. This is also true in infected primigravidae (12) and non-infected primigravidae (18); 474.0(151.04) ng/ml vs. 463.6(197.9) ng/ml, $P = 0.897$ or multigravidae in both groups, table 2. In all the patients (infected and non-infected), there was no significant difference in cortisol level between the primigravidae (31) and multigravidae (68); 469.6 (169.1) vs 574.3(1302.2) ng/ml, $P = 0.657$. In women with uncomplicated *P. falciparum* malaria, the mean (SD) of the total cortisol levels were not different in primigravidae (12) and multigravidae (38), table 2.

Table 2 showing mean (SD) of the cortisol level in the different subgroups of pregnant women of eastern Sudan.

	Total		Primigravidae		Multigravidae		Pvalue
Infected women	646.3	(1512.9)	474.0	(151.04)	743.3	(1891.7)	0.097
Control	434.7	(173.08)	463.6	(197.9)	424.2	(165.0)	0.487
Pvalue	0.333		0.897		0.317		

In infected group of women; a positive correlation was observed in cortisol level and parasite count ($r = 0.332$, $P = 0.02$), but there were no significant correlations between the total cortisol levels and temperature ($r = 0.069$, $P = 0.64$), gravidity ($r = 0.174$, $P = 0.233$), or the gestational age ($r = 0.087$, $P = 0.552$). Likewise, there was no significant difference in prolactin levels between the infected and non infected groups, or subgroups and primigravidae (31) and multigravidae (68), 8445.9 (5648.8) mu/lvs. 7103 (5402.6) mu/l, $P = 0.261$, table 3.

In infected group of women: a positive correlation was observed in prolactin levels and the gestational age ($r = 0.472$, $P = 0.001$), but there were no significant correlations between the total prolactin levels and temperature ($r = 0.005$, $P = 0.971$), parasite count ($r = 0.126$, $P = 0.390$), or gravidity ($r = 0.150$, $P = 0.303$).

Table 3 showing mean (SD) of the prolactin level in the different subgroups of pregnant women of eastern Sudan

	Total	Primigravidae	Multigravidae	Pvalue
Infected women	8123.9 (5310.9)	9788.2 (5182.7)	7187.2 (5228.8)	0.551
Control	6911.2 (5650.9)	6587.3 (5939.2)	7028.2 (5625.4)	0.812
Pvalue	0.274	0.121	0.904	

DISCUSSION

The study showed that, the cortisol levels were not significantly different between pregnant women infected with *P. falciparum* malaria and the controls. This contradicts previous findings, where cortisol level was significantly higher in pregnant women infected with *P. falciparum* malaria in comparison to the control group (Vleugels et al., 1987; Vleugels et al., 1989) and also in non-pregnant populations with uncomplicated *P. falciparum* malaria than in the control (Shwe et al., 1998). The significantly higher level of serum cortisol in the infected patients previously reported indicated intact hypothalamous/pituitary/ adrenal axis in these reports. Activation of this axis in malaria might be due to release of cytokines and/ or results of stress generated by the disease; it had been observed earlier that cytokines level was associated with basal and peak levels of ACTH (Wilson et al., 2001). Interestingly in this study, the serum cortisol levels were not significantly different between primigravidae and multigravidae infected with uncomplicated *P. falciparum* malaria. We have recently found that, pregnant Sudanese women in the same hospital are at risk for *P. falciparum* malaria irrespective to their age or parity (Adam et al., 2005a). However, significantly higher cortisol levels were found in primigravidae compared with multigravidae (Vleugels et al., 1986).

In the present study, cortisol was not correlated with the gravidity, gestational age or initial temperature, but a positive correlation was observed between cortisol and parasite count. This goes with previous findings reporting, a positive correlation between cortisol levels and parasite load in primigravidae infected with *P. falciparum* malaria (Vleugels et al., 1989). Yet, recently Libonati and colleagues had found no correlation between cortisol and the parasite count in non-pregnant population infected with falciparum malaria (Libonati et al., 2006). This is expected as pregnancy is a unique situation where the immunomodulation is mediated by cortisol and other steroidal hormones as estrogen and progesterone (Roberts et al., 1996).

Even in healthy pregnant women, the serum concentration of total cortisol increased linearly with progression of amenorrhea. Significantly higher cortisol levels were found in nulliparas compared to multiparas and independent of amenorrhea (Vleugels et al., 1986). Recently, Bouyou-Akotet and colleagues observed that, cortisol concentrations increased with gestational age (Bouyou-Akotet et al., 2005). This study showed that, prolactin was not significantly different between the infected women and control. However, a positive correlation was observed between prolactin levels and the gestational age. This is in agreement with the previous study (Bouyou-Akotet et al., 2005). The Interactions between natural killer cells, cortisol and prolactin in malaria during pregnancy were recently discussed (Mavoungou , 2006).

The present study has many limitations; it is small sample sized, cortisol and prolactin levels were measured from different patients only once. Ideally these hormones need to be analyzed in the same pregnant women at different intervals and at different gestational age and according to the parasitemia. However, our findings are totally different from the previous reports. So larger studies in this area and other areas of unstable malaria transmission are recommended.

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Chapter 8

Perceptions of the causes of malaria and of its complications, treatment and prevention among midwives and pregnant women of eastern Sudan

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ABSTRACT

Background

Malaria infection during pregnancy is a big burden in Sudan and has many adverse effects on both mother and fetus. There are no data concerning the local socio-cultural knowledge on malaria, its complications and prevention during pregnancy.

Aim

This study was conducted to assess the perceptions of the causes of malaria, its complications, treatment and prevention among midwives and pregnant women of eastern Sudan, so as to provide policy makers and malaria programme managers with information needed to improve the design of malaria control.

Methods

Eighty-seven midwives and 168 pregnant women were interviewed.

Results

More than three quarters (78.2%) of the midwives and (82.7%) pregnant women perceived that mosquitoes were the transmitters of malaria. The coverage of ITNs was 65.5% among the interviewed pregnant women.

There was poor knowledge about the complications of malaria during pregnancy, and the effect of malaria treatment on the fetus among the interviewed midwives and pregnant women. More than sixty percent, 59 (67.8%) of the midwives and almost all the pregnant women 162 (96.4%) had no knowledge towards the IPT.

Conclusion

Thus, inspite of good knowledge towards symptoms of malaria during pregnancy, there was lack of perception on the prevention and the safety of intermittent preventive treatment.

