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Effectiveness of Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine During Pregnancy on Maternal and Birth Outcomes in Machinga District, Malawi

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Abstract

Background—Malaria during pregnancy is associated with low birth weight and increased perinatal mortality, especially among primigravidae. Despite increasing prevalence of malarial parasite resistance to sulfadoxine-pyrimethamine (SP), SP continues to be recommended for intermittent preventive treatment in pregnancy (IPTp).

Methods—Women without human immunodeficiency virus infection were enrolled upon delivery. Data on the number of SP doses received during pregnancy were recorded. The primary outcome was placental infection demonstrated by histologic analysis. Secondary outcomes included malaria parasitemia (in peripheral, placental, cord blood specimens) at delivery and composite birth outcome (small for gestational age, preterm delivery, or low birth weight).

Results—Of 703 women enrolled, 22% received <2 SP doses. Receipt of ≥2 SP doses had no impact on histologically confirmed placental infection. IPTp-SP was associated with a dose-dependent protective effect on composite birth outcome in primigravidae, with an adjusted prevalence ratio of 0.50 (95% confidence interval [CI], .30–.82), 0.30 (95% CI, .19–.48), and 0.18 (95% CI, .05–.61) for 1, 2, and ≥3 doses, respectively, compared with 0 doses.

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Conclusions—IPTp-SP did not reduce the frequency of placental infection but was associated with improved birth outcomes. Few women received no SP, so the true effect of IPTp-SP may be underestimated. Malawian pregnant women should continue to receive IPTp-SP, but alternative strategies and antimalarials for preventing malaria during pregnancy should be investigated.

Keywords

malaria; pregnancy; intermittent preventive treatment; sulfadoxine-pyrimethamine; Malawi

Malaria in pregnancy is a major, preventable cause of maternal morbidity, mortality, and poor birth outcomes in sub-Saharan Africa [1, 2]. Pregnant women are at increased risk of more frequent and severe malaria, compared with nonpregnant women [3–5]. Pregnancy-specific immunity develops during the first pregnancy; thus, women are at reduced risk of malarial parasite infection during subsequent pregnancies [2].

Intermittent preventive treatment during pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) is currently recommended for human immunodeficiency virus (HIV)–uninfected women in all areas with stable moderate-to-high malaria transmission [6]. IPTp-SP remains effective at reducing the negative consequences of malarial parasite infection in pregnancy, even when the treatment failure rate by day 14 among children is as high as 39%, likely because of the effect of the woman's preexisting immunity [7]. However, the increasing prevalence of SP resistance, particularly in East and Southern Africa, has raised concerns about the continued efficacy of IPTp-SP [8, 9], and some data from Tanzania suggest that the use of IPTp-SP might even be harmful [10]. These concerns have led to a suggestion that the use of IPTp-SP should be discontinued in East Africa [11].

Studies evaluating alternative drugs for IPTp and new strategies, such as intermittent screening and treatment, are underway in a number of countries. However, it will be several years before there is sufficient evidence to recommend a policy change. Therefore, it is crucial that, in the interim, we continue to monitor the effectiveness of IPTp-SP. This cross-sectional delivery survey in Malawi was undertaken as part of a group of studies in 6 countries aimed at assessing the current effectiveness of IPTp-SP.

METHODS

Study Site

The study was conducted in the delivery ward of Machinga District Hospital, in the Southern Region of Malawi, between March and August 2010. Residents in Machinga are mainly of the Yao ethnic group, who earn their living through subsistence farming, fishing, and small businesses. Machinga District Hospital is the primary hospital for a catchment area including 369 614 people, with approximately 5712 child births per year. In 2011, there were 57 999 clinically diagnosed malaria cases, of which 29 626 (51%) involved people aged ≥5 years [12]. Transmission of malaria in the district is stable throughout the year, with a peak in the rainy season, from December to March. Parasite prevalence was 42.3% among children <5 years old in the Southern Region in the most recent malaria indicator survey

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[13]. The vast majority of malarial parasite infections are caused by *Plasmodium falciparum*.

