Malaria during pregnancy in Rwanda
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CHAPTER 1

General Introduction
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Introduction
Malaria is one of the most significant infectious diseases worldwide. Malaria is endemic mainly in tropical and subtropical regions especially in Africa, Asia and South and Central America (1). Approximately half of the world’s population is at risk of malaria (2). Most malaria cases and deaths occur in sub-Saharan Africa (3). However, Asia, Latin America, and to a lesser extent the Middle East are also affected. In 2010, 99 countries and territories had ongoing malaria transmission.

According to the World Malaria Report 2011, there were about 216 million cases of malaria (with an uncertainty range of 149 million to 274 million) and an estimated 655 000 deaths in 2010 (with an uncertainty range of 537 000 to 907 000). Malaria mortality rates have fallen by more than 25% globally since 2000, and by 33% in the WHO African Region(4). Most deaths occur among children living in Africa where a child dies every minute from malaria (3). Malaria is caused by the Plasmodium parasite and is transmitted to humans by the bite of an infected female mosquito. Thereafter the parasite is able to enter the blood stream, invade the red blood cells and multiply.

This form of malaria (the presence of parasites in the blood stream) is called peripheral malaria. Several species are known to infect and cause disease in humans i.e. Plasmodium falciparum, P. ovale, P. vivax, P. malariae and recently P. knowlesi. The P. falciparum parasite, which causes the most severe disease and the most deaths, is also thought to be the only one responsible for placental malaria and is the focus of this thesis (5). Placental malaria is the condition when a pregnant woman becomes infected with malaria parasites and these parasites hide in the placenta. This phenomenon can have severe consequences for both the mother and the fetus. This thesis describes maternal and fetal effects of malaria and malaria treatment during pregnancy in Rwanda and focuses on the effects of current treatment for malaria on the baby and on the effects of malaria on the fetus in utero.
Epidemiology of malaria in pregnancy

Pregnant women are most vulnerable of getting infected with malaria, after children below the age of 5 years. In spite of the possible measures to prevent the disease, the prevalence of malaria during pregnancy remains high. An estimated 54.7 million pregnancies occurred in areas with stable *P. falciparum* transmission in 2007 and an additional 70.5 million in areas with low malaria transmission or with *P. vivax* only (6). The incidence and thus the risk of getting malaria in the areas of low transmission is much lower than stable transmission areas, so only a small proportion of the 70 million women actually acquired malaria. In Africa approximately 25 million women are at risk of *P. falciparum* infection during pregnancy every year, and one in four women has evidence of placental infection at the time of delivery (7). In African areas of low or seasonal transmission the median prevalence of peripheral and placental parasitaemia was approximately 14% and 7% (8).

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Malaria remains to be one of the causes of mortality and morbidity in Rwanda according to the Rwanda 2010 Demographic and Health Survey (DHS) and the Rwanda Health Sector Strategic Plan 2009-2012. Children under five and pregnant women are the most affected (9). In 2010, the number of confirmed malaria cases in Rwanda was 8,517, corresponding to a 76% decline compared to 35,688 confirmed cases during 2000-2005 (10).

The Malaria Indicator Survey (MIS) conducted in 2007 focused on household characteristics, key malaria indicators and the malaria and anaemia prevalence in children under five. This national survey showed that on average 53.8% of households use mosquito nets: 65.7% of urban households versus 51.4% of rural households. In addition, during the survey it was found that approximately 35.3% of children under five had anaemia: 19.6% had mild anaemia, 15.3% moderate anaemia while 0.4% had severe anaemia. A study in 2005 reported that the overall prevalence of malaria (i.e. asymptomatic carriers of detectable malaria parasites in blood) was 13.6% in the six health districts that were studied with considerable variability among districts ranging from 11.5% and 15.4% in four districts with a prevalence below <5% in two other districts (11).
The 2010 DHS also measured the malaria prevalence. In that survey the general malaria prevalence in Rwanda had significantly declined. This is in line with findings in our household survey in eastern province, which showed a malaria prevalence of less than 5% in Ruhuha, an area with relatively high transmission (Chapter 2).