BACKGROUND

It has been estimated that 40% of the pregnant women are exposed to malaria infection during pregnancy and most of this burden is in Sub-Saharan Africa, where 90% of the global malaria burden occurs (Steketee et al., 2001). Malaria during pregnancy poses a substantial risk to the mother, her fetus, and the neonate. Malaria infection contributes to maternal anemia, low birth weight, and infant mortality (Cot and Deloron, 2003). Malaria is a major health problem in Sudan (Malik and Khalafalla, 2004). It has been reported that pregnant women are more attractive to the main malaria vector and more susceptible to malaria than their non-pregnant counterparts (ElGhazali et al., 2003; Himeidan et al., 2004; Adam et al., 2005a). In Sudan: malaria during pregnancy has been reported to be associated with maternal anaemia, low birth weight infants and as the main cause of maternal mortality (Dafallah et al., 2004; Adam et al., 2005b).

Sleeping under an insecticide-treated bednet (ITN) can reduce the risk of a pregnant woman being infected with malaria and reduce the risks of maternal anaemia and low birth weight (Ter Kuile et al., 2003). Another preventive measure against the adverse effects of malaria during pregnancy is intermittent preventive treatment (IPT) with two doses of sulphadoxine-pyrimethamine (SP). IPT with SP has been reported to reduce low birth weight deliveries in malarious areas (Parise et al., 1998; Verhoeff et al., 1998).

On 25 April 2000, 44 African heads of state and government delegations adopted the Abuja Declaration on Roll Back Malaria in Africa (AFRO, 2002). Among other goals, they pledged that by 2005, 'at least 60% of all pregnant women who are at risk of malaria, especially those in their first pregnancies, will have access to chemoprophylaxis or presumptive intermittent treatment. Thus far, this promising intervention, named IPT has not been widely implemented in malaria-endemic areas of Africa. Following this recommendation, many researchers and the Sudanese Federal ministry of health recommended IPT and ITN for pregnant women in areas of stable malaria transmission and irrigated areas-the study area (Adam et al., 2005a; b). Only 13% and 1.8% of pregnant Sudanese women have used ITNs and IPT respectively (Malik, unpublished), thus far from the recommendations.

It has been shown that acceptance of IPT and ITN depends on cultural, behavioural and demographic factors (Govere et al., 2000). The perception and attitude towards malaria and its prevention during pregnancy has been extensively studied in other African countries with stable malaria transmission (Launiala et al., 2006; Mbonye et al., 2006a; Mbonye et al., 2006b). The aim of this study was to explore knowledge, perception, beliefs and practices associated with malaria, its complication, treatment and prevention among midwives and pregnant women of eastern Sudan since no proper published data exist.

METHODS

The study was conducted during July 2006 in New Halfa area, eastern Sudan which is characterized by unstable malaria transmission (Himeidan et al., 2005). After obtaining an informed consent, all the midwives in the area and all the pregnant women in 21 villages- out of 176 villages- were interviewed. Pre-tested structured questionnaires were administered to collect the socio-demographic characteristics including residence, age, parity, gestational age and the level of education (Govere et al., 2000). Then the interviews began with broad unstructured and non-directive questions about pregnancy, delivery and health of pregnant women and gradually focused towards malaria during pregnancy, its causes, symptoms, complications (miscarriage, preterm labour, anemia and maternal death), treatment seeking behaviors and the safety of antimalarials. Special questions were raised regarding their perception of the preventive measures (ITN and IPT) during pregnancy and the women's willingness to use these preventive packages in the future.

Ethical clearance

The study received ethical clearance from the Sudanese National Committee of the Federal ministry of Health.

RESULTS

During the study period, 87 midwives and 168 pregnant women were interviewed. The mean (SD) of the age and parity of the pregnant women were 25.6 (9.4) years and 2.5 (2.8) respectively. More than three quarters, 68 (78.2%) and 139 (82.7%) of the midwives and pregnant women respectively had knowledge that mosquitoes were the cause of malaria. While, 10 (6.0%) of the pregnant women did not know the cause of malaria and 5 (3.0%) of them mentioned stagnant water as the cause of malaria, table 1. Above ninety percent of the midwives, 83 (95.4%) and pregnant women, 163 (97.0%) mentioned two or more symptoms of malaria. The majority, 137 (81.5%) of the pregnant women would go to the doctor and 15 (8.9%) would go to the midwife if they felt unwell or had symptoms suggestive of malaria, while the rest (9.5%) would take medicine by themselves or just take good food.

Anaemia was mentioned as a complication of malaria during pregnancy by 31(35.6%) and 87(51.8%) of the midwives and the pregnant women respectively. More than one quarter, 27 (31.0%) and 15 (8.9%) of the midwives and pregnant women respectively mentioned miscarriage as a complication of malaria. Low birth weight as a complication of malaria was mentioned by 24 (27.6%) and 11 (6.5%) of the midwives and pregnant women respectively, table1. More than one quarter, 48 (28.6%) of the pregnant women did not mention any complication of malaria on pregnancy. Around one fifth, 19 (21.8%) and 65 (38.7%) of the interviewed midwives and pregnant women mentioned that malaria treatment is harmful for the fetus. More than two fifth, 73 (43.5%) of the pregnant women were not using bed nets; either because it was not available (21), hot (7), nasty (1), unpleasant (18), restrict their movement (13), they were lazy (13) or it would not be protective (1). Around two thirds 95 (65.5%) of the pregnant women using nets, did not use it last night.

More than sixty percent, 59 (67.8%) of the midwives and almost all the pregnant women 162 (96.4%) had no knowledge towards the IPT. More than one third, 29 (33.3%) and 14 (8.3%) of the interviewed midwives and pregnant women mentioned that SP was harmful and unsafe to be used during pregnancy.

Table 1 component of the knowledge score among interviewed midwives and pregnant Sudanese women

Statement	Number (%) of the midwives Total number = 87		Number (%) of the pregnant women Total number = 168	
Malaria transmission				
Mosquitoes	68	(78.2%)	139	(82.7%)
Flies	7	(8)	14	(8.3)
Stagnant water	6	(7)	5	(3.0%)
No cause	6	(7)	10	(6.0%)
Consequences				
Maternal anemia	31	(35.6)	87	(51.8)
Low birth weight	24	(27.6)	11	(6.5)
Miscarriage	27	(31)	15	(8.9)
Others	3	(3.4)	7	(4.1)
No answer	2	(2.3)	48	(28.6)

DISCUSSION

Probably, this is the first published data investigating the perceptions of the causes of malaria and of its complications, treatment and prevention among midwives and pregnant women of eastern Sudan. The study showed that, the interviewed midwives and pregnant women had good knowledge towards malaria symptoms; perceived mosquitoes as the cause of malaria and the coverage of ITNs was 65.5%. The main reasons for not using ITNs were; not available, hot, smelly, and unpleasant and restrict the movement. Previously, women of the central Sudan were less likely to be involved in drying mosquito breeding sites and spraying activities of insecticides because of fear of allergy and bad odour of these materials (A/Rahman et al., 1996). In the neighboring Uganda, mosquitoes were perceived as the cause of malaria but as the same time use of ITNs was only 26%. People who did not use ITNs cited discomfort due to heat and humidity; and the high cost of ITNs as reasons for non-use (Nuwaha, 2002; Mbonye et al., 2006a). In Kenya, although malaria was perceived to be an important disease, ITNs were believed to be partially beneficial because of the perception that malaria has multiple causes and the belief that chemicals used to treat ITNs were associated with family planning (Alaii et al., 2003). However, thirty-six percent of Malawian women did not know what causes malaria and ninety-five percent of them mentioned one or more symptoms of malaria (Launiala et al., 2006).