Sample Size

To detect a 6% difference in prevalence of placental malaria by histopathologic analysis among women who received <2 SP doses, compared with those who received ≥2 doses, with a 95% confidence level and 80% power, on the assumption of a baseline prevalence of 26% among women who received <2 doses and that 60% of enrolled women would have received ≥2 SP doses, 635 pregnant women would have to be enrolled. To account for losses due to compromised specimen quality, 710 women were recruited.

Enrollment and Study Procedures

Consenting women who met the study inclusion criteria (singleton pregnancy, IPTp-SP history available, documented HIV negative) were enrolled at the time of delivery. During March–May, enrollment occurred from 8:30 AM to 4:30 PM Monday through Friday, whereas during June–August, enrollment occurred from 7:30 AM Monday through 12:00 PM on Friday. Participant antenatal care cards were examined to obtain information on the number and timing of IPTp-SP doses taken during pregnancy; other antenatal medications received, including iron and folate supplementation; and results of HIV and syphilis tests.

Full thickness placental biopsy specimens were obtained from a healthy pericentric area and placed into 10% neutral buffered formalin at delivery [14]. Biopsy samples were stored at room temperature until processing and were embedded in paraffin wax by standard techniques. Paraffin sections were stained with hematoxylin-eosin. Placental tissue samples were examined for parasites and pigment, using the 5-point scale described by Rogerson et al [15].

A maternal finger stick or venipuncture blood sample was collected before delivery for peripheral smear and hemoglobin measurement, using Hemocue Hb 201+ Analyzer (Hemocue, Cypress, CA). Maternal anemia was defined as a hemoglobin level of <11 g/dL [16]. At delivery, placental blood and tissue samples and a cord blood sample were obtained, and infant birth weight was measured. Blood smears were stained with Field's stain A and B (azure dye and eosin). Parasite densities were calculated by counting the number of asexual stage parasites per 200 white blood cells (WBCs), on the assumption of 8000 WBCs/dL of blood. Blood smears were considered negative if no parasites were found after counting 1000 fields. All smears were examined at study laboratory facilities in Machinga District Hospital. All slides were read by 2 independent microscopists blinded to each other's results. In case of discordant findings, a third reader was used.

Low birth weight (LBW) was defined as a birth weight <2500 g. Gestational age was assessed by Ballard examination within 24 hours of delivery, by trained study nurses. The Ballard score was used to define preterm delivery (gestational age, <37 weeks) and to determine whether the infant was small for gestational age (SGA), using the normogram defined by Landis et al [17]. The composite birth outcome was defined as SGA, LBW, or preterm delivery.

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Twenty tablets of SP were taken from the study facility and sent for drug quality testing in Dr. Michael Green's laboratory at the Center for Disease Control and Prevention, using the standard method detailed in the United States Pharmacopeia monograph for content (using high-performance liquid chromatography) and dissolution [18]. These tablets were noted to contain an adequate amount of both sulfadoxine and pyrimethamine, and dissolution was acceptable.

Statistical Analysis

Our primary outcome was any evidence of placental infection revealed by placental histologic analysis. Our secondary outcomes included maternal anemia; maternal, placental, and cord blood parasitemia; and birth outcomes, including SGA, LBW, and preterm delivery. A composite birth outcome included any of SGA, LBW or preterm delivery.

Statistical analysis was done using SAS, version 9.3 (SAS Institute, Cary, NC). Comparisons between groups were made using the χ^2 test or Fisher exact test, for categorical variables, and the Student *t* test or Wilcoxon rank sum test, for continuous variables. A 2-sided *P* value of < .05 was considered statistically significant. Clopper-Pearson confidence intervals (CIs) were computed for prevalence rates of outcomes stratified by gravidity [19].