The World Health Organisation (WHO) has developed guidelines for controlling malaria in areas with stable malaria transmission, which consist of providing prompt and effective antimalarial treatment combined with prevention of infection by intermittent preventive treatment during pregnancy (IPTp) and insecticide treated nets (ITNs) (9)(12)(13). In low transmission areas there are no specific guidelines for prevention of malaria in pregnant women and malaria control is based primarily on case management (12)(14). Malaria in Rwanda is varying from perennial transmission in the east to seasonal and even none in the north where altitude is very high.

IPTp is the administration of anti-malarial treatment at specified time points during pregnancy, regardless if the woman is infected at that time (9). In this way it should reduce the malaria burden in the target population. In areas of stable malaria transmission, it is recommended that pregnant women should receive two doses of sulfadoxine-pyrimethamine (SP) at the first and second scheduled antenatal visit after quickening; in the case of HIV infection three doses of IPTp are recommended (15)(9). This type of non-specific medical treatment has not been studied for low transmission areas where the numbers needed to treat (NNT) become unrealistic and where infected individuals usually develop symptoms that lead to seeking help and treatment and where asymptomatic parasite carriers are rare (16). In addition, due to resistance against SP, IPTp-SP is becoming less effective at preventing malaria infection in pregnant women. As a result of low transmission, IPTp policy was stopped in Rwanda (17).

Long lasting insecticide-treated nets (LLIN) are another preventive measure that has proven to be successful in the prevention of malaria and their impact has been studied. These studies have shown that the LLINs have a beneficial effect on pregnancy outcome in low and high malaria transmission areas in Africa in the first few pregnancies (18). Infants born from pregnant women in high transmission areas using bed nets showed higher mean birth weights and there was a reduced risk of placental infection, low birth weight (LBW) and stillbirths compared to pregnant women who did not sleep under a bed net. From 2005 to 2012, more than 5 million ITNs were distributed through out Rwanda (10).
Alternative strategies, such as intermittent screening and treatment (IST), which has been employed in South-East Asia, are becoming more popular in Africa and subject to study. IST could be especially useful in areas with low transmission such as Rwanda as it limits the number of women receiving possibly ineffective drugs during IPTp-SP (19)(20). For all these interventions to work it is essential that women visit the antenatal care facilities or health centres at regular basis in order to get advice, prevention or treatment for malaria. But even if all preventive measures are taken correctly birth outcome can be influenced by the way a woman delivers the baby. Assisted delivery by a midwife or in a health centre reduces the number of adverse birth outcomes. Therefore WHO propagates assisted delivery as much as possible (21). It is however not clear what the factors are in Rwanda that determine if a women goes to the health centre to deliver or not. In chapter 3 we studied what the determinants are for a women to give birth in a health facility in Bugesera district (Eastern Rwanda).

**Effects of malaria in pregnancy on mother and fetus**

The hormonal changes and reduced immunity during pregnancy also increase the susceptibility to malaria in pregnant women (22)(23). In addition, the risk of attaining malaria is further increased if pregnant women are below the age of 20, who are pregnant for the first time and who are infected with HIV, which reduces anti-malarial immunity even more (24)(25).

The symptoms and complications of malaria in pregnancy differ with the transmission intensity. Women living in stable high transmission areas do less frequently present with clinical signs of malaria due to acquired immunity but this will not prevent them from developing placental malaria.

