New approaches to pathogenesis of malaria in pregnancy

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SUMMARY

Malaria infection during pregnancy is associated with poor maternal and foetal outcomes including low birth weight. In malaria-endemic areas, low birth weight is primarily a consequence of foetal growth restriction. Little is known on the pathogenesis of foetal growth restriction and our understanding of the relationship between epidemiological observations and the pathogenesis or consequences of disease is incomplete. In this review, we describe these gaps in our knowledge and also try to identify goals for future research into malaria in pregnancy. Foetal growth restriction results from a complex four-dimensional interaction between the foetus, the mother and the malaria parasite over gestation, and research into its pathogenesis may be advanced by combining longitudinal studies with techniques and approaches new to the field of malaria in pregnancy. Such approaches would greatly increase our knowledge on the pathogenesis of this disease and may provide new avenues for intervention strategies.

Key words: Malaria, low birth weight, foetal growth restriction, *Plasmodium*, HIV.

INTRODUCTION

Pregnant women are at increased risk of malaria compared to non-pregnant counterparts (Gilles *et al*. 1969; Diagne *et al*. 1997), experiencing more frequent and higher density infections (Brabin, 1983; Steketee *et al*. 2001). Malaria in pregnancy (MiP) causes major complications for mother and child, which tend to be most severe in first pregnancy (Brabin, 1991*a*). Each year, 75 000–200 000 newborns are born with low birth weight (LBW <2500 g) due to malaria (Steketee *et al*. 2001), and 400 000 women develop severe anaemia, of whom an estimated 10 000 may die as a direct result of malarial anaemia (Guyatt and Snow, 2001). In Africa, LBW associated with malaria is more commonly due to foetal growth restriction (FGR) than to pre-term delivery (PTD). Malaria is a leading preventable cause of LBW, but prevention is increasingly difficult due to emerging antimalarial drug resistance, and to the lack of good safety data for many antimalarial drugs. Several recent reviews cover malaria prevention in pregnancy in detail (Nosten *et al*. 2006; Menendez, D'Alessandro and ter Kuile, 2007; Rogerson *et al*. 2007).

In this review, we have taken two approaches. First, we direct readers to areas where there are major gaps in our understanding of the relationship between the observed epidemiology of malaria in pregnancy and the pathogenesis or consequences of disease. Second, we try to look 'over the horizon', to identify goals for future research into malaria in pregnancy.

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HISTOLOGICAL, BIOLOGICAL, CLINICAL AND EPIDEMIOLOGICAL FINDINGS IN MiP: SOME DOGMAS NEED TO BE CHALLENGED

IEs adhere to placental CSA in vivo

The ability of *Plasmodium falciparum*-infected erythrocytes (IE) to sequester in the placenta is a key determinant of predisposition to malaria in pregnancy, and immune responses to antigens expressed on the surface of these IE appear to mediate protection from malaria (Fried and Duffy, 1996; Fried *et al*. 1998*b*). Recent reviews in this special issue (Duffy; Hviid and Salanti; Scherf) and elsewhere (Beeson and Duffy, 2005; Rogerson *et al*. 2007) summarize current understanding regarding how IE sequester in the placenta and how pregnancy specific malaria immunity develops, in detail. The accumulation of IE in the maternal circulation or intervillous spaces of the placenta occurs through adhesion of IE to placental receptors such as chondroitin sulphate A on the syncytiotrophoblast surface or within the intervillous space. There is compelling evidence that the VAR2CSA form of PfEMP1 binds to chondroitin sulphate A, and that placental parasites almost always transcribe the gene encoding this protein (Duffy *et al*. 2006; Salanti *et al*. 2003; Tuikue Ndam *et al*. 2005, and see also Hviid and Salanti, in this special issue). Few IE are apposed to the syncytiotrophoblast on histology; they may adhere to secreted chondroitin sulphate A in the intervillous space (Muthusamy *et al*. 2004). There may be artefacts from the histological preparation process or it may be that IE are

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frequently trapped in fibrin deposits initiated by activated macrophages expressing Tissue Factor (Imamura *et al*. 2002). Immunoelectron microscopy and immunochemical studies could resolve some of these questions regarding site of sequestration, while probing histological sections with antibodies to specific VAR2CSA epitopes will allow comparison of parasites in different sites in the same placenta, and between placentas.

