Malaria during pregnancy in Rwanda
Rulisa, S.

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CHAPTER 7

General Discussion and Conclusions
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Malaria poses a heavy burden of disease in many countries. 219 million cases of malaria were recorded in 2010, with an estimated associated annual death toll of 666,000.1 Each year, about 30 million women are at risk for an infection.2-4 The risks for these women are associated with a down regulation of maternal immune responses to protect infection of the fetus in the uterus. Malaria in pregnancy (MIP) causes over 10,000 maternal deaths worldwide each year.5-9 The harmful effects of MIP depend on transmission rates and levels of acquired immunity. This thesis explores aspects of malaria in pregnancy in Rwanda and takes into account the epidemiology of malaria in Rwanda, the health seeking behavior of pregnant women, the effects of infection on pregnancy and fetal outcome, the pharmacodynamics, pharmacokinetics and safety of artemisinin-based combination therapy, in particular artemeter-lumefantrine, the drug combination that is most often used to treat malaria in Rwanda.

Does malaria endemicity influence the way malaria should be targeted?

Malaria in Rwanda is still a major public health concern and has been the main cause of morbidity and mortality for several years. The definition of malaria endemicity in Rwanda is difficult due to the fact transmission intensity varies with the large variations in altitude. Rwanda is classified into four transmission zones, each with a different prevalence of P. falciparum.10 Transmission intensity ranges from high to nil. Rwanda has five provinces (North, South, East, West and Kigali) and 30 districts. A seasonal peak of transmission appears in two-thirds of the districts while it is stable year-round in the remaining third of districts.10 A dramatic decline of malaria transmission over the last 5 years in Rwanda was reported with the incidence declining by 70 per cent between 2005 and 2010 (DHS 2010). The data presented in this thesis from the one study where we collected data all over the country to study the effects of malaria on birth outcomes (Chapter 4) do not corroborate this decline for all studied sites. Most of the other studies on malaria treatment presented in this thesis were performed between 2007 and 2011 and conducted in eastern province, which has a high transmission intensity. Therefore generalization of these results to the whole country should be treated with caution. Irrespective of the exact size of the decline, in general the malaria transmission in Rwanda is at most mesoendemic.
If transmission is indeed very low then the questions that come are two fold. The first is if it would be possible to have a more targeted approach to malaria case detection. The second would refer to the protection and treatment of malaria for the vulnerable subjects such as pregnant women.

In an attempt to eradicate malaria in a country like Rwanda where endemicity is not uniform, identification of malaria clusters and hotspots is inevitable, index circle surveillance following fever cases from the health center could be a good entry point in identifying these hotspots, and these would be one of the cornerstones of pre-elimination.

This would require an investigation on the prevalence of the disease and its distribution pattern (i.e. is there clustered malaria or not). To assess this in Bugesera district we conducted a two-stage health center and household based survey in Ruhuha sector, Eastern province of Rwanda in April-October 2011 (chapter 2). This included a health center fever survey, and, a follow-up household survey, including performing malaria diagnosis for all household members and collecting individual, environmental and household risk factor data.

It was found that malaria prevalence among febrile patients attending the health center was 22.9%, that on average at least one family member among the index fever patients’ households surveyed carried malaria parasites and that the malaria prevalence was 5.1% in Ruhuha sector, clustered in households close to water bodies.

Being young and poor as measured by quality of the house is still on top among risk factors for having malaria and until these are addressed, malaria elimination may be difficult. Rwanda has aggressively addressed this by improving housing and eradicating grass-thatched houses; this is thought to have a significant impact on malaria transmission.

The second question refers to the risk for malaria of pregnant women. Birth outcomes of pregnant women are related to many factors. Contracting malaria and correctly applying malaria preventive measures are some of these factors. However, we think that giving birth at a health facility may improve the outcome as assisted delivery would reduce most of the complications that lead to severe morbidity and mortality.

In any attempts to control diseases or improve health, understanding health seeking behavior of the population is as important as understanding disease dynamics. Therefore we investigated in chapter 3 the health seeking behavior of women in Bugesera district, eastern province, Rwanda
and more specific, why women chose for assisted delivery in a health center and not for home delivery.