In low or unstable transmission areas, malaria in pregnancy usually presents as a symptomatic, severe disease that can result in death of mother and foetus. Most people in these areas, including pregnant women, have not acquired any significant level of immunity against malaria and are at risk of developing severe disease (26). Symptoms of malaria in these areas are fever, headache, abdominal pain, nausea and vomiting and can rapidly progress to severe disease. Maternal death may result from severe malaria directly or indirectly due to severe anaemia (8)(27). Additionally, malaria in pregnancy can result in adverse pregnancy outcomes, such as spontaneous abortion,
neonatal death and preterm delivery. Low birth weight probably requires prolonged infection and in Rwanda we did not find an positive association between malaria incidence and low birth weight (chapter 4). In high transmission areas most women have acquired sufficient immunity, and malaria infection rarely results in symptomatic disease. The main impact in these areas is malaria-related anaemia in the mother and low birth weight and stillbirth in infants (8)(27). Up to half of the 3.5 million low birth weight babies born in sub-Saharan Africa each year may be attributable to placental malaria (28). Stillbirth is also associated with placental malaria, which doubles the risk of this complication. Other adverse outcomes which are significantly associated with placental malaria are intrauterine growth restriction (IUGR) and preterm delivery (29). The fatal complications of placental malaria result into an estimated amount of 75,000 to 200,000 deaths of infants each year on a global level according to The Africa Malaria Report of the World Health Organization (30). Fetal exposure to malaria through transplacental transmission of *P. falciparum* can result in congenital malaria. Studies have shown that 6 to 11% of pregnancies with placental malaria are resulting in this form of malaria (31)(32). Anaemia is one of the signs that is strongly associated with malaria during pregnancy. This is thought to be caused by the cytoadherence and destruction of red blood cells, added to the usual anaemia of pregnant women, leading to low birth weights. However, studies performed in areas outside Africa and where *P. vivax* is common (which does not cytoadhere to placenta) show that also there malaria is associated with maternal anaemia and low birth weight (8). These conflicting reports indicate that the immunopathogenesis of placental malaria and how it leads to low birth weight and anemia is still poorly understood. Recent studies showed that even a single episode of symptomatic or asymptomatic malaria in the first trimester significantly results in fetal growth restriction (33). It is however worth noting that this growth restriction does not significantly affect brain development by fetal cortical development or brain volumes at any time in pregnancy between women with immediately treated malaria infections and non-infected pregnancies (18). The effect malaria during pregnancy on birth weight in Rwanda is discussed chapter 4.

All of the above highlights the harmful consequences of malaria during pregnancy at delivery but little is known about what happens to the fetus during an acute episode of malaria. These studies are difficult to perform since it is impossible to do a full physical examination in utero. However, certain hemodynamic parameters, although limited in number, and their changes and fetal behavior patterns can be measured reliably by cardiotocography (CTG) and ultrasound in the
developing fetus. With these simple and non invasive methods the fetal heart rate, FHR, variability and behavioral state of the fetus can be measured and correlated to the cardiovascular parameters of the mother and may thus reveal the direct effects of acute infection on the fetus and show if these effects are transient or not. Recent Doppler studies showed that during an acute episode of malaria umbilical artery resistance increases and cerebral artery resistance decreases[34][35][36][37]. Fetal outcome can also be predicted by measuring placenta volume. It has been shown that infection with P. falciparum before 24 weeks’ gestation appears to be associated with smaller placental volumes. Placental volumetry has been shown to predict IUGR and adverse pregnancy outcome [38][39]. This is probably due to impaired trophoblastic invasion; in addition, small placentas in the first trimester are associated with high resistance of uterine perfusion in the second trimester but further information on the wellbeing of the fetus and recovery time after a period of acute stress such as during malaria infection is limited [18]. Data on maternal and fetal hemodynamics in acute malaria are presented in chapter 5.

Malaria treatment during pregnancy

Drugs that are known to be safe especially in pregnancy, such as chloroquine and sulfadoxine-pyrimethamine, have become widely ineffective, due mainly to drug resistance. Therefore many countries switched to WHO recommended artemisinin-based combination therapy (ACT) for their first line treatment of malaria. Rwanda also adopted artemether- lumefantrine in 2006 as its first line treatment for all patients with uncomplicated malaria, including pregnant women. It is generally agreed that this currently offers the best opportunity for effective treatment and for the prevention of selection of resistant parasites [40][41]. The introduction of ACTs over the last years had an impact on mortality and on the overall incidence of malaria [42].

