Name of Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

MALARIA TREATMENT IN PREGNANCY

Summary of the impact:

Research by the University of Oxford's Shoklo Malaria Research Unit (SMRU), Mae Sot (Thailand), has had a significant impact on the health outcomes of pregnant women and infants in malaria affected areas, with findings leading to major changes in World Health Organization recommendations for the prevention and treatment of malaria in pregnancy. Its studies have established the optimum treatment regimes (using artemisinin-based drugs) and have shown that early detection and treatment of malaria, including asymptomatic infection, during pregnancy prevents maternal mortality, morbidity, and improves the outcome of pregnancy.

Underpinning research:

Contracting Malaria during pregnancy is estimated to cause as many as 10,000 maternal deaths and up to 8% of all infant deaths each year[1]. Despite these statistics, malaria in pregnancy has been a relatively neglected problem, with less than 5% of pregnant women having access to effective interventions. This situation has been due to both the absence of data measuring the impact of malaria during pregnancy, and the lack of information regarding the safety of malarial drugs for both the mother and fetus. To address these problems, Professor François Nosten and his research team at the University of Oxford's Shoklo Malaria Research Unit (SMRU) set out to study the epidemiology, prevention and treatment of malaria during pregnancy, in an area of multidrug resistance in South East Asia. Over 26 years SMRU has carried out the largest prospective cohort study of malaria in pregnancy, with detailed assessment and follow up of over 50,000 pregnancies between 1986 and 2012. It also undertook a number of randomised controlled treatment trials (including pharmacokinetic studies) on malaria in pregnancy.

Epidemiological Studies:

In the largest published series of epidemiological studies on malaria in the first trimester (17,613 women), SMRU found that the risk of miscarriage increases in women with malaria, whether symptomatic or not. They also found that there was no significant effect on miscarriage or congenital abnormality rates as a result of the antimalarial drugs they used, and that *P. vivax* malaria, which is often considered a benign infection, is also associated with fetal loss in the first trimester[2]. To further understand the effects of malaria on the fetus, SMRU also conducted detailed ultrasonography studies using 3D imaging technology. The studies showed that the fetal head diameter is reduced after a single (often asymptomatic) infection[3], as well as the placenta volume; this provided further evidence of the deleterious effect of malaria (both falciparum and vivax) on early fetal growth.

Treatment Trials and Pharmacokinetic Studies:

Early detection of parasitaemia and prompt treatment with a safe and effective therapy, are paramount to the reduction of maternal mortality and the adverse effects of malaria in pregnancy. Due to the ineffectiveness of generally recommended drugs (quinine, sulfadoxine-pyrimethamine, and chloroquine) against multidrug resistant *P.falciparum* parasites, SMRU set out to study the safety and efficacy of various antimalarials in pregnancy[4]. Of all treatment tested, 7 days of quinine/clindamycin and 3 days of Malarone/artesunate provided the best outcome, with more than 90% efficiency. These trials also provided evidence that the artemisinins were safe in pregnancy[5]. SMRUs final pharmacokinetic trial, published in 2008, showed that the standard six-dose (3 days)

artemether-lumefantrine regimen was well tolerated and safe in pregnant Karen women with uncomplicated falciparum malaria. This trial also showed that the efficacy was lower than the 90% recommended by the WHO because of low concentrations of lumefantrine[6].

References to the research:

1. Roll Back Malaria. Malaria in pregnancy [online]. Geneva: World Health Organization, Available at: http://www.rbm.who.int/cmc_upload/0/000/015/369/RBMInfosheet_4.htm (Accessed 2012)

   World Health Organisation's statistics on malaria during pregnancy.

2. McGready, R. *et al.* Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. *Lancet Infect Dis* **12** 388-96(2012).doi:10.1016/S1473-3099(11)70339-5

   Research from SMRU showing there is no significant effect on miscarriage or congenital abnormality rates as a result of antimalarial use.

3. Rijken, M. J. *et al.* Ultrasound evidence of early fetal growth restriction after maternal malaria infection. *PLoS One* **7**, e31411 (2012). doi: 10.1371/journal.pone.0031411.

   Study showing the fetal head diameter is reduced after a single malarial infection.

4. McGready, R. & Nosten, F. The Thai-Burmese border: drug studies of Plasmodium falciparum in pregnancy. *Ann Trop Med Parasitol* **93 Suppl 1**, S19–23 (1999).

   Paper reporting on the safety and efficacy of various antimalarials in pregnancy.

5. McGready, R. *et al.* Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant Plasmodium falciparum. *Clin. Infect. Dis.* **33**, 2009–2016 (2001).

   Study showing ACTs are safe in pregnancy.

6. McGready, R. *et al.* A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated plasmodium falciparum treatment in pregnancy. *PLoS Med.* **5**, e253 (2008). doi: 10.1371/journal.pmed.0050253.

   SMRUs final pharmacokinetic trial showing the standard six-doze antimalarial treatment is safe in pregnant women with malaria.

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Details of the impact:

In 2007 there were an estimated 54.7 million pregnancies in areas with stable *P. falciparum* malaria, and a further 70.5 million in areas with low malaria transmission. With the increasing use of artemisinin combination treatments for malaria, the survival rates of those in affected areas have increased. As pregnant women are often excluded from drug treatment trials, however, (particularly trials of newer antimalarials) they have continued to receive ineffective treatment[7].

