

# Malaria in Pregnancy and the Newborn

Stephen J. Rogerson

## 1 The Global Burden of Malaria

Each year, 40% of the world's population is exposed to the risk of malaria infection. Approximately 500 million people suffer clinical disease episodes of malaria, and around one million die from it. The greater part of the world's malaria burden falls on Africa, but recent analyses suggest the amount of malaria in Asia has been underestimated (Snow et al., 2005). Five *Plasmodium* species infect humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. The last, which is a common parasite of monkeys, has only recently been described as a human pathogen (Singh et al., 2004), but appears to be quite widespread in South East Asia. The great majority of severe disease episodes and deaths are due to *P. falciparum*, but it is becoming increasingly clear that *P. vivax* can also cause severe disease episodes and deaths (Genton et al., 2008; Tjitra et al., 2008). The main presentations of severe and life-threatening malaria are severe anaemia, cerebral malaria (unrouseable coma associated with malaria infection) and respiratory distress. Most deaths occur in young children, but pregnant women are also at particularly high risk, especially when they have lower malaria immunity.

## 2 The Burden of Malaria in Pregnancy

Each year, over 50 million pregnancies occur in malaria-endemic areas, and many pregnant women suffer effects of malaria in pregnancy. In Africa, around one in four women have placental malaria infection at delivery (Desai et al., 2007). Malaria contributes to maternal deaths, most often due to maternal anaemia. Estimates suggest that 10,000 women die, each year, from severe anaemia due to malaria (Guyatt and Snow, 2001). Low birth weight (LBW, < 2500 g) due to malaria is even more common, with an estimated 600,000 babies born with LBW each year, and

---

S.J. Rogerson (✉)  
Department of Medicine (RMH/WH), Post Office Royal Melbourne Hospital, Parkville,  
VIC 3050, Australia  
e-mail: sroger@unimelb.edu.au

75,000–200,000 infant deaths ascribed to LBW consequent upon maternal malaria (Steketee et al., 2001). Moreover, the long term effects of these in utero insults due to malaria are unknown, and maternal malaria is likely to have effects on growth, development and even risk of adult-onset diseases (Barker, 2006).

### 3 Malaria Species in Pregnancy

Of the five species, *P. falciparum* is the most widely studied, is more common in pregnant than non-pregnant women, and is associated with adverse birth outcomes. *P. vivax*, the second most prevalent infection, has been associated with LBW and maternal anaemia in studies from India, Thailand and Indonesia (Nosten et al., 1999; Poespoprodjo et al., 2008; Singh et al., 1999), but it is not clear whether it becomes more common or severe in pregnancy. Of the different species, only *P. falciparum* is known to sequester in the placenta, and this placental sequestration is believed to be central to many of the manifestations of falciparum malaria in pregnancy. For *P. ovale*, *P. malariae* and *P. knowlesi*, the risks and consequences of infection during pregnancy are unknown.

### 4 Clinical Malaria in Pregnancy

In semi-immune adults, clinical disease from malaria is rare, and it has been thought that pregnant women are similarly unlikely to be symptomatic from the infections they carry. Two recent studies and some indirect data suggest this may not be the case. Women in Mozambique and Ghana who were parasitaemic more frequently had fever and other malaria symptoms, such as headache, dizziness and fatigue than matched, aparasitemic women, but these symptoms had a poor predictive value for malaria (Bardaji et al., 2008; Tagbor et al., 2008). In our Malawi studies, a history of febrile symptoms in the preceding week was strongly associated with placental malaria at delivery (odds ratio (OR) 5.8, 95% confidence interval (CI) 3.4–9.7,  $p < 0.001$ ). Whilst it has been recognized that non-immune women frequently have symptoms (and sometimes severe disease) associated with malaria in pregnancy, these recent studies suggest such symptoms are not uncommon in high transmission areas, but warn that confirmation of infection is important to avoid inappropriate treatment with antimalarials.

### 5 Timing of Infection

Most cohort and cross-sectional studies of parasite prevalence have tested for parasitaemia in mid to late pregnancy, or at delivery (reviewed in Desai et al., 2007), in part because few women present in Africa to antenatal care before the second trimester of pregnancy. However, a few studies have managed to examine women

in first or early second trimester for parasitaemia, and compare parasite prevalence across gestation. Interestingly, all studies show that the prevalence of infection is highest in the late first or early second trimester, and falls over gestation, and this seems to be the case regardless of transmission intensity and gravidity (Brabin, 1983; Brabin and Rogerson, 2001; Coulibaly et al., 2007). One possible explanation is that immunity to malaria develops over the course of the pregnancy, helping to suppress parasitaemia.

## 6 Susceptibility to Malaria in Pregnancy

There are a number of reasons why pregnant women may be at particular risk for malaria (Table 1). They are more attractive to mosquitoes than non-pregnant adults, probably because they exhale more carbon dioxide (Lindsay et al., 2000). The altered immunological and hormonal environment in pregnancy predisposes to a number of infectious diseases, such as listeriosis, CMV and hepatitis E (Hart, 1988). Malaria has been associated with elevated levels of corticosteroids in pregnancy (Vleugels et al., 1989), and other hormones have not been systematically studied. It has been postulated that changes in the Th1/Th2 cytokine balance in pregnancy predispose to malaria, while on the other hand malaria infection itself induces active Th1 and inflammatory cytokine responses (reviewed in Rogerson et al., 2007). One particularly important factor in the predisposition to malaria is the ability of *P. falciparum*-infected erythrocytes to sequester in the placenta. Such infected erythrocytes express a unique subset of variant surface antigens, or VSAs on their surface (Beeson et al., 1999; Maubert et al., 1999). As expression of these VSAs is restricted to pregnancy, a woman who is pregnant for her first time has a well-developed immunity to parasites expressing other VSAs, but lacks immunity to pregnancy-specific VSAs expressed by placental parasites, which exploit this “hole” in her existing immune response (Hviid, 2004).