In Rwanda artemether- lumefantrine is recommended for treatment of uncomplicated malaria even in pregnant mothers after their first trimester. It has been reported to lead to embryo lethality and dysmorphogenesis in early pregnancy in animals [43] [44]. In humans there has never been any indication of fetotoxicity when used in therapeutic doses. Consequently, artemether-lumefantrine is classified in pregnancy category C [45]. Recent studies have shown that it can be safely used in the first trimester as well [46]. Although now widely used in pregnancy, the pharmacokinetics, safety and efficacy of these drugs in pregnancy are not well known since

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pregnant women are often excluded from clinical trials. Since malaria remains a threat and no other safe alternative is available, surveillance systems to monitor drug safety in pregnancy after introduction are required. Pregnancy is usually not part of the market authorization of a drug so in principle drugs are prescribed off label to pregnant women. Off label prescription should formally be done on named patient basis, in most countries, and follow up of side effects is usually passively reported to a central agency. This is different for compassionate use programs in which a drug has no marketing authorization but is available for study purposes. Such programs usually include compulsory registration to the producer of the drug. This thesis, chapter 6, describes a prospective cohort study of 2000 pregnant women, comparing women with malaria and treated off label with artemether-umefantrine during pregnancy and women without malaria to determine the effects of this drug on pregnancy and babies.

Pharmacokinetics of malarial drugs in pregnancy

It is known that pregnancy changes the normal physiology of a woman and that this can alter the disposition of drugs (46). However, drug-dosing regimens are usually not adapted to the state of pregnancy. Some of the physiological changes that could theoretically alter drug absorption include reduction in intestinal motility an increase in gastric pH owing to a reduction in gastric secretions (46) Limited studies suggest that the bioavailability of drugs is not altered during pregnancy. Increased plasma volume and protein binding changes can alter the apparent volume of distribution (Vd) of drugs. Through changes in Vd and clearance, pregnancy can cause increases or decreases in the terminal elimination half-life of drugs. Due to changes in many physiological parameters as well as variability in the activity of maternal drug-metabolizing enzymes, the efficacy and toxicity of drugs used by pregnant women can be difficult to predict. Enzymatic activity exhibited by the placenta and fetus may also affect maternal drug distribution and clearance (35). It is also known that plasma volume of pregnant women is higher than in normal adults which may also have effect on drug dosing that are otherwise calculated based on normal non pregnant adults. This raises a need to study efficacy and pharmacokinetics of drugs in pregnancy specifically antimalarials in this case.

The major chemical group of antimalarial agents that is now being used is artemisinin and its derivatives; the most prescribed during pregnancy is artemether in combination with lumefantrine. Artemether is a lipid-soluble derivative of artemisinin and after oral administration,
it is rapidly absorbed reaching the maximum plasma concentration (Cmax) approximately 2 hours after drug intake (40)(41). Artemether undergoes extensive first-pass metabolism to dihydroartemisinin (DHA) in the liver but probably also in the intestinal lumen. The Cmax of DHA is reached after approximately 2-6 hours. Cmax declines after repeated dosages, limiting the effective duration of dosing to 5 days (47). The rapid elimination and time dependent pharmacokinetics require a second drug to ensure complete parasite eradication and complete cure. The curative efficacy of ACT is as good as the efficacy of the combining drug. In the case of AL, it is artemether that determines the initial parasite clearance and recovery, lumefantrine dictates the parasite eradication and complete cure rates. There are limited data on the pharmacokinetics of lumefantrine given as a single agent, and most studies stem from combined administration with artemether. However, there is no significant interaction with artemether, and the pharmacokinetics of lumefantrine is not changed by co-administration of artemether (48). The pharmacokinetics of lumefantrine is significantly different from that of artemether. Absorption is incomplete and erratic, and enhanced by co-administration of a little bit of fat (37). Cmax occurs after 6 to 10 hours. Binding to plasma lipoproteins is strong and apparent Vd ranges from 33 to 144 l/kg. Biotransformation is mediated by CYP3A4, and lumefantrine possibly inhibits CYP2D6. The elimination half-life is rather long, ranging from approximately 1.5 to 6 days. Since the complete cure of malaria by AL depends on the efficacy of lumefantrine, an increasing number of studies addressed the PK and pharmacodynamics (PD). It appears that dosing regimens and the consequent plasma concentrations of lumefantrine are important and that the therapeutic width is narrow. Changes of dosing regimens may have significant effects on cure rates (37).