Our study showed that, anaemia, miscarriage and low birth weight as complications of malaria during pregnancy were mentioned by 51.8%, 8.9% and 6.5% of the pregnant women respectively, and around one quarter (28.6%) of the pregnant women did not mention any complication of malaria during pregnancy. Recently Mbonye and colleagues (Mbonye et al., 2006b), reported poor knowledge towards the complications of malaria during pregnancy e.g. anaemia and low birth weight.

Substantial concern about the use of IPT during pregnancy was expressed by the midwives and pregnant women in this study and the majority of the midwives and almost all the pregnant women (98%) had no knowledge towards the IPT. More than one third of the interviewed midwives and pregnant women mentioned that SP is harmful and unsafe to be used during pregnancy. Although, the majority of women considered antimalarials to be less harmful than effects of malaria itself on pregnancy; they didn't realize the role of malaria chemoprophylaxis during pregnancy. Previously, a negative perception towards SP usage during pregnancy has been reported and SP has been believed to be a strong drug and might lead to abortion and congenital malformations (Mbonye et al., 2006c).

Thus, more effort is needed through different programmes (health education, training and teaching) urgently to raise the coverage of these preventive measures among the vulnerable group of pregnant women.

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Chapter 9

General discussion

DISCUSSION

The studies in this thesis investigated different aspects of malaria during pregnancy in Eastern Sudan. The results showed that malaria during pregnancy is a substantial burden since pregnant women in eastern Sudan are susceptible to malaria, both peripheral and placental, and its related anaemia irrespective to their age or parity. While anaemia and low body mass index were found to be risk factors for poor perinatal outcomes, malaria alone was not found to be associated with low birth weight. While both pregnant women and midwives in the area had good knowledge about malaria and its complications, there was poor knowledge about the effects and use of preventive measures, notably intermittent preventive treatment.

Epidemiology of malaria and anemia in pregnancy

Most of the studies on epidemiology and pathogenesis of malaria during pregnancy emerged from areas of stable malaria in Africa; while on the other hand data on the treatment of malaria during pregnancy emerged from western border of Thailand, which is characterized by unstable malaria transmission. The studies in Thailand investigated displaced Karen women located in a limited area in camps following local conflict in the area; these condensed living conditions themselves might have influenced the epidemiology of malaria during pregnancy. In the Karen women studied, malaria and malaria-related anaemia affect mainly primigravidae and secundigravidae (Nosten et al., 1991), while malaria and its related anaemia in eastern Sudan affect pregnant women irrespective to their age and parity (Adam et al., 2005a). This might be explained by the relatively high prevalence of malaria among the women in the refugee setting described in the Thailand study (37.2%) versus the relatively low prevalence (13.7%), especially in the second study (Chapter 3), in Eastern Sudan. In addition, in the study from Thailand most parasitemic women were asymptomatic (90%), which suggests that these women had existing antimalarial immunity, which in turn indicates a more stable transmission pattern than in eastern Sudan. Most of the studies in Thailand were community-based (with data obtained in camps), while 5 out of 7 of the studies included in this thesis were hospital-based, which potentially has an inherent bias. Hospital-based studies have several limitations, including not being representative of the disease pattern at the community level. Perhaps women opt for hospital delivery when they anticipate a complicated delivery. Furthermore, while both in Thailand and Sudan *P. falciparum* are endemic, in Thailand, *P. vivax* brings also a considerable burden on pregnant women. In summary, it is understandable that the results of the studies conducted in Thailand among Karen women and the studies presented in this thesis do deviate in their results.

In spite of differences, some similarities between data of Thailand and the data of eastern Sudan do exist, such as the existence of severe cases among the pregnant women (Luxemburger et al., 1997; Adam et al., 2004a).

In the first study in this thesis, which was designed mainly to investigate susceptibility of pregnant women in eastern Sudan to malaria, the birth weight of the babies born to infected mothers was significantly lower in comparison to the non-infected group. Although, it had a relatively small sample-size, the findings are in line with those of Nosten et al., who followed the infected women till the delivery and the birth weight was compared between the infected and non-infected women. In a follow-up study, we used malaria placental histopathology, and birth weight was compared between infected and non-infected women. With this design, there was no association between placental malaria and low birth weight. Multiple causes can be taken into consideration to explain these differences. These include submicroscopic malaria infections, stillbirth due to acute malaria, changing treatment for malaria, other infections (e.g. Schistosomiasis) and other confounding factors leading to low birth weight, that were not taken into consideration in our studies.

Several studies have shown that malaria is the most important cause of low birth weight in stable malaria-endemic areas, especially among primigravidae (McGregor, 1984; Brabin & Piper, 1997). The mean birthweight in all parities was significantly lower at two sites with different transmission in Uganda (Ndyomugenyi et al., 2001), and that was attributed to frequent and persistent malaria infection in pregnancy leading to maternal anaemia and intra-uterine growth retardation (Kramer, 1987). However, in areas of unstable transmission, acute malaria is common and could lead to abortion, stillbirths or premature delivery (Nosten et al., 1991). The high; rates of stillbirth observed at Kabale hospital compared to Hoima hospital in Uganda (with unstable and stable

malaria transmission, respectively) support these findings. Malaria has been observed to affect primigravidae more than multigravidae in areas of stable transmission. Therefore, in these areas the influence of malaria infection on birthweight is more significant in primigravidae than multigravidae (McGregor, 1984). However, in areas of unstable malaria transmission, pregnant women of all parities are equally exposed to the risk of malaria and its associated hazards on birthweight owing to lack of sufficient malaria immunity. The rates of low birth weight decreased with parity in the area of stable transmission, but not in an area of unstable transmission (Verhoeff et al., 1999).