**Table 1** Reasons why pregnant women are at special risk of malaria

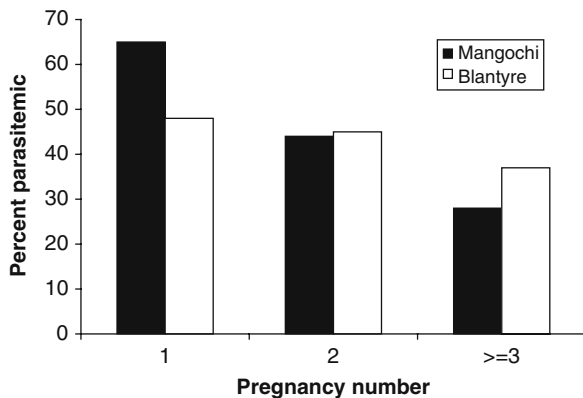
---

Increased susceptibility to mosquito bites
Altered cell mediated immunity in pregnancy
Hormonal changes associated with pregnancy
Placental sequestration of parasitized cells
Immune evasion by placental parasites

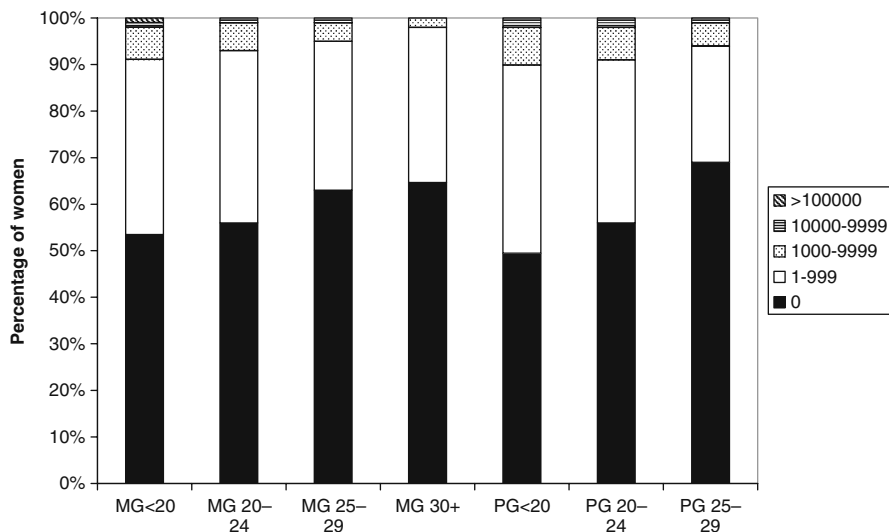
---

## 7 Gravidity and Age Influence Parasite Prevalence in Pregnancy

Women in their first pregnancy are at increased risk of malaria infection, and with subsequent pregnancies, their predisposition decreases (Desai et al., 2007). The intensity of malaria transmission may influence the rate of this decline (Fig. 1). In a high-transmission area of Malawi, pregnant women were highly likely to be parasitaemic at first antenatal clinic visit, and the rate fell quite steeply with



**Fig. 1** Rates of malaria parasitaemia among pregnant women at first antenatal visit in Mangochi (black; high transmission) and Blantyre (white; moderate transmission), Malawi. Parasite rates decline with gravidity, and do so from a higher base and with greater rapidity in the higher transmission area. Adapted from Rogerson and Menendez, 2006 with permission of Expert Reviews Ltd



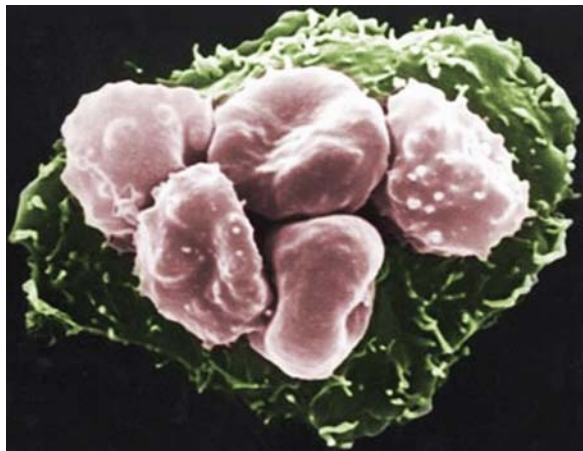
**Fig. 2** Age is a co-determinant of susceptibility to malaria in pregnancy. At first antenatal visit, the proportion of multigravidae (MG) or primigravidae (PG) who were parasitaemic declined as maternal age increased. A parasitaemic women are shown in (black), women with low grade parasitaemia in (white), moderate in (stippled), high in (grey) and very high in (hatched lines). Moderate and high density parasitaemia (stippled, grey or hatched sections) was uncommon among older women

subsequent pregnancies. On the other hand, in Blantyre, lower malaria transmission was associated with lower parasite prevalence in first pregnancy, and relatively little decrease in prevalence with subsequent pregnancies, suggesting a slower acquisition of pregnancy-specific immunity.

Gravidity undoubtedly influences protection from malaria, and development of immunity to pregnancy-specific VSAs forms a key component of such protection. Some epidemiological evidence suggests that non-pregnancy-specific immunity may also be important. In Malawi, for example, we found that age was a more important predictor of parasitaemia at antenatal booking than gravidity (Fig. 2), and similar findings have been reported from Mozambique (Saute et al., 2002). While immunity that controls malaria parasitaemia generally develops over the course of childhood (Marsh and Kinyanjui, 2006), where malaria transmission is lower, women may still be developing immunity against blood-stage infection in early reproductive life. One important consequence of this is that adolescents in developing countries, who are at high risk of poor reproductive outcomes (Brabin, 2004), may also be particularly likely to suffer from malaria in pregnancy.