Using census data and a survey methodology with samples proportional to cluster size, 30 villages were selected for community-based, cross-sectional surveys of women aged 18–50 who had given birth in the previous three years. This showed that the strongest correlates of facility-based delivery in Bugesera District included previous delivery at a health facility, possession of health insurance, greater financial autonomy among women, more recent interactions with the health system, and proximity to a health center. Recent structural interventions in Rwanda, including the rapid scale-up of community-financed health insurance, likely contributed to the dramatic improvement in the health facility delivery rate observed in our study. Community health insurance is a system in which the insured person pays an upfront amount for health services regardless of the current health status and only pays a small fee (affordable) when the individual becomes ill. Due to the upfront contributions the health seeking behavior is improved for any health condition because there are no financial related barriers to seeking care. Mubyazi et al has reported a similar phenomenon in neighboring Tanzania\(^\text{20}\). Previous research has shown that pregnant women are relatively knowledgeable and aware of preventative measures for malaria, especially those classified as antenatal care users\(^\text{21}\). In this period of aggressive interventions to reduce malaria, special attention should be put to women because both cerebral and placental malaria can coexist and lead to severe mortality and morbidity to bother mother and fetus\(^\text{19}\). If the women’s health seeking behavior would be tapped correctly and used for malaria prevention during pregnancy and general malaria control, this could lead to substantial reduction in neonatal mortality\(^\text{18}\).

**Malaria in pregnancy in low endemic countries, are we on the right track?**

Chapter 2 and 3 investigated 2 important factors contributing to malaria in pregnancy; being the presence of the malaria parasite and the way pregnant women seek care. Even though malaria during pregnancy can in principle be prevented, many pregnant women in Rwanda still contract malaria even though malaria incidence has shown to be low.

With the commitment of the government, Rwanda launched an aggressive nationwide campaign in 2006 to scale up malaria control tools and adopted prevention as its main strategy for
controlling malaria, through use of long-lasting insecticidal mosquito nets (LLINs) as well as appropriate and timely treatment of malaria cases with efficacious antimalarial drugs. Over the past few years, malaria has also been among the major focus of the country’s comprehensive poverty reduction strategy, health policy reforms, and overall investment on health (DHS 2010). As a consequence of these parallel measures malaria in Rwanda reduced significantly (DHS 2008, DHS 2010).

In pregnancy the one indicator that is always associated with malaria in pregnancy is birth weight. Many studies\textsuperscript{\textordf專業viii, \textordf專業ix} have shown that malaria during pregnancy can lead to low birth weight. Traditionally these studies were conducted in high transmission areas. In Rwanda however, it was not clear whether a marked decline in malaria transmission could be expected to have a positive effect on birth weight as well. In chapter 4 we set out to investigate if in a country with low transmission intensity the same effects on birth weight could be observed. We found significant increase of birth weight over the years (2002- 2007) with a significant seasonal fluctuation. But, malaria incidence had no significant effect on birth weight whereas other birth outcomes such as prematurity and stillbirth decreased over time correlating with decreasing malaria. These findings lead to the question whether in a relatively low transmission area such as Rwanda, intensive measures to protect women from malaria are justified and whether more priority should be given to rapid detection and treatment of malaria in pregnancy.

Optimal pregnancy outcomes should be obtained by interventions during the most harmful period of malaria infection during pregnancy. Several studies evaluated the relationship between timing of infection and consequences of MiP\textsuperscript{\textordf專業x} by following a large group of pregnant women in Malawi between 2001 and 2003. They found a higher risk of LBW when infections occurred during the second trimester (13-26 weeks) as compared to infections during the third trimester or at delivery, however other studies have indicated that even infections in the third trimester lead to fetal growth alteration in an area where transmission intensity ranges from holo-endemic to low transmission\textsuperscript{\textordf專業xi-xii} implying that maximum protection against malaria during pregnancy is required irrespective of endemicity. In these studies the risk of LBW and maternal anemia increased with the number of malaria episodes during the gestation, irrespective of gravidity. This suggests an accumulation of sequestration of malaria parasites. Other studies with Burmese pregnant women\textsuperscript{\textordf專業xiii} showed that placental malaria infection is particularly harmful at the beginning of
pregnancy (<4 months of gestation), both in terms of birth weight and maternal anemia. Valea et al. reported a strong association between infections occurring in the first trimester and LBW. This could be due to the infection per se at that particular time, or it could be related to a higher risk these mothers have throughout their pregnancy. In addition evidence from a Gambian cohort study shows that MiP can also have more long-term effects. It found that, independent of low birth weight, children who were exposed to placental malaria (PM), were the following year 2.4 times more wasted at the age of three months and 3.1 times more likely to be underweight at the age of 12 months compared with infants born with no PM. This negative impact on the infant’s weight development suggests that the longer-term effects of PM have been underestimated and must be dealt with firmly. If this is also a problem in low transmission areas needs to be assessed.