Stillbirth is common in areas with unstable malaria (Brabin et al., 2004; Cot and Deloron, 2001; Ndyomugenyi et al., 2001). Newman et al. (2003) reported a seven-fold increased risk of stillbirth in association with placental parasitaemia in areas with unstable malaria transmission in Ethiopia. The impact of malaria on the risk of stillbirth and neonatal mortality is still under debate. Malaria could increase stillbirth risk through fetal anaemia or preterm delivery (Brabin et al., 1991). However, neither McGregor et al., (1983) in the Gambia, nor Anagnos et al. in Zaire (Anagnos et al., 1986), detected any statistical association between stillbirth and placental malaria. McGregor et al. reported some seasonal differences in stillbirth rates, with the lowest rate occurring during the three months of the late dry season when placental malaria prevalence was low. This difference occurred across all parities. Conversely Okoko et al., (2002) also in the Gambia, observed a two-fold increased risk of stillbirth among mothers with malaria-infected placenta. Recently, van Geertruyden et al., (2004) performed a meta-analysis of 17 cross-sectional studies mostly from Africa, and observed an overall odds ratio of stillbirth of 2.19 (95% confidence interval = 1.49-3.22, $P < 0.001$)

In Africa, there have been few studies of malaria during pregnancy in areas of unstable, or epidemic-prone, transmission. One hospital-based retrospective study conducted in 2 different regions of Uganda found that the risk of hospitalization with malaria and the rate of stillbirths were significantly more common in an area of unstable than an area of stable transmission (Ndyomugenyi et al., 2001). The two cross-sectional studies in Ethiopia found that peripheral parasitemia, as well as placental parasitemia, was very uncommon in areas of unstable transmission during a non-epidemic year and only moderately common in an area of stable but low transmission. However, although rates of parasitemia were relatively low, malaria during pregnancy was strongly and significantly associated with adverse pregnancy outcomes, including maternal anemia, low birth weight, premature delivery, and stillbirths. This in contrast to our findings in eastern Sudan (Chapter 3).

During the conduct of the studies included in this thesis, multidrug resistant *P. falciparum* strains were observed among pregnant and non-pregnant populations in eastern Sudan (the study area) (Adam et al., 2004c). For this reason, Sudan as well as many other African countries changed their policy in the treatment of malaria from chloroquine to artemisinin based chemotherapy. Artesunate plus sulfadoxine/pyrimethamine is the recommended first line treatment for uncomplicated *P. falciparum* malaria including pregnant women. Thus, many of these pregnant women were treated effectively and safely with these compounds (Adam et al., 2006). This might explain the lack of an association in between placental malaria and low birth weight in our follow up study and might indicate a need to focus attention on other causes of low birth weight.

In the studies included in this thesis, peripheral, placental malaria and anaemia were not associated with age or parity. A plausible explanation includes the low endemic density of malaria during the study period in the area of eastern Sudan. This point needs to be considered in the implementation of the preventive measures for malaria in this vulnerable group. Thus, any preventive measures in eastern Sudan should be directed to all pregnant women irrespective to their age and parity.

Currently, In Africa the impact of malaria on maternal and perinatal outcomes are influenced by infections with the Human Immunodeficiency Virus (HIV). Not only the the burden of malaria and its unfavourable effects might be higher in the presence of HIV infections, but also its treatment and its prevention (e.g. intermittent preventive treatment) can be negatively influenced too (Parise et al., 1998). These points need to be remembered when comparing the data in this thesis with that of other African countries. The prevalence of HIV among pregnant women of central Sudan was reported to be low (1%) (Gassmelseed et al., 2006), despite poor knowledge of HIV counseling and

testing (Mahmoud et al., 2007). Based on the low prevalence of HIV in Sudan, it is unlikely that the results of our studies would have been influenced by prevalent HIV infections.

In this thesis neither cortisol nor prolactin were found to have a role in the pathogenesis of malaria during pregnancy. These findings are not in line with the previous reports from other settings (Bouyou-Akotet et al., 2005). However, consistent with the data from Western and Southern Africa (Loscertales and Brabin, 2006), the susceptibility of pregnant with blood group O to placental malaria has been confirmed in this thesis.

In summary, it seems that many factors intermingle with each other in the pathogenesis and susceptibility of malaria during pregnancy leading to multiple plausible hypotheses to be tested. Effective measures to reduce the burden of malaria in unstable transmission settings would differ from those recommended for high transmission areas. For instance, insecticide-treated bednets were not effective for preventing anaemia in pregnancy in a high transmission area in Kenya (Shulman et al. 1998), while they reduced anaemia in an area of low transmission on the Thai-Burmese border (Dolan et al. 1993). Chemoprophylaxis is effective in reducing the burden of malaria in primigravidae in high endemic areas (Shulman et al. 1999). However, it is not clear whether chemoprophylaxis during pregnancy should be offered routinely in low transmission areas and if so what parities should be targeted.

PUBLIC HEALTH IMPLICATIONS

Malaria has been reported as an important cause of morbidity and mortality in Sudan (Malik and Khalafalla, 2004). Malaria has deleterious effects on the maternal health. The core of this thesis is the report of the substantial burden of malaria during pregnancy (peripheral and placental malaria) in eastern Sudan, where it affects pregnant women irrespective to their age or parity. Based on these results public health officials, in cooperation with the antenatal clinic workers in Halfa, started implementing preventive measures including house spraying, insecticide-treated bednet and intermittent preventive treatment to prevent these complications, and especially anaemia. Unfortunately, while both pregnant women and midwives had a good knowledge about the risks of malaria and recognized its vector, they had a poor knowledge of the effects of the preventive measures, which were consequently underused. These latter findings are of interest for the public health workers, where efforts are needed in many dimensions. Guided by the results of this thesis, preventive measures should be given to all pregnant women in the Halfa area (eastern Sudan) irrespective to their age or parity. However, there is a need for continuous health education both to pregnant women and to midwives. Future approaches should include not only the provision of preventive measures, but also health education, targeted at increasing knowledge about the effects of preventive measures. Furthermore, in the antenatal care package in those areas where malaria is an important issue routine investigation for malaria could be incorporated. Although, this thesis failed to find association between malaria and poor perinatal outcomes, it brought other important factors for poor perinatal outcome to the attention. These are maternal low body mass index and anaemia. Thus, public health workers might be in need to implement more efforts in the field of nutritional health for these women. To our knowledge there is no data concerning the types of anaemia in Sudan, in pregnant and non-pregnant women. Hence, research into additional contributors to anaemia (folate, vitamin B12, iron, other infections) is urgently needed and could lead to targeted dietary supplements.