## 8 Modelling Placental Malaria In Vitro

In vitro models of sequestration of infected erythrocytes have been in use for some time. Chinese hamster ovary (CHO) cells express chondroitin sulphate A, and parasites “panned” on these cells adhered to CSA (Rogerson et al., 1995, Fig. 3). When chondroitin sulphate A from animal sources, or extracted from placenta, is spotted onto Petri dishes, parasitized cells from placenta adhere to the CSA (Fried et al., 2006; Fried and Duffy, 1996). Frozen sections of placenta, the BeWO cell line and in vitro-derived syncytiotrophoblast are also useful (Haase et al., 2006; Lucchi et al., 2006). By using these tools, it has been demonstrated that parasitized cells panned



**Fig. 3** Scanning electron micrograph of parasitised erythrocytes bound to Chinese hamster ovary cells

on CSA transcribe a *var* gene called *var2sca*, which encodes a protein on the surface of the infected red cell that mediates adhesion to CSA. This protein is the main target of the protective antibody response directed against the infected red cell surface (Duffy et al., 2005; Salanti et al., 2003). The parasite genome contains 60 *var* genes, each encoding a different red cell surface protein, but when *var2sca* is knocked out, parasites lose the ability to bind to CSA or to placenta (Duffy et al., 2006b; Viebig et al., 2005; Yosaatmadja et al., 2008). Parasites extracted from the placenta generally transcribe *var2sca* at high levels (Duffy et al., 2006a; Tuikue Ndam et al., 2005).

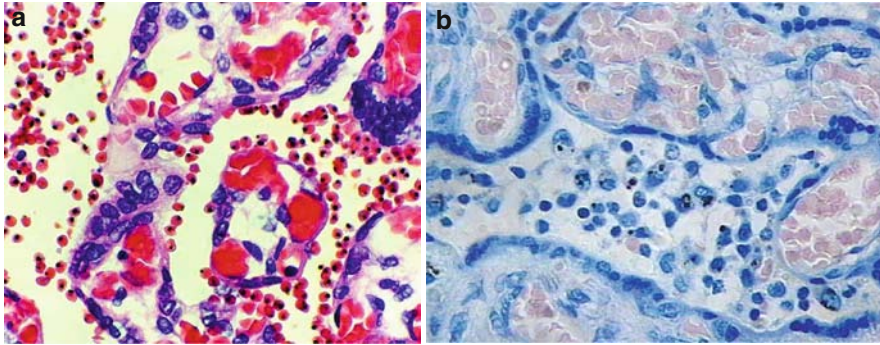
While expression of some other genes and proteins has been associated with placental malaria (Francis et al., 2007; Tuikue Ndam et al., 2008), the importance of these in sequestration or immunity is presently unclear.

Antibody immunity to parasite lines expressing the *var2csa* protein develops in a gender- and parity-dependent manner, and in some studies, levels of antibodies have been correlated with protection against adverse pregnancy outcomes (Duffy and Fried, 2003; Staalsoe et al., 2004). Because the *var2sca* gene is the most highly conserved of the *var* genes, and because it is an important target of immunity (Salanti et al., 2004), there is significant interest in developing a vaccine based on the *var2csa* protein. Identifying epitopes within the protein that are targets of protective immunity, and determining the degree of polymorphism within *var2csa* in isolates from different geographic regions are critical areas for future studies.

## 9 Placental Inflammation, Monocyte Infiltrates, and Pregnancy Outcomes

Clinically, LBW due to malaria results from a combination of fetal growth restriction and preterm delivery. In malaria-endemic Africa, the risk of LBW is approximately doubled by the presence of placental malaria, and this risk is highest in first pregnancy (Brabin et al., 1999; Guyatt and Snow, 2004). Here, the burden is principally that of fetal growth restriction, and malaria may be responsible for up to 70% of fetal growth restriction (Desai et al., 2007). Preterm delivery is more characteristically a feature of malaria in low-transmission settings, but even in Africa it may be responsible for over a third of premature deliveries (Desai et al., 2007). Given this substantial contribution to poor pregnancy outcomes, what have we learnt about the mechanisms underlying the development of LBW associated with malaria?

Placental histology studies have been very informative. Together with sequestration of infected erythrocytes in the placenta, there are often infiltrates of host leukocytes in the intervillous space (the maternal circulation of the placenta – Fig. 4). These cells are primarily monocytes and macrophages, with lymphocytes and neutrophils to a lesser extent, and many of these macrophages contain hemozoin, the by-product of the parasite's digestion of hemoglobin (Walter et al., 1982). Presence of hemozoin-laden macrophages correlates with low birth weight due to fetal growth restriction, while the density of infected red cells sequestered in the placenta correlates with pre-term delivery (Menendez et al., 2000; Rogerson et al.,



**Fig. 4** Placental pathology. (a) dense parasite sequestration (b) dense monocyte infiltrates (a) haematoxylin and eosin (b) Giemsa;  $\times 1000$

2003b). This suggests two distinct pathophysiological mechanisms: acute events leading to premature parturition associated with dense placental parasitization, and more sub-acute or chronic events resulting in growth restriction.