The value of placental histology examination

The association between placental histology and pregnancy outcome has recently been reviewed in detail (Brabin *et al*. 2004). Placental malaria is associated with accumulation in the intervillous space of mononuclear cells, predominantly monocytes and macrophages that often contain the malaria pigment haemozoin (Walter, Garin and Blot, 1982), and deposition of haemozoin in fibrin. These features of placental pathology can only be accurately detected using histology, which is also more sensitive than peripheral or placental blood microscopy at detecting infection. Both current infection (presence of parasites) and past infection (haemozoin without parasites) have been associated with reduced birth weight (Rogerson, Mkundika and Kanjala, 2003*b*). Dense monocyte infiltrates are particularly common in primigravid women, and are associated with LBW due to FGR, whereas high parasitaemia is associated with PTD (Menendez *et al*. 2000; Ordi *et al*. 1998). Whenever possible, intervention studies should use histology as an outcome measure, while studies of pathogenesis should examine the relationship between timing of infection and subsequent pathology (reviewed below).

The importance of malaria in early pregnancy

In one of the few studies to recruit women in early pregnancy, malaria parasite prevalence peaked at 13–16 weeks gestation (Brabin, 1991*b*). A recent study suggests that women most frequently present to antenatal clinics with symptomatic malaria (febrile symptoms accompanied by parasitaemia) in the second trimester, but that such episodes are not uncommon in first trimester (Bardaji *et al*. 2006). This is important both for prevention – should we start antenatal care and intermittent preventive therapy (IPTp) in the first trimester? – and for understanding pathogenesis. Placental blood flow only begins at 10–12 weeks gestation, so IE cannot sequester in the placenta before this time (Jauniaux, Gulbis and Burton, 2003). We need further studies examining malaria infection and disease in early pregnancy, to determine the significance and consequences of these early infections, the characteristics of the parasites infecting women in early pregnancy and (if there is a predilection to malaria before placental circulation develops) what the immunological or hormonal basis may be for this susceptibility.

Age and gravidity are separate components of susceptibility to malaria in pregnancy

In a community-based study in Senegal, age-related disease incidence and parasite density data showed that acquisition of immunity to malaria extends into adulthood (Trape *et al*. 1994); thus young women are more susceptible to malaria than their older peers, and this susceptibility may be exacerbated in pregnancy. In several recent studies, age has been a more important independent predictor of malaria parasitaemia in pregnant women than gravidity, and, in some studies, women of equal gravidity but younger age were shown to be more likely to carry malaria infection (Rogerson *et al*. 2000; Saute *et al*. 2002; Tako *et al*. 2005; Wort *et al*. 2006). The mechanisms underlying the age-dependent predisposition to malaria are worthy of exploration. Practically, these observations provide strong support for programmes that target adolescent girls for antenatal interventions including malaria prevention (Brabin and Brabin, 2005; Wort *et al*. 2006).

Symptomatic and severe malaria in pregnancy

In areas of low malaria transmission, almost all malaria episodes in pregnant women become symptomatic if untreated and pregnant women are especially susceptible to severe malaria, with high case fatality rates (Nosten *et al*. 2004; Wickramasuriya, 1935). In sub-Saharan Africa, much malaria infection is asymptomatic, but febrile symptoms are more common in women with malaria infection than in uninfected women (Diagne *et al*. 1997; Rogerson *et al*. 2003*c*). Symptoms of febrile illness have a low positive predictive value for malaria parasitaemia, so parasitological diagnosis is important (Bardaji *et al*. 2006). Symptomatic malaria requires prompt treatment, as it may otherwise lead to miscarriage or premature labour, while fever without parasitaemia should lead to the search for alternative explanations.

Maternal mortality is a devastating problem in sub-Saharan Africa, such that in many countries a woman's lifetime risk of dying during pregnancy or the puerperium is over 5%. Effective management of obstetric complications is absolutely critical (Campbell and Graham, 2006), but 50% or more of deaths may be clinically of infectious aetiology (Lema *et al*. 2005), and in Mozambique malaria was the third most common cause of maternal death at autopsy. Malaria and other treatable infectious diseases were frequently misdiagnosed in life. Autopsy studies, combined with facility based descriptions of the spectrum of symptomatic disease and with

community based surveillance for symptomatic disease are required to delineate the importance of symptomatic, severe and fatal malaria in pregnancy.