The only available data for the PK of AL in pregnancy suggest that pregnant women have lower plasma concentrations of artemether, DHA and lumefantrine (49). This is likely to be of therapeutic significance since the plasma concentrations of lumefantrine, after elimination of artemether, are an important determinant of cure (49). Elimination of lumefantrine was more rapid than in non-pregnant women (49). However, absorption, first pass elimination and plasma protein binding may also be different. Most of the pharmacokinetic studies were conducted in Asia (Thailand) but it is not clear whether these data can be freely extrapolated to the African population with different parameters like body weight, genetic make-up, food, etc. There have been conflicting data about artemether- lumefantrine in pregnancy. In Thailand (north –west

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border), low cure rates were reported (n = 124, PCR-corrected cure rate of 82.0% (95% CI. 74.8-89.3) at delivery or day 42 if later) with a standard fixed combination explained by low drug concentrations in late pregnancy (50)(51). In contrast, a study in pregnant women in Uganda reported high efficacy (PCR-corrected cure rate of 98.2% (95% CI. 93.5-99.7) at delivery or day 42 if later) (n = 152) when treated with a standard regimen of artemether-lumefantrine (15). Transmission, immunity, diet or race may be potentially responsible for this difference. A recent study done in Mbarara, Uganda also hypothesized that ethnicity may be responsible for the lower concentrations of artemether and its metabolite DHA in pregnant women (51). Pharmacokinetic studies may therefore be of great importance to point out the difference and if necessary the need for dose adjustment in pregnant women.

In this PhD program we also studied the PK of artemether-lumefantrine in pregnancy. However, the population pharmacokinetic modeling did not arrive at a stable model that adequately fits the data. Therefore, these data will not be presented in this thesis.

**Aim and outline of this thesis**

Malaria in pregnancy is a major health problem not only for the pregnant women but also for the unborn baby. Although a lot of effort has been put in unraveling the pathogenesis of malaria in pregnancy a lot remains unknown. This also hampers the development of new effective treatment and diagnosis options. There is thus a great need of research on malaria in pregnancy and the aim of this thesis is to contribute to filling this gap. Not only on molecular pathogenesis and placental interactions but also the macroscopic effects of malaria in pregnancy both in utero and safety of antimalarial drugs during pregnancy.

In Chapter 1 we describe malaria in Rwanda and the gaps in knowledge for the treatment of pregnant women.

In Chapter 2 we present results of a household survey following fever-presenting patients to the healthcare facilities and determine spatial distributions and evidence of malaria clustering amongst households.

In Chapter 3 we studied what the determinants are for women to attend a health facility to deliver a baby as assisted delivery is one of the major contributors to better birth outcome.
In Chapter 4 we showed the association between malaria incidence and birth weight in Rwanda and found that this was marginal and decreasing with time following interventions targeting malaria reduction.

In Chapter 5 we studied maternal and fetal hemodynamics during acute malaria by monitoring in utero fetal reactions during and acute malaria episode and followed progress with treatment.

In Chapter 6 we studied pharmacovigilance of artemether–lumefantrine during pregnancy by following a cohort of 2000 women with and without malaria to determine the effects of AL during pregnancy.
References


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