Placental malaria is associated with release of inflammatory cytokines in the placenta. Increased levels of mRNA or protein of the cytokines tumour necrosis factor alpha, interferon gamma and interleukin 1 have been associated with malaria and low birth weight in different studies (Fried et al., 1998; Moormann et al., 1999; Rogerson et al., 2003a; Suguitan et al., 2003), and presumably, these cytokines affect the normal growth and functioning of the placenta. These studies do not yet reveal the events that interfere with fetal growth at the cellular level, or the exact mechanisms by which malaria can lead to premature parturition, but overall they suggest that placental accumulation of infected erythrocytes and inflammatory cells, together with products released by those inflammatory cells, probably have major effects on placental function, potentially interfering with successful pregnancy progression and fetal growth.

## 10 Treating Malaria in Pregnancy

The systematic exclusion of pregnant women from drug trials means that there is a profound lack of information regarding the safety, efficacy and dosing of antimalarials in pregnancy. The choice of drugs to treat malaria in pregnancy depends on the stage of the pregnancy, and the clinical state of the mother. When a woman is severely ill, our priority is to save her life, and the best available treatment is required. This means intravenous therapy with either quinine or artesunate (Rogerson and Menendez, 2006). Present data do not show either to have a clear advantage in pregnancy (Dondorp et al., 2005), and larger comparative studies are needed. Quinine is classed by the FDA as a Class C drug, but hard evidence that it is abortifacient is lacking (Phillips-Howard and Wood, 1996). Artesunate is associated with fetal resorption and congenital defects in rodents when used in early pregnancy

(Clark et al., 2004), but similar defects are not reported in humans (Ward, 2007). The pregnancy should be followed to term, and the outcome carefully documented.

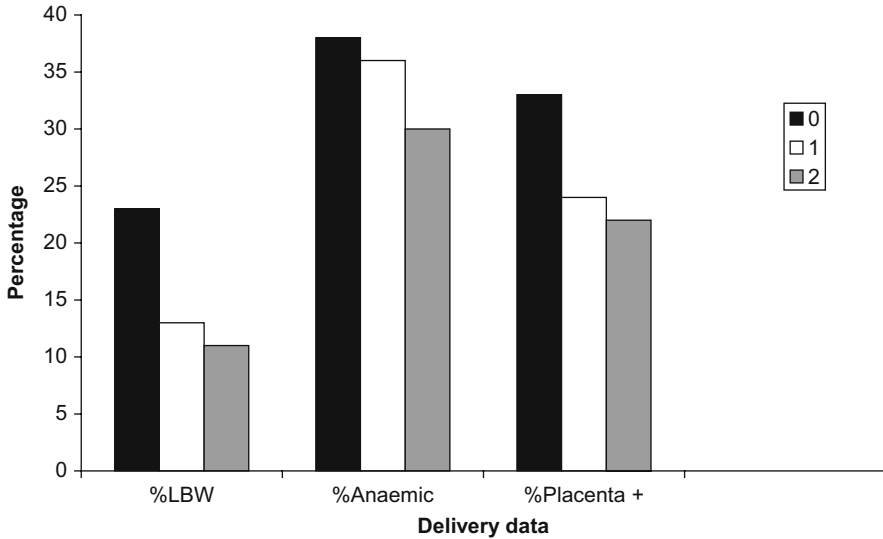
For uncomplicated malarial illness, the choice of treatment depends on the trimester. During the first trimester, quinine, mefloquine and (for vivax malaria) chloroquine are all reportedly safe, whereas in the second and third trimesters sulphadoxine-pyrimethamine (SP) has been widely used. Artemisinins and artemisinin combination treatments, such as Coartem and dihydroartemisinin-piperaquine (Artekin) also can be used, with similar caveats about documenting pregnancy outcome to intravenous artesunate. For almost of these drugs there is a major lack of pharmacokinetic data; however, available data suggest dose modification may be required to achieve adequate therapeutic levels in pregnancy (Green et al., 2007; Ward et al., 2007). Such dose-modification studies have recently begun under the auspices of the Malaria in Pregnancy Consortium ([www.mip-consortium.org](http://www.mip-consortium.org)).

## 11 Intermittent Preventive Treatment in Pregnancy

Intermittent preventive treatment in pregnancy, or IPTp, is the delivery of treatment doses of an antimalarial, at specified times, regardless of the presence of symptoms or infection. Based on studies from the 1980s and 1990s, the World Health Organization recommends at least two doses of an appropriate drug, at least a month apart, starting after quickening (when the mother detects fetal movements). A Cochrane review showed an increase in birth weight of 126 g among women receiving IPTp, compared to controls (Garner and Gulmezoglu, 2006). Presently, SP is the only proven safe effective drug in Africa, but neither the optimal number of doses, especially in women with HIV co-infection, who may require more than two doses (Parise et al., 1998), nor the appropriate dose for pregnant women (Green et al., 2007) are fully resolved. It is important that an IPTp policy using SP or other agents is properly implemented. When we compared women who went to ANC and did, or did not, receive IPTp doses, women who received the recommended two doses had a reduction of >50% in their prevalence of LBW babies, as well as reductions in anaemia and parasitaemia at delivery (Rogerson et al., 2000) (Fig. 5).

SP resistance is now common in much of Africa, and rates of parasitological treatment failure in children vary widely across the continent. Because pregnant women are semi-immune to malaria, it is less clear that SP resistance translates into loss of protection against pregnancy malaria, and a recent meta-analysis suggests that SP maintains its utility in pregnant women, up to moderately high levels of resistance (ter Kuile et al., 2007). If high-level resistance to SP emerges in Africa, as it did in Asia, it is probable that SP will have little role in the prevention of malaria in pregnancy, so a number of new drugs, including Artekin, mefloquine and artesunate, and SP plus azithromycin, are entering IPTp studies as part of the Malaria in Pregnancy Consortium's activities.