CURRENT GAPS IN OUR KNOWLEDGE

Malaria and HIV

HIV infection increases maternal susceptibility to malaria, and this effect is most pronounced in multigravid women (ter Kuile *et al*. 2004). This susceptibility may be explained by a failure to develop adequate variant-specific immunity (Mount *et al*. 2004) or by altered cellular immune responses (reviewed by Ned *et al*. 2005). HIV impairs response to antimalarial therapy (Kamya *et al*. 2006; Shah *et al*. 2006; Van Geertruyden *et al*. 2006), and HIV infected women may need more frequent administration of IPTp (Parise *et al*. 1998), although clear benefit of increased dosing has yet to be demonstrated (Meshnick, Mwapsa and Rogerson, 2006). Cotrimoxazole prophylaxis improves health and prolongs life in highly immunosuppressed HIV infected adults (Mermin *et al*. 2006), and may improve neonatal outcomes in women with low CD4 counts (Walter *et al*. 2006). Moreover, cotrimoxazole has antimalarial activity, decreasing malaria episodes among HIV infected and uninfected recipients (Mermin *et al*. 2004; Thera *et al*. 2005), and appears safe in pregnancy (Forna *et al*. 2006). Therefore, malaria-exposed HIV-infected pregnant women should receive cotrimoxazole and sleep under insecticide-treated bed nets (Brentlinger, Behrens and Micek, 2006). If receiving antiretroviral drugs, they should be monitored closely for interactions between antimalarials and these agents (Brentlinger *et al*. 2006). Whether they should receive additional IPTp (with non-sulphur based drug combinations), and whether antiretroviral therapy will diminish the particular susceptibility of HIV infected women to malaria in pregnancy are important and unresolved questions.

Nutrition and malaria

Women with short stature (<145 cm), low body weight (<45 kg), and/or mid-upper arm circumference < 22 cm are at increased risk of adverse pregnancy outcomes. These parameters may reflect acute or chronic under-nutrition. Maternal undernutrition and malaria frequently occur together in poor rural women, and each condition is most common in the rainy season, when work demands are greatest, malaria transmission is highest and food is scarcest (Rayco-Solon, Fulford and Prentice, 2005). Nutritional supplementation at these times of food scarcity increased birth weight (Ceesay *et al*. 1997). To date, these studies have not systematically examined malaria and maternal nutrition in parallel, and an important challenge is to determine whether combining nutritional and malarial interventions has additive or synergistic effects on pregnancy outcomes.

MiP outside of Africa

A large proportion of pregnant women at risk of acquiring malaria reside in Asia and South America, but we know little about the burden of disease or its pathophysiology in these regions. Important questions include disease manifestations in women with little prior malaria exposure; the role of *P. vivax* in pregnancy (which has been shown to decrease birth weight in one Asian study (Nosten *et al*. 1999)); and the optimal strategies for prevention. The burden of malaria in pregnancy outside Africa is reviewed in detail by Desai *et al*. (2007), and malaria in pregnancy is compared between high and low transmission regions by Nosten *et al*. (2004).

SUGGESTIONS FOR FUTURE RESEARCH ON MiP PATHOGENESIS

Defining the role of intervillous monocytes as independent markers of LBW

Monocyte infiltrates can develop in the intervillous space in response to malaria (Walter *et al*. 1982), and have been associated with FGR and anaemia (Menendez *et al*. 2000; Rogerson *et al*. 2003*c*). IE sequestered in the placenta induce the secretion of β-chemokines by maternal mononuclear cells (Abrams *et al*. 2003; Chaisavaneeyakorn *et al*. 2003; Suguitan *et al*. 2003) and by foetal syncytiotrophoblast (Abrams *et al*. 2003; Lucchi *et al*. 2006*a*), attracting monocytes to the placenta. Macrophage migration inhibitory factor is found in increased levels in women with placental malaria (Chaisavaneeyakorn *et al*. 2005), and it may help to retain the recruited monocytes and to activate them to secrete β-chemokines, setting up a positive feedback loop. How these monocytes are activated, what molecules they secrete and how this affects birth weight is largely not understood.

Activation of placental monocytes and cytokine secretion

Placental monocytes are relatively more activated than circulating monocytes (Diouf *et al*. 2004). Several factors present in the intervillous space of malaria-infected placentae could activate monocytes. In particular, IEs (Bate, Taverne and Playfair, 1988), malaria pigment (haemozoin) (Pichyangkul, Saengkrai and Webster, 1994), glycosylphosphatidylinositol (Krishnegowda *et al*. 2005) and fibrinogen (Smiley, King and Hancock, 2001) have all been shown to induce TNF production by monocytes.