Prevalence ratios (PRs) and 95% CIs were calculated using a Poisson regression model with robust standard errors. All outcomes of interest were modeled; however, only the results from the primary outcome (placental infection), the composite birth outcome, and LBW are presented. The composite birth outcome was chosen as the best measure of fetal morbidity because it combines several adverse outcomes, allowing detection of a clinical difference with a smaller sample size than if individual outcomes were used [20, 21]. Predictors in multivariable models were selected on the basis of prior reports in the literature, model fit statistics, and recommendations on the number of outcome events per predictor [22, 23]. Models included number of SP doses, maternal age (dichotomized as ≤25 vs >25 years), gravidity (secundigravidae were grouped with multigravidae on the basis of results of bivariate analysis), insecticide-treated net (ITN) use (used last night or not), and month of delivery [24]. Number of years of schooling, wealth status (perceived wealth status [25] or wealth status determined by principal component analysis), and other antimalarial use in pregnancy were not found to increase model fit for any of the outcomes and were not included in the final models. The number of SP doses was categorized in 3 ways. Because of the small number of women who received 0 SP doses, for most analyses women were categorized as having received either <2 or ≥2 doses. For the primary outcome and secondary outcomes in which an effect of SP was seen (ie, composite birth outcome and LBW), the dose-response effect was explored by modeling the number of SP doses as both an unordered categorical variable (0, 1, 2, or ≥3 doses), to allow maximum flexibility, as well as a continuous variable, to show trend *P* values. The interaction between number of SP doses and gravidity was included in all models in which the number of SP doses was dichotomized because we found a significant interaction between gravidity and number of SP doses for some outcomes. Because of this interaction, we present our bivariate analyses stratified by gravidity. We were unable to include this interaction term in the models looking

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at number of SP doses as a categorical variable with 4 levels (0, 1, 2, and ≥3) because the models did not converge when the interaction term was included. When possible, we stratified these analyses by gravidity, by restricting the analysis to primigravidae or multigravidae. A separate model was run to explore the effect of the timing of the final dose of SP. This analysis was restricted to women who received 2 SP doses so that the effect of number of doses would not confound the effect of the timing of the second dose. Receipt of the final dose of SP >30 days prior to delivery was defined as early, while receipt of SP within 30 days of delivery was defined as late.

Ethics

The study was approved by the ethical review boards of the University of Malawi College of Medicine (Blantyre, Malawi) and the Centers for Disease Control and Prevention (Atlanta, GA). Written informed consent was obtained from all participating women.

RESULTS

Maternal Characteristics

A total of 710 women were enrolled out of 2524 total deliveries during the study period. Seven women were excluded from the analysis because the dates of SP receipt were invalid: 14 (2%) received 0 SP doses, 140 (20%) received 1 dose, 524 (75%) received 2 doses, 24 (3%) received 3 doses, and 1 (0.1%) received 4 doses. Overall, 33% of enrolled women were primigravid, 9% were secundigravid, and 58% were multigravid (Table 1). Approximately one-third of women reported sleeping under an ITN the previous night. All women reported having received iron and folate supplementation during pregnancy. In addition, 26 women had been treated with artemether-lumefantrine, 2 with quinine, and 12 with cotrimoxazole.

Maternal Outcomes

Overall, 32% of women had histopathologic evidence of placental infection with malaria parasites, with the majority of these events classified as past infection (Table 2). The prevalence of placental infection dropped with increasing gravidity, with a prevalence of 62% in primigravidae, 26% in secundigravidae, and 16% in multigravidae. The number of SP doses was not associated with placental infection in analyses stratified and unstratified by gravidity (Figure 1). Interestingly, unstratified analysis but not stratified analysis revealed that women who received ≥2 SP doses were significantly more likely to have maternal parasitemia (Table 2). When we examined the effect of the number of SP doses stratified by gravidity, no statistically significant differences were seen. Notably, receipt of ≥2 doses of IPTp-SP did not significantly affect the prevalence of active, past, or chronic placental infection; positive findings of a maternal peripheral blood smear; or anemia (Table 3).

As expected, multigravidae (G2+) had lower rates of placental infection detected by histologic analysis (17% vs 62%; $P < .0001$) and impression smear (4% vs 8%; $P = .02$), as well as a lower prevalence of parasitemia on a peripheral smear (3% vs 10%; $P = .0001$), compared with primigravidae. In addition, multigravidae had a significantly higher mean hemoglobin level than primigravidae (11.2 mg/dL vs 10.7 mg/dL; $P = .002$).

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In multivariable modeling, receipt of ≥2 vs <2 SP doses was not significantly associated with placental infection among either primigravidae or multigravidae (Table 4). Increased gravidity and older maternal age were both associated with a decreased risk of placental infection.

Infant Outcomes

Multigravidae had significantly lower rates of the composite birth outcome (20% vs 30%; *P* = .003) and delivered fewer SGA infants (20% vs 30%; *P* = .005) than primigravidae, and their infants had a higher mean birth weight (3293 g vs 3154 g; *P* < .0001) than those of primigravidae.

