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REVIEW ARTICLE

A systematic review of the impact of malaria prevention in pregnancy on low birth weight and maternal anemia

Elizabeth M. McClure [a,b,*], Robert L. Goldenberg [c], Arlene E. Dent [d], Steven R. Meshnick [a]

[a] Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, USA
[b] Research Triangle Institute, Durham, USA
[c] Columbia University, NY, USA
[d] Center for Global Health and Diseases, Case Western Reserve University, Cleveland, USA

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ABSTRACT

Background: Malaria in pregnancy is a significant contributor to adverse pregnancy outcome, especially in Sub-Saharan Africa. Prevention with sulfadoxine/pyrimethamine (SP) during pregnancy has been recommended in malaria-endemic areas but concerns remain about its benefit. *Objectives:* To evaluate the association between recommended preventative SP programs in pregnancy and low birth weight (LBW) and maternal anemia through available clinical trial, observational, and programmatic evaluation studies. *Search strategy:* Systematic review of published studies on malaria in pregnancy and pregnancy outcomes. *Selection criteria:* Clinical studies from Sub-Saharan Africa from the past 10 years were included. *Data collection and analysis:* English articles published since 2002 and listed in PubMed were identified using defined keywords, and their source documents were reviewed. Thirty-three studies involving malaria in pregnancy that recorded treatment rates and birth outcomes were included. *Main results:* SP use among primigravidae was consistently associated with decreased LBW and anemia rates in clinical trials. Effects were less consistent in observational studies. *Conclusions:* Although randomized trials have demonstrated the efficacy of SP, studies evaluating scale-up programs found less consistent reductions in LBW and maternal anemia. Additional strategies to improve SP coverage may reduce the LBW and maternal anemia associated with malaria in pregnancy.

1. Introduction

Malaria in pregnancy is an important public health problem that affects more than 25 million pregnant women who give birth in malaria-endemic areas each year, as well as many others who deliver in areas of low malaria transmission [1]. Although those living in endemic areas generally develop immunity to malaria, pregnancy is a period of increased vulnerability. Beginning in the late 1960s, published studies described lower birth weights among women who were infected with malaria during pregnancy. Adverse outcomes associated with malaria for both mother and newborn include maternal anemia, stillbirth, preterm birth, and low birth weight (LBW). Of these outcomes, maternal anemia and LBW are the most commonly documented serious effects associated with malaria in pregnancy [1]. Eisele et al. [2] estimated that malaria infection was responsible for up to 14% of all LBW infants worldwide and 11% of LBW-related infant mortality in Sub-Saharan Africa—probably the single largest cause of adverse newborn outcomes in this region. Similarly, malaria is an important contributor to maternal anemia, which is associated with significant maternal morbidity and mortality in Sub-Saharan Africa.

Because of the adverse outcomes associated with malaria in pregnancy, several strategies to reduce malaria have been studied [2–4]. A 2006 Cochrane review of 16 trials evaluating antimalarial treatment concluded that the administration of antimalarials to all pregnant women significantly reduced prenatal parasitemia compared with no treatment (relative risk [RR] 0.53; 95% confidence interval [CI], 0.33–0.86) [4]. Numerous antimalarial treatments have been tested; for example, the Cochrane review included trials of proguanil, chloroquine, and sulfadoxine/pyrimethamine (SP). However, for low-resource settings, where the highest burden of malaria remains, treatment ideally needs to be low-cost and effective with limited dosing, and to have a good safety profile. In particular, the relatively low-cost SP had promising results in clinical trials [5]. In 2004, WHO recommended intermittent preventive treatment for pregnant women with 2 doses of SP (IPTp-SP) administered at least 1 month apart beginning in the second trimester (3 doses for women with HIV) as standard care in malaria-endemic areas [5]. With the increased availability of SP and the 2004 WHO endorsement, many countries in Sub-Saharan Africa implemented IPTp-SP programs [3].

* Corresponding author at: Research Triangle Institute, 3040 Cornwallis Road, Durham, NC 27709, USA. Tel.: +1 919 316 3773; fax: +1 919 541 6416.
E-mail address: mcclure@rti.org (E.M. McClure).

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However, there are potential limitations to IPTp-SP. First, adherence is often suboptimal. Second, geographic areas of SP resistance, which is becoming increasingly common, were found to be associated with reduced effectiveness [6–8]. Third, there may be a differential impact based on other risk factors; most notably, primigravidae, who are at higher risk in general, also have a higher risk of adverse birth outcomes associated with malaria [1,2]. Fourth, the interactions of malaria with other common infections such as HIV are important—especially in Sub-Saharan Africa, where HIV remains prevalent and optimal treatment has not been determined [9]. Fifth, there are different ways to measure malaria during pregnancy, including peripheral or placental blood smears, polymerase chain reaction (PCR), and placental histopathology; these measures are often not concordant [1].

Since the WHO guidelines were issued, a number of studies have evaluated the impact of intervention programs (IPTp-SP and/or insecticide-treated nets [ITNs]) on birth weight and other pregnancy outcomes. Given these efforts, the aim of the present article was to review recent studies evaluating the impact of IPTp-SP, with emphasis on birth weight and anemia, to determine the effectiveness of SP to reduce adverse outcomes associated with malaria in pregnancy and factors influencing these outcomes.