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Placental levels of TNF and interleukin 6 (which come mainly from monocytes) and of interferon γ (a major activator of monocytes) have been associated with LBW in at least one study (Fried *et al.* 1998*a*; Moormann *et al.* 1999; Rogerson *et al.* 2003*a*). The mechanism by which these cytokines might cause FGR is not known, and studies of pathological pregnancies leading to FGR (reviewed below) may hold relevant insights for understanding pathogenesis of FGR due to malaria.

Could malaria-activated macrophages impair placentation?

Pre-eclampsia is another pathological pregnancy condition that leads to LBW (Sibai, Dekker and Kupferminc, 2005). Similarities (and discrepancies) between pre-eclampsia and MiP have been recently reviewed (Brabin and Johnson, 2005) and common pathogenic mechanisms may be involved. Pre-eclampsia is characterized by an impaired cytotrophoblast invasion, sub-optimal uterine arterial remodelling and defective replacement of maternal endothelium by endovascular cytotrophoblasts (Redman and Sargent, 2005), such that the normal development of a low-resistance, high-capacity blood flow through spiral arteries feeding the placenta is impaired (Goldman-Wohl and Yagel, 2002).

Malaria has been identified as a risk factor for pre-eclampsia and hypertension in pregnancy in some studies (Sartelet *et al.* 1996; Muehlenbachs *et al.* 2006) but not others (Dorman *et al.* 2002). A recent study (reviewed by Duffy, in this special issue) showed an association between chronic placental malaria and hypertension in primigravidae (Muehlenbachs *et al.* 2006). There are no published data on the effect of malaria during placentation on cytotrophoblast invasion and spiral artery remodelling, but the peak prevalence of *P. falciparum* parasitaemia early in the second trimester overlaps with the period when spiral arteries undergo remodelling (complete by 20–22 weeks of gestation). Thus, there is a window in time during which malaria infection could indeed impair the establishment of an optimal placental blood flow.

Trophoblast invasion of spiral arteries is vulnerable to factors causing activation of maternal cells in the uterine bed. In particular, TNF and interleukin 1β (both increased in placental malaria) dramatically increase secretion of the monocyte chemokine MCP-1 by uterine decidua (Lockwood *et al.* 2006), a chemokine found increased in placental malaria (Abrams *et al.* 2003; Suguitan *et al.* 2003). It has been recently shown *in vitro* that activated macrophages could inhibit trophoblast invasion (Renaud *et al.* 2005) probably through TNF production (Bauer *et al.* 2004; Renaud *et al.* 2005).

Maternal malaria infection during placental development could thus increase numbers of activated macrophages in the maternal decidua, and reduce trophoblast invasiveness, impairing the remodelling of spiral arteries leading to a sub-optimal placentation and a possible placental hypoxia. Studies investigating the migration/invasion potential of first trimester cytotrophoblasts in the context of gestational malaria are critically needed.

Could various monokines trigger an impairment of nutrient transport?

In recent years, there have been marked improvements in our understanding of placental nutrient transport and its role in pathogenesis of FGR of other causes (Regnault *et al.* 2005; Sibley *et al.* 2005; Zamudio, Baumann and Illsley, 2006) and it is now clear that amino acids and glucose act as regulators of placental and foetal development (Regnault *et al.* 2005). Foetal concentrations of amino acids are decreased in babies with FGR compared to normal babies (Cetin *et al.* 1990, 1996; Economides *et al.* 1989), and FGR is associated with impairment of the active transport mechanisms operating at the level of the syncytiotrophoblast. The importance of changes in transcription, expression, localisation and function of nutrient transporters and their encoding genes is more and more recognised in FGR. Increasing numbers of techniques to examine them have become available in the last 5 years (Glazier and Sibley, 2006; Regnault *et al.* 2005; Zamudio *et al.* 2006) but these have yet to be applied to studies of the pathogenesis of MiP. For example, interleukin 1β, which is increased in MiP (Moormann *et al.* 1999), inhibited amino acid uptake of the trophoblast-like cell line (BeWo) in a dose-dependent manner (Thongsong *et al.* 2005), while TNF has been shown to down-regulate amino acid transport across the placenta *in vivo* (Carbo, Lopez-Soriano and Argiles, 1995). Local inflammation, triggered by malaria infection and supported by maternal monocyte infiltrates, could thus cause a decrease in amino acid transfer across the placenta, impairing foetal growth.