In unstratified analysis, we found a significant reduction in LBW infants among mothers who received ≥2 doses of SP (Table 2); in stratified analysis, this association was significant only among multigravidae (Table 3). Among primigravidae, receipt of ≥2 doses of SP was associated with a significant reduction in SGA and the composite birth outcome (Table 3 and Figure 1) and with a 134-g increase in mean birth weight, which approached statistical significance (*P* = .05).

In multivariable modeling, receipt of ≥2 SP doses was significantly associated with a reduction in the composite birth outcome among primigravidae (Table 5). This was driven primarily by the protective effect of SP against SGA (adjusted PR, 0.55 [95% CI, .37–.81] among primigravidae; *P* = .003). There was no significant protective effect of IPTp-SP in multigravidae. Use of an ITN was associated with a decreased risk of the composite birth outcome. Receipt of ≥2 SP doses was associated with a reduction in LBW infants among both primigravidae (adjusted PR, 0.67; 95% CI, .14–3.16) and multigravidae (adjusted PR, 0.20; 95% CI, .06–.64), although this was statistically significant among multigravidae only. SP was not associated with protection from preterm delivery; stratification by gravidity was not possible because of the small number of events (only 4 preterm infants were identified).

Dose-Dependent Effects of SP

Modeling the number of SP doses as a categorical variable, we noted a nonsignificant but dose-dependent association between placental infection and number of SP doses (Table 6). The effect of IPTp-SP on the composite birth outcome seen in primigravidae was dose dependent, with an adjusted PR of 0.50 (95% CI, .30–.82), 0.30 (95% CI, .19–.48), and 0.18 (95% CI, .05–.61) for 1, 2, and ≥3 doses, respectively, compared with 0 doses (Table 6), when the number of SP doses was modeled as a categorical variable. If SP dose number is modeled as a continuous variable, the same pattern is seen. The adjusted PR was 0.60 per SP dose (95% CI, .46–.77; *P* ≤ .0001) among primigravidae and 0.91 per SP dose (95% CI, .66–1.26; *P* = .57) among multigravidae. We were unable to model the effect of number of SP doses as a categorical variable on the risk of LBW because none of the women who received ≥3 SP doses delivered an infant with LBW.

Timing of SP Doses

In a model among women who received 2 SP doses, adjusted for gravidity, age, ITN use last night, and month of delivery, we did not find a significant effect of the timing of the final

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dose of SP on the prevalence of placental infection detected by histopathologic analysis (adjusted PR, 1.01; 95% CI, .77–1.33; *P* = .94). Receipt of both doses of SP >30 days prior to delivery was associated with a nonsignificant increase in the prevalence of maternal peripheral parasitemia (adjusted PR, 1.96; 95% CI, .73–5.35; *P* = .18), positive findings on a placental impression smear (adjusted PR, 1.91; 95% CI, .67–5.49; *P* = .23), and active placental infection detected by histopathologic analysis (adjusted PR, 4.86; 95% CI, .68–34.64; *P* = .11). However, receipt of both doses of SP >30 days before delivery was associated with a significant protective effect on the composite birth outcome (adjusted PR, 0.56; 95% CI, .40–.78; *P* = .0006). This was driven by a protective effect of early dosing of SP on SGA (adjusted PR, 0.58; 95% CI, .41–.81; *P* = .001) and a trend toward protection from LBW(adjusted PR, 0.32; 95% CI, .10–1.04; *P* = .06).

DISCUSSION

Despite concerns that IPTp-SP no longer provides benefit to mothers in areas of East Africa with high rates of SP resistance [11], we show a continued benefit of providing IPTp-SP to both primigravid and multigravid Malawian women. Although we did not find a significant reduction in the prevalence of placental infection, we document a dose-dependent decrease in the frequency of the composite birth outcome and increased mean birth weight among primigravidae and a reduction in LBW among multigravidae. Importantly, there was no evidence of harm associated with receipt of IPTp-SP. This is reassuring, given that Malawi has some of the highest rates of SP resistance documented, with fixation of the quintuple mutant profile (mutations at dhfr codons 51, 59, and 108 and dhps codons 437 and 540) most highly associated with clinical failure of SP in clinical efficacy studies [26–28]. Unlike other studies of IPTp-SP in settings with high rates of SP resistance, which suggested the absence of effectiveness or even the presence of harm from IPTp-SP, we demonstrated that IPTp-SP was beneficial in a setting with high rates of SP resistance [10].