IMPLICATIONS FOR FUTURE RESEARCH

Although studies in this thesis provide additional information on malaria and anaemia during pregnancy in eastern Sudan, still more questions need to be answered. The susceptibility of the pregnant women to malaria need to be investigated in more depth. In other parts of the world the plausible hypothesis of the chondroitin sulfate A, has been tested and it is worth to be investigated in this area. The peak time of the malaria during pregnancy, has been found to be in the later second trimester and early third trimester. The susceptibility of malaria has been reported to extend beyond pregnancy, to the postpartum period. The underlying mechanisms need to be investigated in the future and could lead to new insights, not only in pathogenesis, but potentially

also for other treatment venues. The area of the eastern Sudan is endemic for *Schistosomiasis mansoni*, which could have its own effects on anaemia and other morbidity during pregnancy, this needs to be considered if anaemia is to be investigated and the overlap with malaria needs to be explored.

The thesis highlighted the poor community reaction to intermittent preventive treatment. However, their effects on malaria and anaemia and pregnancy was not investigated, so this area need to be explored.

A study included in this thesis showed no association between malaria and low birth weight. Low birth weight deserves more elaboration, with regard to other risk factors in relation to malaria, including the role of submicroscopic parasitaemia. An important, potentially confounding, issue is stillbirth, which we did not address in the current studies. This confounding factor should be addressed in future studies.

Anaemia was shown to be related to poor neonatal outcome, hence other causes of anaemia in these women deserve exploration. Although, pica, which is relatively common in eastern Sudan has been found to be associated with anaemia, its association, whether causative or not, with pregnancy outcomes need to be investigated further.

Anaemia during pregnancy itself, through many endocrine alterations may influence the maternal and fetal environment. Few data exist concerning the role of endocrine factors e.g. prolactin in restricting fetal growth in anaemia during pregnancy (Mahajan et al., 2008). So maternal and fetal endocrine profiles need further exploration.

Recently, reports of associations between malaria and hypertension during emerged from other African settings (Brabin, 2005). No doubt that hypertension during pregnancy is another eranda that has a substantial burden of fetal and maternal morbidity. So it will be worth to investigate the linkage between hypertension and malaria during pregnancy.

In conclusion, malaria and anaemia are important threats to maternal and neonatal health in the area of eastern Sudan that was studied in this thesis. Until a complete evidence-based model of epidemiology and pathophysiology is ready, the information in this thesis could be used for the guidance in planning health care provision to other parts of Sudan as well as for other settings with similar background.

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SUMMARY

The study was conducted in New Halfa area in the eastern Sudan, which is characterized by unstable malaria transmission. The predominant malaria parasite species is *Plasmodium falciparum* and *Anopheles arabiensis* is the sole malaria vector in the area. The study aimed to investigate: the susceptibility of pregnant women to malaria in comparison to non-pregnant controls, the burden of malaria and anaemia and their risk factors among pregnant women, effects of malaria on maternal and perinatal outcomes, pathogenesis of malaria during pregnancy in the area and to investigate ways to prevent malaria in the area.

A longitudinal community-based study was conducted at a village antenatal clinic (Chapter 2), 89 non-pregnant controls and 86 pregnant women were enrolled and followed every 2 weeks until 6 weeks after delivery to investigate the susceptibility of pregnant women to *P. Falciparum* malaria in comparison to their non-pregnant counterparts.

The incidence of *P. falciparum* infection was significantly higher among pregnant than control women (17.4% versus 5.6%) with no difference between primigravidae and multigravidae (22.2% versus 15.2%).

A cross sectional study was conducted (Chapter 3 and 4), where antenatal clinical attendants were investigated for malaria and anaemia and risk factors for these conditions were assessed. In this group of patients both the prevalence of malaria and its risk factors and the prevalence of anaemia was and its risk factors were described.

A total 102 (13.7%) of 744 women had *P. falciparum* malaria, 18 (17.6%) of these were severe cases (jaundice and severe anaemia). Univariate and multivariate analysis showed that, age and parity were not associated with malaria. Women who attended the antenatal clinic in the third trimester were at highest risk for malaria (OR = 1.58, 95% CI = 1.02-2.4; $P < 0.05$).

Of the 74 women, 466 (62.6%) had anaemia (haemoglobin [Hb]: < 11 gm/dl). 52.4% had mild anaemia (Hb: 9.0-10.9 gm/dl), 8.1% had moderate anaemia (Hb: 7.0-8.9 gm/dl), and 2.2 % had severe anaemia (Hb: < 7 gm/dl), respectively. The prevalence of anaemia (73.2%) was significantly high in grandmultigravidae. Univariate and multivariate analysis showed that age and parity, were not significantly associated with anaemia. Malaria (OR = 4.5, 95% CI = 2.5-8.1; $P < 0.0001$) and pica (OR = 1.6, 95% CI = 1.05-2.6; $P = 0.03$) were the risk factors for anaemia.

In a cross-sectional study, parturient women were investigated for anaemia, peripheral and placental malaria (Chapter 5 and 6). The prevalence and risk factors for placental malaria in eastern Sudan were described, as well as the effect of malaria and anaemia on maternal and perinatal outcomes.

114 (39.7%), 61 (22.1%) and 118 (38.2%) women were primiparae, secundiparae and multiparae, respectively. The ABO blood group distribution was 82(A), 59 (B), 24 (AB) and 128 (O). Placental histopathology showed acute placental malaria infections in 6 (2%), chronic infections in 6 (2%), 82 (28.0%) of the placentae showed past infection and 199 (68.0%) showed no infection.

There was no association between the age (OR = 1.02, 95% CI = 0.45-2.2; $P = 0.9$), parity (OR = 0.6, 95% CI = 0.3-1.2; $P = 0.1$) and placental malaria infections. In all parity blood group O was associated with a higher risk of past (OR = 1.9, 95% CI = 1.1-3.2; $P = 0.01$) placental malaria infection. This was also true when primiparae were considered separately (OR = 2.6, 95% CI = 1.05-6.5, $P = 0.03$).

Among women with all placental infections / past placental infection, the mean haemoglobin was higher in women with the blood group O, but the mean birth weight, feto-placental weight ratio was not different between these groups and the non-O group.

A case-control study was conducted to investigate the role of cortisol and prolactin in the pathogenesis of malaria. There was no significant difference in concentration of total cortisol in pregnant women with malaria in comparison with the control group, and this is true for both primigravidae and multigravidae.

In women with uncomplicated malaria cortisol concentration did not differ significantly between primigravidae and multigravidae (Chapter 7). Cortisol was not correlated with the gravidity, gestational age or initial temperature, but positive correlation was observed in cortisol and parasite count. The total serum prolactin was not significantly different between the infected and non-infected group for both primigravidae and multigravidae.