Beside amino acids, glucose transport across the placenta could also be reduced during MiP. GLUT1 is the main glucose transporter in the placenta and sits in the microvillous and basal membranes of the syncytiotrophoblast. Since the microvillous membrane contains more transporter than the basal membrane, alteration in the density of transporters in the basal membrane is the main factor regulating glucose transplacental transport. For example, at high altitude the amount of basal membrane GLUT1 decreases relative to microvillous membrane levels (Zamudio *et al.* 2006). Glucose transport is impaired in FGR (Baumann, Deborde and Illsley, 2002) and recently, the insulin-insulin growth factor axis has been identified as a major pathogenic mechanism of LBW (Bajoria *et al.* 2002; Kajimura,

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Aida and Duan, 2005). The basal membrane expression of GLUT1 is positively regulated by insulin-like growth factor I, low levels of which have been reported in human malaria (Mizushima *et al*. 1994). This could lead to a decrease of glucose flux across the placenta, possibly leading to FGR.

Determining the activity of the different nutrient transport pathways in MiP would greatly advance our understanding of the pathogenesis of LBW and could provide avenues for intervention strategies.

Hypoxia during pregnancy : a double-edged sword

Hypoxia is a physiological driving force for cytotrophoblast migration during implantation (Graham *et al*. 2000), but in term placental tissue, hypoxia leads to apoptosis (Levy *et al*. 2000), increased production of pro-inflammatory cytokines (Benyo, Miles and Conrad, 1997) and impaired amino acid (Nelson *et al*. 2002; Zamudio *et al*. 2006) and glucose (Zamudio *et al*. 2006) transport.

Placental hypoxia could be caused by sub-optimal placental blood flow due to inadequate placentation, as discussed above, or by the massive monocyte and IE infiltrates in the intervillous spaces. Moreover, by adhering to the syncytiotrophoblast, IEs and monocytes could physically decrease the surface of exchange between maternal and foetal blood leading to a further decrease in nutrient and oxygen transport across the placenta. From peak oxygen saturation of 60% in mid pregnancy, foetal blood oxygen saturation falls to around 40% by term, due to increasing foetal demand (Soleymanlou *et al*. 2005). Any fall in oxygen saturation in uteroplacental blood, or significant decrease in blood supply, will result in decreased oxygen availability to the foetus.

Placental hypoxia appears to be a well-defined cause of LBW whether it is normobaric hypoxia in animal models of FGR (Regnault *et al*. 2006) or hypobaric hypoxia in high-altitude pregnancies (Zamudio, 2003). Studies addressing the potential role of placental hypoxia in MiP-associated FGR would provide valuable insights in our understanding of MiP pathogenesis.

MiP-associated FGR : a complex network of potential pathogenic mechanisms

In the previous sections, we have tried to present MiP-associated FGR as a condition induced by different pathogenic processes. It is increasingly evident that the pathogenesis of FGR (associated with MiP but also with other pathological pregnancies) is multifactorial and that all those processes interact in a complex network. For example, hypoxia can induce a decrease in amino acid transport activity (Nelson *et al*. 2002) and so do pro-inflammatory cytokines (Thongsong *et al*. 2005). But, in addition, hypoxia can induce the release of pro-inflammatory cytokines (Benyo *et al*. 1997). Deciphering the relative importance of each of these potential pathogenic mechanisms in MiP-associated FGR is a challenging but necessary task that may require prospective studies.

THE NEED FOR PROSPECTIVE STUDIES

To improve our understanding of the relationship between timing of malaria episodes and clinical outcomes of MiP longitudinal cohort studies should be undertaken, incorporating accurate dating of the pregnancies, repeated parasitological status assessment and ultrasound monitoring of foetal growth. Such studies would have implications for the design and implementation of IPTp, which aims at controlling placental malaria infection by administering a curative regimen of an effective antimalarial in the second trimester of pregnancy, followed by at least one more dose, at least 1 month later (World Health Organization, 2004). A better understanding of the kinetics of MiP would allow better targeting of IPTp. For example, infection in late pregnancy may be missed when IPTp is complete by 30 weeks gestation. If infections in early pregnancy during placental development were shown to have long-term sequelae, the difficult issues regarding administration of antimalarials in early pregnancy would need to be confronted.