The primary goal of administering IPTp-SP is to prevent poor maternal and birth outcomes. As the occurrence of adverse birth outcomes is rare, requiring large sample size to demonstrate an effect, researchers sought a surrogate outcome. Placental infection seemed to be the logical choice because this measures infections occurring throughout pregnancy. Initial studies of IPTp demonstrated a clear reduction in placental parasitemia following receipt of SP [16, 29, 30]; however, we failed to show a significant effect of SP on any of the maternal outcomes, despite demonstrating an improvement in infant outcomes. Because the majority of the placental infections were past infections, the lack of effect of SP may reflect that women were infected before receipt of their first dose of SP or during the intervals between doses. Because the majority of women received 2 SP doses, even if SP provided a prophylactic effect for 4–6 weeks after exposure, a woman would be at risk of malarial parasite infection during most of her 40-week pregnancy. The SP doses might have helped to clear the placental infection and provide a prophylactic effect resulting in fewer infections, even if not all infections could be prevented. Our data suggest that placental histologic analysis might not be a good measure of IPTp effectiveness.

A recent study from Mali showed that adding a third dose of SP resulted in a significant reduction in peripheral parasitemia and LBW infants delivered by women of all gravidities

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[31]. A similar trend was seen in data collected in Malawi during 2002–2005 among women who switched from a 2-dose regimen to a monthly dosing regimen (median of 5 doses) [32]. Another study from Malawi, which looked at polymerase chain reaction– confirmed peripheral parasitemia at delivery, showed a significant benefit of switching from a 2-dose regimen to a monthly SP regimen (risk ratio, 0.33; 95% CI, .17–.64; $P < .001$) [33]. Data from a meta-analysis suggest that ≥3 doses of IPTp-SP confer an additional benefit, compared with 2 doses, even in areas where there is fixation of the quintuple mutant to SP [34]. Although our study was not undertaken to assess the effect of 2 vs ≥3 doses and our 3-dose group was small, the modeling data suggest that increasing the number of doses confers additional protection. It is thought that IPTp-SP works largely through a prophylactic effect [7]. SP resistance increases the minimum inhibitory concentration, leading to a shorter duration of prophylaxis. Therefore, one would expect that, under conditions of resistance, more doses would be required to achieve the same benefit seen with only 2 doses in areas without resistance. Our data on the timing of SP doses suggest that, whereas earlier dosing has a greater influence on birth outcomes, later dosing provides continued protection against infection, supporting the idea that more doses would be beneficial.

Malawi's 2-dose IPTp-SP policy was implemented in 1993. However, in the 2010 Demographic and Health Survey (DHS) [35], only 55% of women received 2 doses of IPTp-SP. Although this is far better coverage than in many other countries in sub-Saharan Africa [36], it still falls far short of the Roll Back Malaria target of 100% coverage [37]. Ninety-five percent of women in the 2010 DHS reported attending at least 2 antenatal care visits, and 46% of women reported attending antenatal care ≥4 times during their last pregnancy. This highlights the many missed opportunities when IPTp-SP could have been provided. Modifying the policy in Malawi to provide IPTp-SP at each visit, starting in the second trimester, as recommended by the World Health Organization, might improve coverage of 2 doses and would be programmatically simpler than the current policy [38].

These data highlight the importance of ensuring that pregnant women, especially young, primigravidae who are at highest risk for malaria and its adverse outcomes, are targeted for malaria prevention. Early attendance at antenatal care visits should be encouraged, both to ensure that pregnant women receive sufficient doses of IPTp-SP, but also to allow for optimal delivery of other antenatal care services, such as HIV and syphilis testing, provision of iron and folate supplementation, and distribution of ITNs. Because IPTp-SP can only be given starting in the second trimester, it is imperative that pregnant women sleep under an ITN from the beginning of pregnancy and, ideally, even before they become pregnant.

