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Malaria in pregnancy

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During pregnancy, preservation of maternal health without compromise to the fetus can only be achieved through maternal immunomodulation. This is often accomplished without compromise of maternal immunity to infection, but one very notable exception is malaria.

Hippocrates recognized the deleterious effects of malaria in pregnancy. From his observations in fifth century BC Greece to clinical reports in Imperial Rome, and on through to the Renaissance, malaria and its effects in pregnancy were observed in marshy areas of southern Europe, France, Germany, lowland Europe, and apparently even England. During the 17th , 18th and 19th centuries, medical publications on malaria abound with authors' names that are of Italian and French origin. One of these was Lavarian, a French physician working in Algeria in 1878, who first noted the characteristic pigmentation in red blood cells in autopsy specimens and, two years later, the mobile parasite, which he described as *des filaments mobiles qui adhéraient aux corps pigmentés*.

His observation not only gave a face to the cause of the illness but naturally linked scientific medical enquiry to parasitological diagnosis and identification. So it was that after 2300 years of references in the literature, clinical case reports on malaria in pregnancy could finally be linked to microscopic identification and enumeration (density) of specific parasite species. The most clinically important of these proved to be *Plasmodium falciparum*.

From Lavarian's work in 1880 to the beginning of the second world war, scientific reports noted the effectiveness of the placental barrier, parasite sequestration in the placenta, the danger of suboptimal nutrition of the fetus, congenital malaria, poor fetal development, low birth weight, premature interruption of pregnancy, infant mortality, and maternal death. These effects were observed primarily in pregnant women living in areas of low endemicity, thus with little acquired immunity.

Towards the end of the nineteenth century British and South Asian names start appearing in the literature, reporting from the outposts of the British Empire. Medical doctors now working in tropical malarial conditions based their observations on larger numbers and recorded that susceptibility to clinical malaria decreased with parity. The phenomenon was noted in highly endemic areas where the woman would have acquired immunity to malaria by the time she reached reproductive age. Nevertheless, during her first pregnancy she had an increased risk of clinical malaria and severe infection. The risk then diminished with each subsequent pregnancy.

We do not know why this is so, although we observe it in highly malarious areas. It is possible that despite acquired immunity to other antigenically distinct parasite subpopulations, women lack immunity to a specific pathogen to which they are exposed during pregnancy, i.e. to the parasite subpopulation that sequesters in the placenta. With their first exposure as primigravidae they are most likely to develop chronic malaria and poor outcomes, and they acquire immunity over successive pregnancies.

Malaria-associated maternal mortality has been identified as 1% in low transmission areas, and between 84 and 2000 per 100 000 live births (0.00084%–2%) in Africa. Much of this risk is in primigravidae who are at risk of severe anaemia and low-birthweight babies. If the pregnant woman has human immunodeficiency virus (HIV) infection, she and her child are additionally compromised, as the prevalence of malaria and the density of parasites are greater in HIV seropositive than seronegative women. Seropositive women also acquire parity-specific immunity significantly more slowly than their seronegative counterparts. As a quarter of all pregnancies in tropical countries are primigravidae, and low birth weight is directly associated with risk of infant death, malaria in pregnancy is probably the most important preventable cause of infant death in these countries.

Drugs could play an important role in the management of disease and the prevention of malaria in a pregnant woman. However, most drugs are contraindicated in pregnancy, especially the first trimester, to avoid teratogenic effects. Higher doses of sulfonamides have specific toxicity in rats, pyrimethamine has dose-dependent fetal resorption and growth retardation, and high doses of mefloquine have been associated with soft tissue and skeletal anomalies. The relevance of these findings to humans where surveillance does not give similar frequencies of adverse effects is uncertain. Clinical trials have shown that prevention of malaria in pregnancy through complete chemoprophylaxis or intermittent treatment with an antimalarial reduces some of the deleterious consequences of malaria, including severe anaemia and (where it has been studied) low-birthweight babies.

As drug resistance to antimalarials increases, the options for treatment and prevention of malaria become fewer, particularly as newly registered drugs often exclude pregnant populations. Data on safety in pregnancy has therefore to be carefully acquired, and this is usually done where the mortality risk of not treating in pregnancy is high. It can be years before sufficient safety data is available to warrant widespread use of the drug in pregnancy, and in the meantime pregnant women with malaria can be deprived of treatment options available for others.

This makes their protection through insecticide-treated bednets (ITNs) particularly attractive as ITNs have now been shown to protect pregnant women from the negative consequences of malaria in areas of both low and (more recently) high malaria transmission. ITNs offer a cheap and less invasive alternative to drugs in protecting pregnant women, although we do not know what the combined effect of impregnated bednets and intermittent treatment might be.

Duffy & Fried's *Malaria in pregnancy* comes at a time when there are exciting new findings on the epidemiology and prevention of malaria in pregnancy in high transmission areas of Africa, and new scientific avenues for research in this important area for malaria control. It is therefore extremely useful to have a complete review of investigations to date covering the history, epidemiology, pathogenesis, treatment and prevention of malaria in pregnancy in one well-written volume. The work adds to the evidence and builds the case for controlling malaria in pregnancy, showing how there is no excuse for any further delay in doing so. ■

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