**Fig. 5** Effectiveness of SP in Malawi, 1997–1999, by SP doses: 0, *black*; 1, *white*; 2 or more, *grey*. Among women who had attended antenatal clinic, and had opportunities to receive SP, those who were given 2 doses of SP had lower prevalences of low birth weight (%LBW), Hb < 11.0 g/dl (%anaemia) and placental parasitaemia (%Placenta +) than those who received 1 or 0 doses of SP

## 12 Malaria in the Newborn: Congenital Malaria

Congenital malaria is usually defined as peripheral blood parasites in the newborn within the first seven days of life – or longer, if no exposure to infected mosquitoes is possible (Menendez and Mayor, 2007). (The minimum time from an infected bite to parasitaemia is 7–8 days.) Cord blood parasites are quite frequently detected at delivery in endemic areas (Fischer, 2003; Menendez and Mayor, 2007), and detection rates are higher when sensitive PCR approaches are used (Tobian et al., 2000). Interestingly, a significant proportion of cord blood parasites appears to be acquired antenatally (Malhotra et al., 2006), although transmission at delivery also occurs.

Congenital malaria illness is more common in children of non-immune mothers. It usually presents at 2–6 weeks of age, with combinations of fever, hepatosplenomegaly, irritability, jaundice and/or anaemia. Congenital syphilis is an important differential diagnosis, and early presentations may resemble neonatal sepsis (Lesko et al., 2007; Menendez and Mayor, 2007). In the US, most cases are associated with *P. vivax* infection, reflecting the fact that many maternal infections are acquired in Latin America where *P. vivax* predominates (Lesko et al., 2007). Treatment of congenital infections is with quinine for *P. falciparum* and chloroquine for *P. vivax*. Primaquine (used to eliminate liver stage *P. vivax* infections) is not required, because only blood-stage infection occurs.

### **13 Malaria Antibody in Neonates**

In areas of high malaria transmission, not only is symptomatic congenital malaria quite uncommon, but clinical disease is also unusual in the first few months of life. A number of explanations have been proposed, including swaddling of infants (decreasing exposure to mosquitoes), parasites' inability to metabolise fetal haemoglobin effectively, and the lack of para-aminobenzoic acid (an important metabolic substrate) in breast milk (Riley et al., 2001). The relative protection from disease among infants of exposed mothers is more probably explained by the transplacental transfer of antimalarial antibodies to the fetus (Hviid and Staalsoe, 2004; Riley et al., 2001). As passively acquired IgG is catabolized and levels wane, the infant becomes more susceptible to malaria.

### **14 Malaria in the First Year of Life**

In very young infants, asymptomatic infections may occur, and may persist for long periods, presumably contributing to early development of active immunity. Clinical studies attempting to relate placental malaria and risk of infant infections have led to somewhat confusing results. In Senegal, cord blood antibody to isolates that infect the placenta (which may not be able to sequester and survive in the baby) was associated with earlier and higher density infection in the infant, and in Cameroon, placental malaria was associated with parasitaemia until 6 months of age (Le Hesran et al., 1997). In Tanzania, there appeared to be an important interaction between gravidity and an infant's susceptibility to malaria. Whereas first time mothers are at highest risk of parasitaemia, it was the infants of multigravid women with placental infection who were at highest risk of infection in the first year of life (Mutabingwa et al., 2005).

### **15 Future Prospects**

To prevent malaria in pregnancy, and especially to minimize more effectively its impact on young, first-time mothers and their newborns, we require improved coverage with existing interventions, such as bed nets and effective drugs for IPTp. The doses of such drugs may need to be modified for pregnant women, to ensure safe, therapeutic levels. A number of new antimalarials have entered clinical use in recent years, or will soon be introduced, and we need to evaluate carefully their safety and efficacy in pregnant women. Vaccines may have a role to play in protecting against malaria in pregnancy. Vaccines targeting pre-erythrocytic antigens (such as the RTS,S vaccine, or attenuated whole sporozoites) or conserved merozoite antigens could decrease malaria in any at-risk group, while a specific vaccine targeting the *var2csa* protein may have a specific niche in protecting pregnant women from malaria. Improvements in detecting newborns at risk of malaria in utero and after

delivery may decrease the burden of morbidity and mortality in the offspring of malaria-exposed pregnant women.

**Acknowledgments** Stephen Rogerson is supported by the National Health and Medical Research Council of Australia and the Malaria in Pregnancy Consortium.