In many African countries the use of sulfadoxine pyrimethamine (SP) as intermittent preventive treatment during pregnancy (IPTp) is recommended as prophylaxis. IPTp can prevent the adverse effects of MiP. Unfortunately, due to fears of possible teratogenic effects during the first trimester, this drug can only be given from 20 weeks of gestation onwards as evidenced by the national guidelines. During the first trimester of pregnancy, this vulnerable group is unprotected and additional measures should be taken, such as the use of impregnated bed nets. A complementary strategy consisting of screening of pregnant women with rapid diagnostic tests and a subsequent treatment in case of clinical malaria is recommended. However, an important restriction in malarious areas is the late attendance of women to antenatal visit. In Rwanda we have shown (chapter 2 & 3) that the late attendance is no longer a major problem and that health facility utilization among pregnant women is increasing. Therefore the benefits of complementary screening could be explored for this setting. In addition community-based promotional campaigns for the use of LLIN, targeting pregnant women and adolescents, are found to be a good choice to deal with this specific problem.

In low to moderate transmission areas, such as Rwanda, pregnant women who have little or no pre-existing immunity, MiP usually presents as an acute febrile disease. This can cause severe maternal morbidity and mortality. Acute malaria was found to have a specific impact in pregnancy.
In Chapter 5 we also found that malaria infection leads to persistent raised maternal and fetal heart rate, and lowers maternal blood pressure and that the changes in fetal hemodynamics normalize within one week after initiation of therapy, while the maternal heart rate remains elevated for several weeks. In Chapter 4 we found no effects of malaria on birth weight and other birth outcomes, which correlated with the achieved decrease in malaria incidence in Rwanda on population level. However, McGready et al. analyzed 17,613 antenatal records of pregnancies from the Thai-Burmese border with low seasonal transmission of *P. falciparum* and *P. vivax* and they did see an effect. Outcome of pregnancy in women without malaria during pregnancy was compared with those with a single episode during first trimester and both symptomatic and asymptomatic malaria infection was related with miscarriage during first trimester. LBW was not found when a single successfully treated episode of malaria in the first trimester without later infection occurred. These results highlight that although, at population level malaria may not have severe effects on birth weight the importance of malaria prevention at individual level in early pregnancy, possibly even before conception, as well as rapid recognition and treatment for all infected pregnant women remains essential.

**Treatment of malaria; should we change the current policy?**

Adequate treatment is the cornerstone of the fight against malaria during pregnancy. Resistance to conventional antimalarials, such as chloroquine and sulfadoxine-pyrimethamine (SP), is high and there is a great need to identify drugs, which have the most favorable harm-benefit ratio for the mother and the unborn child. In general, in order to improve treatment outcomes and to prevent resistance to monotherapies, the World Health Organization (WHO) recommends a fixed-dose artemisinin-based combination therapy (ACT) as first-line treatment. Recommendations include artemether-lumezantrine (AL), artesunate-amodiaquine (AS+AQ), artesunate-mefloquine (AS+MQ), artesunate + sulfadoxine-pyrimethamine (AS+SP) and dihydroartemisinin-piperaquine (DHA+PPQ). This includes also the treatment of uncomplicated *P. falciparum* malaria during second and third trimesters of pregnancy.