This study has some limitations. These data were collected from a cross-sectional delivery survey. Although we have attempted to correct for potential confounders by using appropriate statistical methods, as in any observational study, unanticipated and unmeasured confounders may still have affected our observations. Because of the study design, we were unable to collect data on early adverse pregnancy outcomes, such as miscarriages or abortions, potentially underestimating the effect of SP. In addition, it is possible that not all of the SP taken by women was of high quality, although it is reassuring that a sample of SP obtained from the health facility for quality testing at the Centers for Disease Control and

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Prevention demonstrated high quality in terms of both content of active ingredients and dissolution.

In conclusion, as SP resistance increases, it is likely that the small benefit of IPTp-SP will continue to decrease; therefore, it is prudent to explore new drugs for prevention. However, until additional data on these new drugs and strategies are available, IPTp-SP should continue to be provided to pregnant Malawian women, and ideally, women should receive more than the currently recommended minimum of 2 doses.

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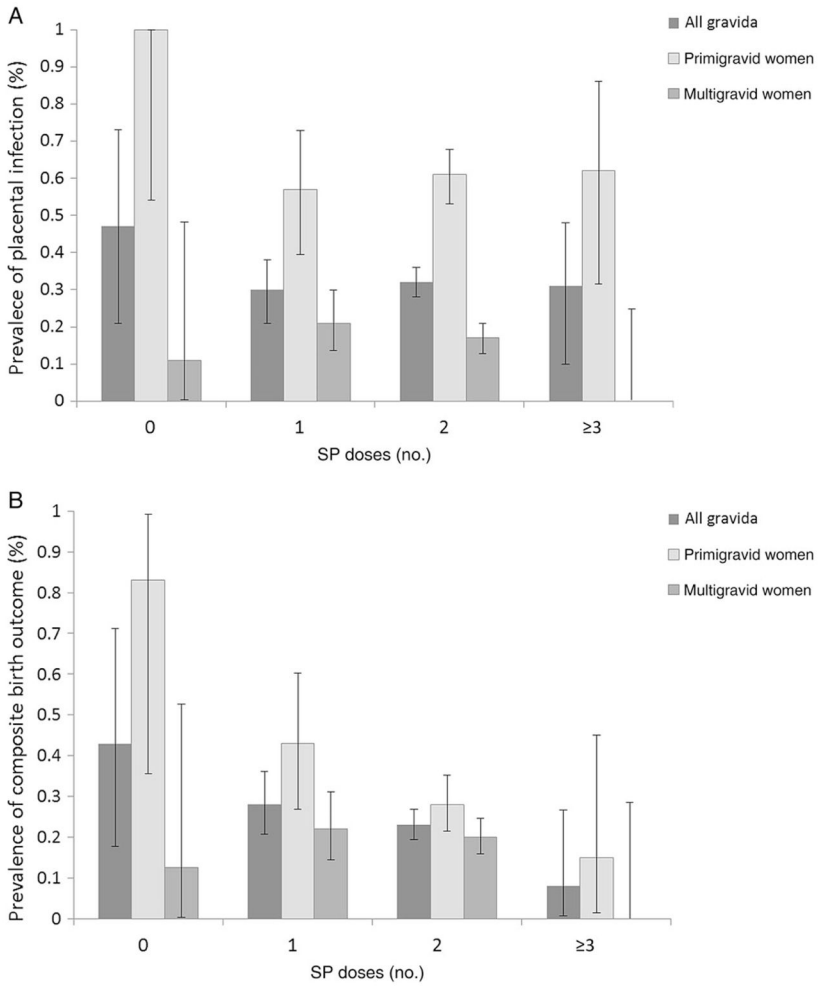

Figure 1.

Prevalence of maternal and infant outcomes stratified by gravidity. *A*, The prevalence of any histologically confirmed placental infection was lower among women who received intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP) than among those who did not. However, this difference was not statistically significant. No significant dose response effect was seen with increasing number of SP doses. Confidence intervals (whiskers) were calculated using the Clopper-Pearson method. *B*, The prevalence of the composite birth outcome (preterm delivery, low birth weight, and/or small for gestational age) was lower among women who received IPTp-SP than among those who did not. This was statistically significant among women of all gravidity, for comparison of ≥3 doses to 0 doses, and among primigravid women, for comparisons of 1, 2, and ≥3 doses to 0 doses, with a dose response seen for increasing number of doses. Confidence intervals were calculated using the Clopper-Pearson method.