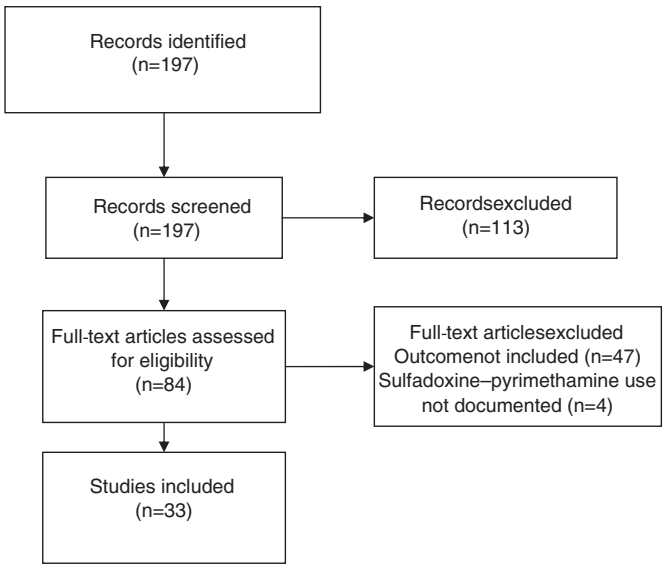

Fig. 1. Published studies identified.

2. Materials and methods

A systematic review of malaria in pregnancy and pregnancy outcomes in Sub-Saharan Africa was undertaken, with emphasis on recent studies of peripheral or placental malaria, antimalarial treatments (IPTp-SP and/or ITNs), and outcomes of birth weight and maternal anemia. English literature in PubMed, WHO publications, and the Cochrane database published since 2002 and relevant source publications were reviewed. Search terms included "malaria in pregnancy," "sulfadoxine-pyrimethamine," "insecticide-treated bed nets," "anemia," and "birth weight." Studies conducted in Sub-Saharan Africa that included rates of LBW, maternal anemia, and maternal malaria infection were included; studies that did not quantify birth outcomes associated with the intervention or that did not quantify the treatment were excluded.

3. Results

Of the 197 papers screened, 84 studies were reviewed in-depth and 33 were included in the present review. Of these, 18 were observational studies, including cohort studies, and 15 were randomized clinical trials (Fig. 1). The randomized clinical trials generally compared standard SP dosing (2 doses, as recommended by the 2004 WHO guidelines) with a number of different strategies: placebo; other antimalarials (chloroquine, mefloquine); and alternate SP-dosing strategies. Five trials also evaluated the impact of ITNs. Across both trials and observational studies, the primary outcomes evaluated were rates of placental malaria, LBW (defined as <2500 g), and maternal anemia, with several studies also examining preterm birth and perinatal mortality.

Table 1 summarizes the randomized clinical trials of SP published since 2004 [8–22]. The rates of ITN use and peripheral malaria at enrollment are included for trials that reported these data. Next, the outcomes associated with 2 doses of SP (IPTp-SP) versus an alternate SP regime or treatment are given. At enrollment, the rate of untreated bed net use was approximately 50%, while rates of ITN use were significantly lower (5%–25%). The rates of malaria at baseline ranged from 7% to 58%. Next, the outcomes associated with the treatment are reported. The placental malaria rates among those treated with IPTp-SP ranged from 2% to 29%. Higher dosing strategies (≥3 doses) showed lower rates of placental malaria infection, ranging from 2% to 8%. The alternate drug treatment groups (chloroquine, mefloquine) generally had similar rates of placental infection to those receiving IPTp-SP, while the placebo groups had significantly higher rates of infection. A similar relationship existed for LBW rates, which ranged from 2% to 13%, with reductions in LBW prevalence in the IPTp-SP group equivalent to the reductions associated with alternate drug treatments. Women who received more than 2 SP doses had decreased risk of LBW outcome. For example, Maiga et al. [19] found that LBW rates in Mali were significantly lower with 3 versus 2 doses of SP (adjusted RR 0.5; 95% CI, 0.32–0.79). A study from Côte d'Ivoire also found that a third dose decreased risk for LBW (adjusted odds ratio [OR] 0.12, 95% CI, 0.05–0.31) [8]. Among HIV-positive women, monthly SP dosing was superior to 2 doses in the trial reported by Filler et al. [17] and there was a non-significant trend for better outcome with monthly doses compared with 2 doses in the trial reported by Hamer et al. [9]. Finally, maternal anemia rates ranged from 2% to approximately 30%; these differences in part reflected different hemoglobin levels defining moderate–severe anemia, but in general within each study the SP-treated group had lower anemia rates than the alternate treatment or placebo group.

Several common findings were reported in the randomized trials. Timing of infection was related to risk of adverse outcomes in several studies. For example, a Burkina Faso cohort study evaluated outcomes by gestational age at infection and found a trend for decreased birth weight among women infected at less than 4 months of gestation and/or more than 6 months (mean birth weight decreased by 68 g [$P=0.08$] and 105 g [$P=0.02$], respectively) [13]. A cohort study of women in Malawi [18] found that LBW risk was higher among women with second-trimester infection (prevalence ratio [PR] 1.7; 95% CI, 1.1–2.7) than among those with third-trimester infection (PR 1.5; 95% CI, 0.9–2.7). The risk for first-trimester infection was not evaluated [18]. Primigravidae treated with IPTp-SP were consistently more likely to have decreased risk for LBW compared with multigravidae. For example, in a Burkina Faso study, IPTp-SP use was associated with reduced risk of LBW among primigravidae (adjusted OR 0.11; 95% CI, 0.07–0.17) but not secundigravidae [12]. Finally, ITNs had an interactive effect with SP treatment in decreasing the risk of adverse outcomes in some, but not all, trials that examined their impact together with SP treatment [14,16].

Next, the non-randomized studies of IPTp-SP treatment were reviewed [7,23–40] (Table 2). These studies included cohort, cross-sectional, and pre–post studies that evaluated the impact of IPTp-SP scale-up on rates of malaria in pregnancy, birth weight, and maternal anemia. In general, they found IPTp-SP use to be associated with reduced malaria rates in pregnancy. However, the impact of IPTp-SP on LBW and maternal anemia rates varied. Feng et al. [30] conducted

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