Many countries, including Rwanda, adopted a management protocol based on these standard treatment guidelines. Women in Rwanda with acute malaria in late pregnancy are treated promptly with artemether-lumezantrine (AL, Coartem®), a combination of a short-acting
artemisinin derivative that rapidly lowers the parasite biomass with a long-acting lumefantrine, capable of eliminating residual parasites. Following the guidelines, infection during the first trimester should be treated with a seven-day course of quinine. In the first trimester of pregnancy, an ACT should only be used if there is no other treatment immediately available, if the first treatment has failed or if the patient’s life is threatened. It has been observed that pregnant women tend to have higher treatment failure rates than non-pregnant adults living in the same area and as immunity to malaria may disappear during pregnancy\textsuperscript{xxiii}. One explanation may be a different pharmacokinetic profile of drugs during pregnancy. Accurate pharmacokinetic data from antimalarials used in pregnancy are an important area of malaria research.\textsuperscript{xxiv} However, there are only few pharmacokinetic studies with antimalarials that include pregnant women. Physiological changes increase volume of distribution, reduced gut motility; increased renal blood flow, hormonal changes, and increased protein binding in pregnancy can change drug metabolism and disposition. Artemether and its related artesunate are rapidly hydrolyzed to dihydroartemisinin in vivo, which has equivalent antimalarial activity. Due to a larger volume of distribution and more rapid clearance during pregnancy, kinetics of artemether and dihydroartemisinin are altered. The plasma concentration of the active metabolite, dihydroartemisinin, is lower than in non-pregnant women. McGready et al.\textsuperscript{xxv} also showed lower artemether and dihydroartemisinin levels following treatment, and a lower concentration and quicker elimination of lumefantrine in pregnant women than previously reported in non-pregnant women. These lower concentrations might decrease the efficacy of treatment, so dose-optimisation studies in pregnant women were recommended. Evaluation of the current standard AL regimen at the Burmese-Thai border in second and third trimesters found no adverse events, but efficacy was inferior to seven days of artesunate monotherapy. Reduced efficacy probably resulted from low drug concentrations in later pregnancy and relatively resistant parasites leading to conclusions like effective treatment may involve a higher-dose regimen to treat pregnant women\textsuperscript{xxvi}. Although, Manyando et al.\textsuperscript{xxvii} suggested these results should be interpreted with caution as they involve between trial comparisons, small populations, high inter-individual variations in plasma levels and the average plasma levels were comparable with data from non-pregnant adults. In our study we did not find any need for dose adjustment in pregnant women in Rwanda. Although AL is still not officially indicated for pregnant women a large body of evidence supports
the use of AL in second and third trimester of pregnancy. A review from Dellicour et al.\textsuperscript{xxvii} included 14 studies on exposure of pregnant women to an artemisinin derivate, with a total of 945 pregnancies. None of those showed an increased risk of serious maternal adverse effects, adverse birth outcomes, or neurodevelopment deficits associated with the use of an artemisinin drug during pregnancy. Our study (Chapter 6) showed that no specific safety concerns were related to AL treatment in pregnancy. Increased obstetric complications, like higher rates of abortion, perinatal mortality, stillbirth and premature delivery, were observed in the treatment group and although in theory this could be caused by the AL treatment the complications are also in line with the presence of malaria episodes themselves. The available studies suggest the use of AL in the second and third trimesters of pregnancy appears to be safe. However, and in order to detect rare adverse events which may not necessarily become apparent in clinical studies, monitoring pregnancy outcomes by following all exposures of pregnant women to anti-malarial treatments remains important. This will increase the amount of safety data to assess which treatments are most appropriate for use in pregnancy.

The restriction of treatment with AL during first trimester of pregnancy is due to limited clinical safety data and evidence of embryo lethality and developmental abnormalities in animal studies following exposure early in pregnancy, comparable to the first trimester in humans.\textsuperscript{xxxii} It is however very difficult to study the safety in a controlled trial in pregnant women as they are usually not aware of a pregnancy during the first trimester. Nevertheless accidental first trimester exposures to artemisinins are common. 96 patients in our study who received AL treatment during first trimester had no greater risk of perinatal or neonatal infant death or stillbirth. So far, only few first-trimester exposures to artemisinin derivatives have been reported with known pregnancy outcomes. Deen et al.\textsuperscript{xxx} also evaluated 77 pregnancies and found no evidence of increased fetal loss or infant death. Adam and colleagues\textsuperscript{xxvii} followed 62 women with confirmed malaria who had received artemisinins, until delivery and their babies until 1 year after birth and also did not find significant adverse events. The largest prospective study was done by Mc Gready et al.\textsuperscript{xxxii} The authors analyzed 64 antenatal records of first-trimester infections who were exposed to artesunate-based antimalarials. No stillbirths or congenital abnormalities have been recorded and compared with other antimalarials, chloroquine- and quinine-based, artesunate-based treatment did not differ significantly birth outcome. A prospective study in Zambia\textsuperscript{xxxii} compared the outcome from women treated with AL against SP exposed during first trimester. No
differences were reported in the event of perinatal mortality, infant malformation or neurodevelopment. However, 4.5% of women treated with AL had a miscarriage during their first trimester, where no abortions occurred in the group exposed to SP and/or quinine in the first trimester. Although confounding factors such as infection were linked to these events and a recent review by Manyando et al. \textsuperscript{126} showed no significant effects in the first trimester, further studies are required to evaluate the outcome of ACT use during the first trimester of pregnancy and in particular, the long term effects on babies. Here we strongly advocate the implementation of proactive pharmacovigilance studies.

**Final remarks**

This thesis aimed at providing more evidence on malaria in pregnancy in Rwanda and it showed mild immediate effects of a malaria during pregnancy and apparent safety of AL in pregnancy. With these effects in combination with the marked reduction of malaria transmission in Rwanda strong measure should be in place to plan for malaria elimination in Rwanda. Meanwhile, maximum protection against malaria during pregnancy, without ignoring the rest of the population, and early treatment should still be high on the agenda of the national malaria control program as low transmission will result in a decrease in immunity against malaria and result in more acute malaria cases. This will mean that more targeted approaches are needed in combination with a new sensitization of the health facilities taking into account the specific challenges for a low endemic area. As indicated in chapter 5 a deeper understanding about fetal physiology during acute malaria may help in managing fetal effect during acute malaria in pregnancy and current screening and treatment strategies need to be revisited to meet the changing transmission patterns.
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