## References

- Bardaji, A., Sigauque, B., Bruni, L., Romagosa, C., Sanz, S., Mabunda, S., Mandomando, I., Aponte, J., Sevene, E., Alonso, P.L., & Menendez, C. (2008). Clinical malaria in African pregnant women. *Malar J*, (7), 27.
- Barker, D.J. (2006). Adult consequences of fetal growth restriction. *Clinical Obstetrics and Gynecology*, (49), 270–283.
- Beeson, J.G., Brown, G.V., Molyneux, M.E., Mhango, C., Dzinjalimala, F., & Rogerson, S.J. (1999). *Plasmodium falciparum* isolates from infected pregnant women and children are associated with distinct adhesive and antigenic properties. *J Infect Dis*, (180), 464–472.
- Brabin, B.J. (1983). An analysis of malaria in pregnancy in Africa. *Bull WHO*, (61), 1005–1016.
- Brabin, B.J., Agbaje, S.O., Ahmed, Y., & Briggs, N.D. (1999). A birthweight nomogram for Africa, as a malaria-control indicator. *Ann Trop Med Parasitol*, 93 (Suppl 1), S43–S57.
- Brabin, B.J. & Rogerson, S.J. (2001). The epidemiology and outcomes of maternal malaria. In: P.E. Duffy, M. Fried (Eds.) *Malaria in Pregnancy Deadly Parasite, Susceptible Host*. pp. 27–52. London and New York: Taylor and Francis.
- Brabin, L. (2004). The adolescent health gap in developing countries. *Ann Trop Paediatr*, (24), 115–116.
- Clark, R.L., White, T.E., S, A.C., Gaunt, I., Winstanley, P., & Ward, S.A. (2004). Developmental toxicity of artesunate and an artesunate combination in the rat and rabbit. *Birth Defects Res B Dev Reprod Toxicol*, (71), 380–394.
- Coulibaly, S.O., Gies, S., & D’Alessandro, U. (2007). Malaria burden among pregnant women living in the rural district of Boromo, Burkina Faso. *Am J Trop Med Hyg*, (77), 56–60.
- Desai, M., ter Kuile, F.O., Nosten, F., McGready, R., Asamoah, K., Brabin, B., & Newman, R.D. (2007). Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*, (7), 93–104.
- Dondorp, A., Nosten, F., Stepniewska, K., Day, N., & White, N. (2005). Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*, (366), 717–725.
- Duffy, M.F., Byrne, T.J., Elliott, S.R., Wilson, D., Rogerson, S.J., Beeson, J.G., Noviyanti, R., & Brown, G.V. (2005). Broad analysis reveals a consistent pattern of *var* gene transcription in *Plasmodium falciparum* repeatedly selected for a defined adhesion phenotype. *Mol Microbiol*, (56), 774–788.
- Duffy, M.F., Caragounis, A., Noviyanti, R., Kyriacou, H.M., Choong, E.K., Boysen, K., Healer, J., Rowe, J.A., Molyneux, M.E., Brown, G.V., & Rogerson, S.J. (2006a). Transcribed *var* genes associated with placental malaria in Malawian women. *Infect Immun*, 74(8), 4875–4883.
- Duffy, M.F., Maier, A.G., Byrne, T.J., Marty, A.J., Elliott, S.R., O’Neill, M.T., Payne, P.D., Rogerson, S.J., Cowman, A.F., Crabb, B.S., & Brown, G.V. (2006b). VAR2SCA is the principal ligand for chondroitin sulfate A in two allogeneic isolates of *Plasmodium falciparum*. *Mol Biochem Parasitol*, (148), 117–124.
- Duffy, P.E. & Fried, M. (2003). Antibodies that inhibit *Plasmodium falciparum* adhesion to chondroitin sulfate A are associated with increased birth weight and the gestational age of newborns. *Infect Immun*, (71), 6620–6623.
- Fischer, P.R. (2003). Malaria and newborns. *J Trop Pediatr*, (49), 132–134.
- Francis, S.E., Malkov, V.A., Oleinikov, A.V., Rossnagle, E., Wendler, J.P., Mutabingwa, T.K., Fried, M., & Duffy, P.E. (2007). Six genes are preferentially transcribed by the circulating and sequestered forms of *Plasmodium falciparum* parasites that infect pregnant women. *Infect Immun*, (75), 4838–4850.

- Fried, M., Domingo, G.J., Gowda, C.D., Mutabingwa, T.K., & Duffy, P.E. (2006). *Plasmodium falciparum*: chondroitin sulfate A is the major receptor for adhesion of parasitized erythrocytes in the placenta. *Exp Parasitol*, 113(1), 36–42.
- Fried, M. & Duffy, P.E. (1996). Adherence of *Plasmodium falciparum* to chondroitin sulfate A in the human placenta. *Science*, (272), 1502–1504.
- Fried, M., Muga, R.O., Misore, A.O., & Duffy, P.E. (1998). Malaria elicits type 1 cytokines in the human placenta: IFN- $\gamma$  and TNF- $\alpha$  associated with pregnancy outcomes. *J Immunol*, (160), 2523–2530.
- Garner, P., & Gulmezoglu, A.M. (2006). Drugs for preventing malaria in pregnant women. *Cochrane Database Syst Rev*, CD000169.
- Genton, B., D'Acremont, V., Rare, L., Baea, K., Reeder, J.C., Alpers, M.P., & Mueller, I.M. (2008). *Plasmodium vivax* and mixed infections are associated with severe malaria in children: a prospective cohort study from Papua New Guinea. *PLoS Med*, (5), e127.
- Green, M.D., van Eijk, A.M., van Ter Kuile, F.O., Ayisi, J.G., Parise, M.E., Kager, P.A., Nahlen, B.L., Steketee, R., & Nettey, H. (2007). Pharmacokinetics of sulfadoxine-pyrimethamine in HIV-infected and uninfected pregnant women in Western Kenya. *J Infect Dis*, (196), 1403–1408.
- Guyatt, H.L. & Snow, R.W. (2001). The epidemiology and burden of *Plasmodium falciparum*-related anemia among pregnant women in sub-Saharan Africa. *Am J Trop Med Hyg*, 64 (Suppl), 36–44.
- Guyatt, H.L. & Snow, R.W. (2004). Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. *Clin Microbiol Rev*, (17), 760–769, table of contents.
- Haase, R.N., Megnekou, R., Lundquist, M., Ofori, M.F., Hviid, L., & Staalsoe, T. (2006). *Plasmodium falciparum* parasites expressing pregnancy-specific variant surface antigens adhere strongly to the choriocarcinoma cell line BeWo. *Infect Immun*, (74), 3035–3038.
- Hart, C.A. (1988). Pregnancy and host resistance. *Baillieres Clin Immunol Allergy*, (2), 735–757.
- Hviid, L. (2004). The immuno-epidemiology of pregnancy-associated *Plasmodium falciparum* malaria: a variant surface antigen-specific perspective. *Parasite Immunol*, (26), 477–486.
- Hviid, L. & Staalsoe, T. (2004). Malaria immunity in infants: a special case of a general phenomenon? *Trends Parasitol*, (20), 66–72.
- Le Hesran, J.Y., Cot, M., Personne, P., Fievet, N., Dubois, B., Beyeme, M., Boudin, C., & Deloron, P. (1997). Maternal placental infection with *Plasmodium falciparum* and malaria morbidity during the first 2 years of life. *Am J Epidemiol*, (146), 826–831.
- Lesko, C.R., Arguin, P.M., & Newman, R.D. (2007). Congenital malaria in the United States: a review of cases from 1966 to 2005. *Arch Pediatr Adolesc Med*, (161), 1062–1067.
- Lindsay, S., Ansell, J., Selman, C., Cox, V., Hamilton, K., & Walraven, G. (2000). Effect of pregnancy on exposure to malaria mosquitoes. *Lancet*, (355), 1972.
- Lucchi, N.W., Koopman, R., Peterson, D.S., & Moore, J.M. (2006). *Plasmodium falciparum*-infected red blood cells selected for binding to cultured syncytiotrophoblast bind to chondroitin sulfate A and induce tyrosine phosphorylation in the syncytiotrophoblast. *Placenta*, (27), 384–394.
- Malhotra, I., Mungai, P., Muchiri, E., Kwiek, J.J., Meshnick, S.R., & King, C.L. (2006). Umbilical cord-blood infections with *Plasmodium falciparum* malaria are acquired antenatally in Kenya. *J Infect Dis*, (194), 176–183.
- Marsh, K. & Kinyanjui, S. (2006). Immune effector mechanisms in malaria. *Parasite Immunol*, (28), 51–60.
- Maubert, B., Fievet, N., Tami, G., Cot, M., Boudin, C., & Deloron, P. (1999). Development of antibodies against chondroitin sulfate A-adherent *Plasmodium falciparum* in pregnant women. *Infect Immun*, (67), 5367–5371.
- Menendez, C. & Mayor, A. (2007). Congenital malaria: the least known consequence of malaria in pregnancy. *Semin Fetal Neonatal Med*, (12), 207–213.