Finally, in a community- based survey the perceptions among midwives and pregnant women of the causes of malaria, its complications, its treatment and methods of prevention were assessed (Chapter 8).

More than three quarters (78.2%) of the midwives and (82.7%) pregnant women perceived that mosquitoes were the transmitters of malaria. The coverage of ITNs was 65.5% among the interviewed pregnant women.

There was poor knowledge about the complications of malaria during pregnancy, and the effect of malaria treatment on the fetus among the interviewed midwives and pregnant women. More than sixty percent, 59 (67.8%) of the midwives and almost all the pregnant women 162 (96.4%) had no knowledge towards the IPT.

SAMENVATTING

De onderzoeken gepresenteerd in dit proefschrift zijn uitgevoerd in "New Halfa" in het oosten van Soedan. Het gebied wordt gekenmerkt door onstabiele malaria transmissie. De meest voorkomende malariaparasiet soort is *Plasmodium falciparum* en de enige malaria vector in het gebied is de *Anopheles arabiensis*.

De beschreven onderzoeken streefden ernaar: de ontvankelijkheid van zwangere vrouwen voor malaria te vergelijken met niet-zwangere controles, de morbiditeit ten gevolge van malaria en anemie gedurende de zwangerschap te beschrijven, in relatie tot de aanwezigheid van risico factoren voor deze condities in het bestudeerde geografische gebied.

Een longitudinaal populatie-gebaseerd onderzoek (Hoofdstuk 2) werd uitgevoerd in een dorps-gebonden prenatale kliniek. Er deden 89 (controle) niet-zwangere vrouwen en 86 zwangeren mee. Deze werden iedere twee weken gevolgd, tot 6 weken na de bevalling van de zwangeren. De incidentie van *P. falciparum* infectie was significant hoger in zwangeren dan in controles (17.4% versus 5.6%), echter er was geen significant verschil tussen primigravidae (22.2%) en multigravidae (15.2%).

In een cross-sectioneel onderzoek (Hoofdstuk 3 en 4) werden zwangeren die een antenatale kliniek bezochten onderzocht op het voorkomen van malaria en anemie en risico-factoren voor deze condities en de relaties tussen deze werden beschreven. Van de 744 zwangere vrouwen hadden er 102 (13.7%) een infectie met *P. falciparum*. Hiervan waren 18 van de 102 ernstig (geelzucht en ernstige anemie). Univariabele en multivariabele analyses lieten zien dat leeftijd en pariteit niet geassocieerd waren met deze malaria infectie. Zwangeren die in hun derde trimester voor het eerst de antenatale kliniek bezochten hadden het hoogste risico voor malaria (OR = 1.58, 95% CI = 1.02-2.4; $P < 0.05$).

Van de 744 zwangeren leden 466 aan anemie (hemoglobine < 11 gram/dl), oftewel 62.6%. Dit was verdeeld in milde anemie (Hb tussen 9.0 en 10.9 gram/dl; 52.4%), matig ernstige anemie (Hb tussen 7.0 en 8.9 gram/dl; 8.1%) en ernstige anemie (Hb onder 7.0 gram/dl; 2.2). De prevalentie van anemie was significant hoger in multi-multigravidae (73.2%). Univariabele en multivariabele analyses lieten zien dat leeftijd en pariteit niet significant met anemie geassocieerd waren. Malaria (OR = 4.5, 95% CI = 2.5-8.1; $P < 0.0001$) en pica (OR = 1.6, 95% CI = 1.05-2.6; $P = 0.03$) bleken geassocieerd met anemie.

In een volgende cross-sectionele studie (opnieuw in het oosten van Soedan; Hoofdstuk 5 en 6) werden zwangeren ten tijde van de bevalling onderzocht op anemie, perifere en placentale malaria infectie. De prevalentie en risico-factoren voor placentale malaria werden beschreven en de invloed van placentale malaria en anemie op maternale and perinatale uitkomsten werd in kaart gebracht.

De prevalentie van anemie (73.2%) was zeer hoog in multi-multigravidae. Univariabele en multivariabele analyses lieten zien dat leeftijd en pariteit niet significant geassocieerd waren met anemie. Echter, malaria (OR = 4.5, 95% CI = 2.5-8.1; $P < 0.0001$) en pica (OR = 1.6, 95% CI = 1.05-2.6; $P = 0.03$) waren significant geassocieerd met anemie. Er bleek geen associatie te bestaan met leeftijd (OR = 1.02, 95% CI = 0.45-2.2; $P = 0.9$), pariteit (OR = 0.6, 95% CI = 0.3-1.2; $P = 0.1$) of placentale malaria infecties. Onafhankelijk van pariteit was bloedgroep O geassocieerd met een hoger risico op doorgemaakte placentale malaria infecties (OR = 1.9, 95% CI = 1.1-3.2; $P = 0.01$). Dit verschil bleef bestaan wanneer de analyse werd beperkt tot primiparae (OR = 2.6, 95% CI = 1.05-6.5, $P = 0.03$).

Bij vrouwen met een placentale infectie (actief of doorgemaakt) was het gemiddelde hemoglobinegehalte hoger bij de groep met bloedgroep O, echter het gemiddelde geboortegewicht, de feuto-placentale gewichts-ratio en het placentale gewicht was niet verschillend.

Een casus-controle onderzoek werd verricht (Hoofdstuk 7) om de potentiële betrokkenheid van prolactine en cortisol bij de pathogenese van malaria te onderzoeken. Er was geen significant verschil tussen de concentraties van totaal cortisol tussen zwangere vrouwen met en zonder malaria, zowel in primigravidae als in multigravidae. Bij vrouwen met ongecompliceerde malaria was de concentratie van cortisol niet significant verschillend tussen primi- en multigravidae. De cortisol concentratie was niet gecorreleerd met graviditeit, zwangerschapsduur of lichaams-temperatuur bij opname. Wel was een positieve associatie tussen cortisol concentratie en

geobserveerd aantal parasieten in het bloed. De totale serum prolactine concentratie was niet significant verschillend tussen de geïnfecteerde en niet geïnfecteerde groep, consistent voor primigravidae en multigravidae.

Tenslotte werden in een populatie-gebaseerde enquête (Hoofdstuk 8) de percepties en kennis bij vroedvrouwen en zwangere vrouwen omtrent de oorzaken van malaria, evenals de complicaties, behandeling en preventie van deze infectie bestudeerd.