Doppler ultrasound studies have revealed disturbances in vascular resistance in the uteroplacental arteries, suggesting inadequate placental blood flow and placental dysfunction, associated with presence of peripheral blood infection on the day of the test (Dorman *et al*. 2002). Such effects could result from an impairment of placentation by malaria infection or from mechanical effects of concurrent placental malaria on blood flow within the intervillous space. Ultrasound assessment of placental function throughout pregnancy would greatly extend our knowledge of the kinetics of events leading to MiP-associated FGR and PTD.

THE NEED FOR NEW TOOLS

Animal models and cell lines : strengths and limitations

Due to ethical reasons, *ex vivo* studies on the pathogenesis of MiP-associated FGR have primarily used placental tissue collected at delivery. If valuable insights have been gained from these studies, such samples give no information on the kinetics of the pathogenic processes leading to LBW and, clearly, longitudinal studies are needed (as discussed above).

Our knowledge of the pathogenesis of FGR in MiP is also limited by the relative lack of relevant animal models easily amenable to experimentation. The

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P. coatneyi – Macaca mulatta model has proven useful (Davison *et al.* 2000), but it cannot be used in most laboratories due to its cost and requirement for specific facilities. Rodent models of MiP have also been developed (Oduola *et al.* 1986; Vinayak *et al.* 1986; Desowitz *et al.* 1989; Hioki, Hioki and Ohtoma, 1990) including a mouse model in which an accumulation of IEs in the placenta was observed together with a spontaneous abortion early in pregnancy (Poovassery and Moore, 2006). However, anatomical and functional differences between primate (Benirschke and Miller, 1982), mouse (Georgiades, Ferguson-Smith and Burton, 2002) and human placentae together with the differences in the species of *Plasmodium* engaged imply many limitations: set-up of the model, type of questions that can be addressed, analysis and relevance of the data obtained.

The same limitations apply to cell lines, such as the choriocarcinoma cell line BeWo, which are used as models of certain cell populations in the placenta. A recent study showed that the binding of IEs to BeWo induced changes in these cells (Lucchi *et al.* 2006*b*) suggesting that the syncytiotrophoblast might have an active role in MiP pathogenesis. Syncytiotrophoblast derived *in vitro* may be preferable to BeWo cells (Lucchi *et al.* 2006*b*).

These previous remarks do not undermine the value of animal models or cell lines but they do support the necessity to conduct studies on human samples as much as possible, which may require the development and use of tools new to this field.

The example of laser capture microdissection

Placentae from LBW babies have various anatomical and histological differences from placentae from normal birth weight babies and MiP is also associated with a remodelling of the structure of placental tissue (Brabin *et al.* 2004). A drawback of placental studies using whole tissue is that changes in the cellular composition of the tissue may lead to misleading differences between cases and controls. Laser capture microdissection allows the guided selection of specific areas of a tissue section for excision and analysis. The downstream applications include real-time RT-PCR (Chan *et al.* 2004), genotyping (Rook *et al.* 2004), microarrays (Elkahloun, Gaudet and Robinson, 2002) and proteomics (Craven and Banks, 2001; Batorfi *et al.* 2003). We have recently adapted this technique to the study of syncytiotrophoblast gene expression using pressure-assisted laser capture microdissection. Captured material is collected directly into RNA extraction buffer and quantitative real-time RT-PCR is performed (Boeuf *et al.* 2005). This approach allowed us to identify differences in syncytiotrophoblast gene expression between *Plasmodium*-infected and control placentae that went unnoticed when we addressed the whole placental tissue. This example shows that technical tools such as laser capture can provide new insights in the pathogenesis of MiP by focusing on some of the many different cell types that compose the complex placental tissue architecture.

CONCLUSIONS

We now have excellent insights into the basis of placental malaria infection (reviewed by Duffy, Hviid and Salanti and Scherf, in this special issue of *Parasitology*). We lack similar understanding of the host response to malaria, and of the mechanisms by which this contributes to pathogenesis of LBW due to malaria. Studies should be designed to address this deficit, and to explore further the importance of age, HIV infections and gestation as risk factors for malaria in pregnancy. Based on such studies, preventive therapies can be better directed to those most at need, to tackle this devastating, yet preventable cause of infant and maternal mortality.

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