- Menendez, C., Ordi, J., Ismail, M.R., Ventura, P.J., Aponte, J.J., Kahigwa, E., Font, F., & Alonso, P.L. (2000). The impact of placental malaria on gestational age and birth weight. *J Infect Dis*, (181), 1740–1745.
- Moormann, A.M., Sullivan, A.D., Rochford, R.A., Chensue, S.W., Bock, P.J., Nyirenda, T., & Meshnick, S.R. (1999). Malaria and pregnancy: placental cytokine expression and its relationship to intrauterine growth retardation. *J Infect Dis*, (180), 1987–1993.
- Mutabingwa, T.K., Bolla, M.C., Li, J.L., Domingo, G.J., Li, X., Fried, M., & Duffy, P.E. (2005). Maternal malaria and gravidity interact to modify infant susceptibility to malaria. *PLoS Med*, (2), e407.
- Nosten, F., McGready, R., Simpson, J.A., Thwai, K.L., Balkan, S., Cho, T., Hkiriyaeroen, L., Looareesuwan, S., & White, N.J. (1999). Effects of *Plasmodium vivax* malaria in pregnancy. *Lancet*, (354), 546–549.
- Parise, M.E., Ayisi, J.G., Nahlen, B.L., Schultz, L.J., Roberts, J.M., Misore, A., Muga, R., Oloo, A.J., & Steketee, R.W. (1998). Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *Am J Trop Med Hyg*, (59), 813–822.
- Phillips-Howard, P.A. & Wood, D. (1996). The safety of antimalarial drugs in pregnancy. *Drug Saf*, (14), 131–145.
- Poespoprodjo, J.R., Fobia, W., Kenangalem, E., Lampah, D.A., Warikar, N., Seal, A., McGready, R., Sugiarto, P., Tjitra, E., Anstey, N.M., & Price, R.N. (2008). Adverse pregnancy outcomes in an area where multidrug-resistant *plasmodium vivax* and *Plasmodium falciparum* infections are endemic. *Clin Infect Dis*, (46), 1374–1381.
- Riley, E.M., Wagner, G.E., Akanmori, B.D., & Koram, K.A. (2001). Do maternally acquired antibodies protect infants from malaria infection? *Parasite Immunol*, (23), 51–59.
- Rogerson, S.J., Brown, H.C., Pollina, E., Abrams, E.T., Tadesse, E., Lema, V.M., & Molyneux, M.E. (2003a). Placental tumor necrosis factor alpha but not gamma interferon is associated with placental malaria and low birth weight in Malawian women. *Infect Immun*, (71), 267–270.
- Rogerson, S.J., Chaiyaroj, S.C., Ng, K., Reeder, J.C., & Brown, G.V. (1995). Chondroitin sulfate A is a cell surface receptor for *Plasmodium falciparum*-infected erythrocytes. *J Exp Med*, (182), 15–20.
- Rogerson, S.J., Chaluluka, E., Kanjala, M., Mkundika, P., Mhango, C.G., & Molyneux, M.E. (2000). Intermittent sulphadoxine-pyrimethamine in pregnancy: effectiveness against malaria morbidity in Blantyre, Malawi 1997–1999. *Trans R Soc Trop Med Hyg*, (94), 549–553.
- Rogerson, S.J., Hviid, L., Duffy, P.E., Leke, R.F., & Taylor, D.W. (2007). Malaria in pregnancy: pathogenesis and immunity. *Lancet Infect Dis*, (7), 105–117.
- Rogerson, S.J. & Menendez, C. (2006). Treatment and prevention of malaria in pregnancy: opportunities and challenges. *Expert Rev Anti Infect Ther*, (4), 687–702.
- Rogerson, S.J., Pollina, E., Getachew, A., Tadesse, E., Lema, V.M., & Molyneux, M.E. (2003b). Placental monocyte infiltrates in response to *Plasmodium falciparum* infection and their association with adverse pregnancy outcomes. *Am J Trop Med Hyg*, (68), 115–119.
- Salanti, A., Dahlback, M., Turner, L., Nielsen, M.A., Barfod, L., Magistrado, P., Jensen, A.T., Lavstsen, T., Ofori, M.F., Marsh, K., Hviid, L., & Theander, T.G. (2004). Evidence for the Involvement of VAR2SCA in pregnancy-associated Malaria. *J Exp Med*, (200), 1197–1203.
- Salanti, A., Staalsoe, T., Lavstsen, T., Jensen, A.T., Sowa, M.P., Arnot, D.E., Hviid, L., & Theander, T.G. (2003). Selective upregulation of a single distinctly structured *var* gene in chondroitin sulphate A-adhering *Plasmodium falciparum* involved in pregnancy-associated malaria. *Mol Microbiol*, (49), 179–191.
- Saute, F., Menendez, C., Mayor, A., Aponte, J., Gomez-Olive, X., Dgedge, M., & Alonso, P. (2002). Malaria in pregnancy in rural Mozambique: the role of parity, submicroscopic and multiple *Plasmodium falciparum* infections. *Trop Med Int Health*, (7), 19–28.