Meer dan drie-kwart (78.2%) van de vroedvrouwen en (82.7%) zwangere vrouwen wisten dat muggen de overbrengers van malaria waren. Ongeveer 65% van de geïnterviewde zwangere vrouwen gebruikten geïmpregneerde muskietennetten. De kennis omtrent de mogelijke complicaties van malaria gedurende zwangerschap, de effecten van behandeling, de effecten van malaria op de foetus was slecht, zowel bij vroedvrouwen als bij zwangeren. De meeste vroedvrouwen 68% en zwangeren (96%) waren niet bekend met intermitterende prophylactisch behandeling, ter voorkoming van de malaria complicaties.

CURRICULUM VITAE

Ishag Adam was born on third January, 1965 in Hajer Elteir, Sudan. He attended at Shendi in Sudan from 1980 to 1983. He obtained his medical degree in January 1991 from Arab University, Libya. Following that, he worked in a number of different centers in order to gain practical experience. He worked during March 1991 to February 1992 as Internship; Arab Medical University Teaching Hospital, Benghazi, Libya.

Then he worked as S.H.O., Internal Medicine Department and Surgery Department, Wad Medani Hospital, Sudan, during June 1992 to Aug1993.

He obtained clinical MD in obstetrics and gynecology in April 1997 from the University of Khartoum, Sudan. Then immediately he shifted to New Halfa Teaching Hospital, where he has settled for eight years, he has established the unit of clinical research with the collaboration of the Ministry of health and university of Khartoum.

He is married to Ashawag A. Ahmed, vit, and has three children, Mohamed, Mustafa and Rahaf, with whom he resides in Khartoum, Sudan.

Ishag has been in teaching and training of the 5th and 6th year medical students at University of Khartoum. This includes lectures, seminars, and bedside clinical teaching. He is also participating in the teaching and clinical training of residents and postgraduate students who are studding MD Obstetrics and gynecology.

He currently works in a big unit in Khartoum Teaching Hospital. He care for general patients in Obstetrics and Gynecology wards with Emergency 24 hour service one per week. He run one outpatient clinic at Fath AlRahman Albashier referred clinic complex in Khartoum.

Ishag has been supervisor to many MD, theses as:

Hepatitis B virus and hepatitis C virus among Sudanese pregnant women, R. M. Elshiekh.

Anaemia and perinatal outcomes, A. A. Abdereldier.

Determinant of interpregnancy interval, K.S. Elfadail.

Jaundice among pregnant women, R. E Mahgoub.

Blood group and deep venous thrombosis, A. A Abdeelgadier.

Malaria and antiphospholipids, E. O. Omer.

Malaria and pre-eclampsia, S. M. Ahmed.

Ishag has been external examiner to many MD theses, Sudan Medical Specialization Board like: Misoprostol for induction of labour, vaginal vs. oral route, N. Eltigani. October 2007. Urogenital complications following Cesarean section, M. Elmardi, November 2006. Trial of labour, S. Nour Elien, April 2006. CTG, N. Ahmed, April 2006.

Knowledge and attitude towards HIV voluntary counselling and testing services among pregnant women attending an antenatal clinic in Sudan, A.B. Fazari, December 2006.

Adherence to Artesunate plus sulfadoxine/pyrimethamine, A.M. Abdulsalam, December 2006.

He has been external examiner to many Faculties of Medicine, like University of Juba, Sudan. Febraury 2007. El Imam El amahdi University, Sudan. August 2006.Elzaim Elazhari University, Sudan. July 2006. University of AlGadarif, 2006. Nile Valley University, May, 2006. Kordofan (Obeid) University, April, 2006. Al-Fashir University, April, 2006-until now. University of Gezira, 2006. University of Shendi, 2005. University of Gezira, 2005. University of AlGadarif, 2005. The Academy of Medical Sciences and Technology 2005. Kassala University, 1997-until now.

Co-supervisor to the MD thesis, like: A. S. Ahmed, University of Gezira, completed. M. H. Ahmed, University of Khartoum, completed. A.M. Ibrahim, Department of Medicine, University of Khartoum, completed.

K.H Bakeit, Department of Biochemistry, Faculty of Medicine, University of Khartoum. N.M. Bayoumi, Department of Biochemistry, Faculty of Medicine, University of Khartoum.

I E. Elagib, Department of Biochemistry, Faculty of Medicine, University of Khartoum.

O.E. Fadiel Elseid, Department of Biochemistry, Faculty of Medicine, University of Khartoum. A. A.

Daak, Department of Biochemistry, Faculty of Medicine, University of Khartoum.

Reviewer to the following Journal:

International Journal of Gynecology and Obstetrics 2007 until now.

Journal of Public health, 2007, until now.

Indian Journal of Medical Sciences 2006 until now.

Journal of Pediatrics infectious Diseases 2006 until now.

Saudi Medical Journal, Jan 2003 until now.

Gezira Journal of Health Sciences since August 2004 until now.

Ishag is the Local contact points for CPN-YAS-PRD project June 2007 till now.

Head department of Obstetrics& Gynecology, Khartoum Teaching Hospital, May -June 2007.

Acting head department of Obstetrics& Gynecology, Faculty of Medicine, December 2005-Feb 2006.

Head, Department of Obstetrics & gynecology (3 consultants), New Halfa Teaching Hospital, 1997-till February 2005.

General Director, New Halfa Teaching Hospital (8 consultants), June 2000-March 2002.

General Director, Health affairs, Nahar Atbara, province, 1997-1998.

Field supervisor of a collaborative research project with Dr. MI Elbashir, Department of Biochemistry, Faculty of Medicine, University of Khartoum, supported by Multilateral Initiative on Malaria MIM/TDR/WHO from Sep1999 until now.

Ishag is a member of the following

Sudanese association of Family Planning;

Sudanese association for obstetricians and gynecologists;

Sudanese association of community physicians;

International committee for antimalarial drugs safety and monitoring during pregnancy;

International Federation of Gynecologist and Obstetrician, FIGO;

Fellowship of the Royal Society of Tropical Medicine and Hygiene;

Editorial Board of the Journal of Sudanese community Physicians Association.

Editorial Board of the Sudan Monitor.

Ishag has attended African Meningococcal Carriage Consortium Meeting 21ST - 23RD November 2007, London.

Workshop and proposal development on ACTs in the treatment of Schistosomiasis, Basel, Switzerland 23 August-2 September 2007.

Presenting to the 5th European conference on Tropical Medicine and International Health, 23rd - 28th May 20, 2007, Amsterdam, The Netherlands.

Workshop on guidelines and technical advices on ethical, Fedral Ministry of Health, Sudan, March 2007.

FP7 training workshop in Ndola, Zambia, 19-29 February 2007.

Invited participant in the Fifth AMANET Biennial Scientific Conference, 26-28 February 2007, Zanzibar, Tanzania (full support for participation) oral presentation.