The prospective research conduced by the SMRU has had a significant impact on the health outcomes of pregnant women and infants in malaria affected areas, with findings leading to major changes in world health policy relating to malaria in pregnancy.

Policy/Guidelines:

Results from SMRU's epidemiological and pharmacokinetic studies, which provided evidence for the first time of the deleterious effect of malaria on early fetal growth, have led to a significant paradigm shift in clinical and world health policy. Although it was once considered acceptable for pregnant women with asymptomatic malaria to remain untreated, SMRU's research has shown that malaria must be prevented and treated as early as possible during pregnancy. This has led to changes in the World Health Organization malaria treatment guidelines in pregnancy[8], and the Green Top Guidelines on Prevention[9] and Treatment[10] of malaria in pregnancy.

SMRU recently provided much of the evidence for the Annual World Health Organization Meeting on treatment and prevention of malaria in pregnancy in the Asia Pacific Region in 2011[11]. Now collaborating with other investigators to promote treatment and pharmacokinetic studies in pregnancy in Africa[12] and Papua New Guinea[13], SMRU is also a partner in the Malaria in Pregnancy Consortium. The research team has produced 96 articles, book chapters and abstracts on the topic of maternal malaria.

Health:

Early detection and treatment of malaria in pregnancy has had clear benefits to Karen woman and the local community on the border of Thailand. This has been highlighted by the large reduction in malaria related maternal mortality (from 1,000 deaths per 100,000 in 1985 to zero in 2005)[14], an increased birth weight in local infants (from 2.7 to 3 kg), and the low prevalence of placental malaria related lesions. Due to SMRU's research, early detection and treatment is increasingly being recognised as an effective strategy to reduce the morbidity and mortality caused by malaria in areas of low transmission. On the Thai-Myanmar border the beneficiary population extends to the refugee and the migrant workers communities – circa 300,000 people. The deleterious effects of malaria (*P.falciparum* but also *P.vivax*) are also increasingly being recognised.

The change in pregnancy surveillance has also had a dramatic impact on mortality rates related to non-malaria febrile illness, including adverse fetal outcomes in those with rickettsial infection. This has also significantly improved health outcomes for mothers and infants in the border area[15].

Sources to corroborate the impact:

7. White, N. J., McGready, R. M. & Nosten, F. H. New medicines for tropical diseases in pregnancy: catch-22. *PLoS Med.* **5**, e133 (2008). doi: 10.1371/journal.pmed.0050133.

   Paper reporting ineffective ACT treatment in pregnant women.

8. World Malaria Report [online]. Geneva: World Health Organization, 2009 Available at: http://whqlibdoc.who.int/publications/2009/9789241563901_eng.pdf (Accessed 2012)

   WHO Malaria treatment guidelines for pregnant women.

9. Royal College of Obstetricians and Gynaecologists The prevention of malaria in pregnancy [online]. (54A RG-tg, ed.):,2010 Available at: http://www.rcog.org.uk/files/rcog-corp/GTG54aPreventionMalariaPregnancy0410.pdf (Accessed 2012)

   The RCOG Green-top Guidelines on the prevention of malaria in pregnancy.

10. Royal College of Obstetricians and Gynaecologists.The diagnosis and treatment of malaria in pregnancy [online]. (54B RG-tg, ed) 2010 : Available at: http://www.rcog.org.uk/files/rcog-corp/GTG54bDiagnosisTreatmentMalariaPregnancy0810.pdf (Accessed 2012)

    The RCOG Green-top Guidelines on the treatment of malaria in pregnancy.

11. Rijken, M. J. *et al.* Malaria in pregnancy in the Asia-Pacific region. *Lancet Infect Dis* **12**, 75–88 (2012). doi: 10.1016/S1473-3099(11)70315-2.

SMRUs report on the treatment and prevention of malaria in the Asia-Pacific region, presented at the Annual WHO Meeting 2012.

12. Piola, P. *et al.* Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated Plasmodium falciparum malaria: an open-label, randomised, non-inferiority trial. *Lancet Infect Dis* **10**, 762–769 (2010). doi: 10.1016/S1473-3099(10)70202-4.

Collaboration study into the efficacy and safety of antimalarials in pregnant women in Africa.

13. Poespoprodjo, J. R. *et al.* Adverse pregnancy outcomes in an area where multidrug-resistant plasmodium vivax and Plasmodium falciparum infections are endemic. *Clin. Infect. Dis.* **46**, 1374–1381 (2008). doi: 10.1086/586743.

Collaboration study into the efficacy and safety of antimalarials in pregnant women in Papua New Guinea.

14. McGready, R, M. *et al.* Effect of early detection and treatment on malaria related maternal mortality on the north-western border of Thailand 1986-2010. *PLoS One.* **7**, e40244 (2012). doi: 10.1371/journal.pone.0040244.

Report showing the large reduction in malaria related maternal mortality on the north-western border of Thailand between 1985 to 2005.

15. McGready, R. *et al.* Arthropod borne disease: the leading cause of fever in pregnancy on the Thai-Burmese border. *PLoS Negl Trop Dis* **4**, e888 (2010). doi: 10.1371/journal.pntd.0000888.

Report showing improved outcomes from mothers and infants on the Thai-Burmese border.