- Singh, B., Kim Sung, L., Matusop, A., Radhakrishnan, A., Shamsul, S.S., Cox-Singh, J., Thomas, A., & Conway, D.J. (2004). A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet*, (363), 1017–1024.
- Singh, N., Shukla, M.M., & Sharma, V.P. (1999). Epidemiology of malaria in pregnancy in central India. *Bull WHO*, (77), 567–572.
- Snow, R.W., Guerra, C.A., Noor, A.M., Myint, H.Y., & Hay, S.I. (2005). The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature*, (434), 214–217.
- Staalsoe, T., Shulman, C.E., Bulmer, J.N., Kawuondo, K., Marsh, K., & Hviid, L. (2004). Variant surface antigen-specific IgG and protection against clinical consequences of pregnancy-associated *Plasmodium falciparum* malaria. *Lancet*, (363), 283–289.
- Steketee, R.W., Nahlen, B.L., Parise, M.E., & Menendez, C. (2001). The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg*, (64), 28–35.
- Suguitan, A.L., Jr., Leke, R.G., Fouda, G., Zhou, A., Thuita, L., Metenou, S., Fogako, J., Megnekou, R., & Taylor, D.W. (2003). Changes in the levels of chemokines and cytokines in the placentas of women with *Plasmodium falciparum* malaria. *J Infect Dis*, (188), 1074–1082.
- Tagbor, H., Bruce, J., Browne, E., Greenwood, B., & Chandramohan, D. (2008). Malaria in pregnancy in an area of stable and intense transmission: is it asymptomatic? *Trop Med Int Health*, 13(8), 1016–1021.
- ter Kuile, F.O., van Eijk, A.M., & Filler, S.J. (2007). Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy: a systematic review. *Jama*, (297), 2603–2616.
- Tjitra, E., Anstey, N.M., Sugiarto, P., Warikar, N., Kenangalem, E., Karyana, M., Lampah, D.A., & Price, R.N. (2008). Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: A prospective study in Papua, Indonesia. *PLoS Med*, (5), e128.
- Tobian, A.A.R., Mehlotra, R.K., Malhotra, I., Wamachi, A., Mungai, P., Koech, D., Ouma, J., Zimmerman, P., & King, C.L. (2000). Frequent umbilical cord-blood and maternal-blood infections with *Plasmodium falciparum*, *P. malariae* and *P. ovale* in Kenya. *J Infect Dis*, (182), 558–563.
- Tuikue Ndam, N., Bischoff, E., Proux, C., Lavstsen, T., Salanti, A., Guitard, J., Nielsen, M.A., Coppee, J.Y., Gaye, A., Theander, T., David, P.H., & Deloron, P. (2008). *Plasmodium falciparum* transcriptome analysis reveals pregnancy malaria associated gene expression. *PLoS ONE*, (3), e1855.
- Tuikue Ndam, N.G., Salanti, A., Bertin, G., Dahlback, M., Fievet, N., Turner, L., Gaye, A., Theander, T., & Deloron, P. (2005). High level of *var2sca* transcription by *Plasmodium falciparum* isolated from the placenta. *J Infect Dis*, (192), 331–335.
- Viebig, N.K., Gamain, B., Scheidig, C., Lepolard, C., Przyborski, J., Lanzer, M., Gysin, J., & Scherf, A. (2005). A single member of the *Plasmodium falciparum* var multigene family determines cytoadhesion to the placental receptor chondroitin sulphate A. *EMBO Rep*, (6), 775–781.
- Vleugels, M.P.H., Brabin, B., Eling, W.M.C., & de Graaf, R. (1989). Cortisol and *Plasmodium falciparum* infection in pregnant women in Kenya. *Trans R Soc Trop Med Hyg*, (83), 173–177.
- Walter, P.R., Garin, Y., & Blot, P. (1982). Placental pathologic changes in malaria. A histologic and ultrastructural study. *Am J Pathol*, (109), 330–342.
- Ward, S.A., Sevene, E.J., Hastings, I.M., Nosten, F., & McGready, R. (2007). Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance. *Lancet Infect Dis*, (7), 136–144.
- Yosaatmadja, F., Andrews, K.T., Duffy, M.F., Brown, G.V., Beeson, J.G., & Rogerson, S.J. (2008). Characterization of *VAR2SCA*-deficient *Plasmodium falciparum*-infected erythrocytes selected for adhesion to the BeWo placental cell line. *Malar J*, (7), 51.