Annual meeting on maternal malaria operations group, Cape Town, 26-28 January 2007.

Teleconference on knowledge and familiarity with the treatment of malaria infection in Africa.

Data monitor Healthcare, USA 6/8/2006

Teleconference, on Pharmacokinetics of Antimalarial during pregnancy, Oxford University, 12/6/2006.

Workshop and Seminar on influence of malaria research on the policy- maker, Sudanese Ministry of Health, 22/3/2006. Oral presentation.

Oral presentation in Fortieth Arab and First African association conference, Khartoum, Sudan, Feb 2006.

Third annual scientific conference of the Academy of Medical Sciences and Technology Sudan, November, 2005.

First conference of the travel medicine and infectious disease, London, U.K, November 2005 an oral prestation.

Fourth MIM pan- African Malaria International Conference, Yaoundé, Cameroon, November 2005. Poster presentation.
 Workshop, Protocol Harmonization for Studies on Home Management of Malaria In Urban Areas, Nairobi, Kenya, 26-29 September 2005.
 The International Conference of Infectious Disease and Parasitic infection, September 2005, Marseille, France.
 The 5th International Conference of Immunology, July 2002, Stockholm, Sweden.
 Workshop on Malaria and pregnancy, Stockholm University, Sweden, July 2002.
 The 18th –20th conferences of Sudanese Society of Obstetricians & Gynecologists, and oral presentation on Praziquantel for the treatment of Schistosomiasis mansoni during pregnancy Feb 2005, Khartoum Sudan.

Ishag is the principle investigator in the projects entitled:

Prevention of meningococcal carriage by conjugate vaccination in countries of the African meningitis belt Supported by London School of Tropical Medicine, 2007.

Cortisol, prolactin and malaria during pregnancy. Supported by Toronto University, Canada, 2007.

Pharmacokinetics of DHA-piperaquine. During pregnancy. Supported by Beijing Holley Cotec Pharmaceutics Co.,Ltd China, 2007.

Maternal and perinatal effects of interpregnancy interval. Supported by Maastricht University, The Netherlands, 2007.

Artesunate plus sulfamethoxy pyrazine/pyrimethamine for the treatment of cutaneous leishmaniasis: A double-blind, placebo controlled clinical trial. Supported by Dafra pharma, Belgium, 2007

Multi-center trial: Two regimens of artesunate plus sulfamethoxy pyrazine-pyrimethamine versus artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in eastern Sudan. Supported by Dafra pharma, Belgium, 2006-2007.

A midwife-based strategy to increase coverage of pregnant women with intermittent preventive treatment and insecticide treated nets in an irrigated area in Eastern Sudan. Supported by EMRO/WHO, 2006-2007.

A fixed-dose 24-hour regimen of artesunate plus sulfamethoxy pyrazine-pyrimethamine for the treatment of uncomplicated *Plasmodium falciparum* malaria in eastern Sudan, Dafra pharma, Belgium, 2005-2006.

Co-investigator in the project entitled: Home management for malaria Supported by EMRO/WHO, 2006.

Collaborator in the following executed projects:

Quinine for severe falciparum during pregnancy with Prof. Mamoun M. Homeida, supported by EMRO/WHO.

Is Praziquantel safe during pregnancy TDR/WHO supported project with Prof. Mamoun M Homeida.

Epidemiology of Malaria during pregnancy in areas of low and unstable transmission in eastern Sudan, small project supported by EMRO/WHO with Dr. Gehad Elghazali.

Clinical pattern and immunopathology of falciparum malaria in areas of low and unstable malaria transmission in Eastern Sudan. It was a three years project (A00003) supported by Multilateral Initiative on Malaria (MIM), MIM/TDR/WHO, with Prof. Mustafa Idris Elbashir.

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- Adam, I., Babiker, S., Mohammed, A., A., Salih, M. M., Martin H Prins, M.H., Zaki, Z. M. (2008). Low body mass index, anaemia and poor perinatal outcome in a rural hospital in eastern Sudan. *Journal of Tropical Pediatrics*, 54(3):202-204.
- Adam, I., Elhardello, O. A., Elhadi, M. O., Abdalla, E., Elmardi, K. A., Jansen, F.H. (2008). Antischistosomal efficacy of artesunate plus sulfamethoxy-pyrazine-pyrimethamine and artemether-lumefantrine administered as treatment for uncomplicated *Plasmodium falciparum* malaria. *Annals of Tropical Medicine and Parasitology*, 102 (1): 39-44.
- Adam I., Karsany, MS (2008). Case report: Rift Valley Fever with vertical transmission in a pregnant Sudanese woman. *Journal of Medical Virology*, 80(5):929.
- Comments on the article: Impact of maternal *Plasmodium falciparum* malaria and haematological parameters on pregnancy and its outcome in southeastern Nigeria by C.J. Uneke et al., *J Vector Borne Dis* 44, 2008, 285-290.
- Haggaz, A. A., Radi, E.A., Adam, I. (2008). High perinatal mortality in Darfur, Sudan. *Journal of Materno-Fetal and Neonatal Medicine*, (4):277.
- Adam, I. Omer, EM, Salih, A., Khamis, Malik. EM. (2008). Perceptions of the causes of malaria and of its complications, treatment and prevention among midwives and pregnant women of Eastern Sudan. *Journal of Public Health*, 13: 129-132.
- Elhassan, E.M., Abubaker M. S, Adam, I. (2008). Sublingual compared with oral and vaginal misoprostol for termination of pregnancy with second-trimester fetal demise. *International Journal of Gynecology and Obstetrics*, 100 (1): 82-83.
- Adam, I., Babiker, S., Mohammed, A., A., Salih, M. M., Prins, M.H., Zaki, Z. M. (2007). ABO blood group system and placental malaria in an area of unstable malaria transmission in eastern Sudan. *Malaria Journal*, 10; 6(1):110.
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- Adam, I., Radi, E.A., Babiker, S. (2007). Comments on the article: Anaemia and pregnancy outcomes in a South African rural population by L.-J. Van Bogaert. *Journal of Obstetrics and Gynaecology* 2006; 26(7):617 - 619. *Journal of Obstetrics and Gynaecology*. 27(7):755
- Elsheikh, R. M., Daak, A. A., Elsheikh, M. A., Karsany, M. S., Adam, I., (2007). Hepatitis B virus and hepatitis C virus in pregnant Sudanese women. *Virology Journal*, 24; 4 (1):104.
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- Salah, M.T., Adam, I., Malik, E.M. Care -seeking behaviour for fever in children under five years in urban area in eastern Sudan. *Journal of Family & Community Medicine* 2007;13(1): 1-5
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