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Table 1

Baseline Characteristics of Enrolled Women

Variable	No. of SP Doses			P[a]
	0–1 (n = 154)	≥2 (n = 549)	Any (n = 703)	
IPTp doses, no.	0.9 ± 0.3	2.0 ± 0.2	1.7 ± 0.5	<.001
Maternal age, y	24.4 ± 6.5	24.0 ± 6.0	24.1 ± 6.1	.47
Gravidity				
Primi	42 (27)	190 (35)	232 (33)	.09
Secundi	20 (13)	46 (8)	66 (9)	
Multi	92 (60)	313 (57)	405 (58)	
ITN use last night	34 (22)	219 (40)	253 (36)	<.001
School level				
None	37 (24)	121 (22)	158 (22)	.23
Some primary	105 (68)	358 (65)	463 (66)	
Some secondary	12 (8)	70 (13)	82 (12)	
Wealth status				
Below average	117 (76)	393 (71)	510 (72)	.11
Average	35 (23)	128 (23)	163 (23)	
Above average	2 (1)	28 (5)	30 (4)	
Floor material, earth/sand	130 (84)	418 (76)	548 (78)	.15
Roof material, thatch/grass	119 (77)	400 (73)	519 (74)	.60

Data are no. (%) of women or mean ± SD.

Abbreviations: IPTp, intermittent preventive treatment during pregnancy; ITN, insecticide-treated net; SP, sulfadoxine-pyrimethamine.

[a] Calculated by the χ^2 test or Fisher exact test, for categorical variables, and the Student *t* test or Wilcoxon rank sum test, for continuous variables.

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Table 2

Maternal and Infant Outcomes, by Number of Sulfadoxine-Pyrimethamine (SP) Doses

Outcome	No. of SP Doses			P[a]
	Any (n = 703)	0–1 (n = 154)	≥2 (n = 549)	
Placental infection[b]				
Any	31.8 (28.3–35.3)	31.8 (24.6–39.8)	31.7 (27.8–35.8)	>.999
Active	4.4 (3.0–6.2)	6.5 (3.2–11.6)	3.8 (2.4–5.8)	.18
Chronic	4.3 (2.9–6.0)	4.5 (1.8–9.1)	4.2 (2.7–6.2)	.82
Past	23.0 (20.0–26.3)	20.8 (14.7–28.0)	23.7 (20.2–27.5)	.52
Smear positivity, by blood source				
Peripheral	5.3 (3.7–7.2)	1.9 (.4–5.6)	6.2 (4.3–8.5)	.04
Placenta	5.4 (3.8–7.3)	3.9 (1.4–8.3)	5.8 (4.0–8.1)	.42
Cord	0.9 (.3–1.8)	100.0 (97.6–100.0)	1.1 (.4–2.4)	.35
Maternal Hb level, g/dL, mean (95% CI)	11.0 (10.9–11.2)	11.0 (10.7–11.3)	11.0 (10.9–11.2)	.69
Maternal anemia[c]	45.0 (41.3–48.8)	46.1 (38.1–54.3)	44.7 (40.5–49.0)	.78
Severe maternal anemia[d]	6.0 (4.3–8.0)	8.4 (4.6–14.0)	5.3 (3.6–7.5)	.18
Secondary outcome[e]				
Composite[f,g]	23.4 (20.3–26.8)	28.8 (21.7–36.6)	21.9 (18.5–25.7)	.08
SGA[f]	23.3 (20.2–26.6)	28.8 (21.7–36.6)	21.7 (18.3–25.5)	.08
LBW	3.0 (1.9–4.5)	6.5 (3.2–11.6)	2.0 (1.0–3.6)	.01
Preterm delivery	0.6 (.2–1.5)	0.7 (0–3.6)	0.6 (.1–1.6)	>.999
Birth weight, g, mean[f]	3246 (3214–3279)	3220 (3137–3303)	3254 (3220–3289)	.45
Gestational age, wk, mean[e]	41.7 (41.6–41.8)	41.6 (41.4–41.8)	41.7 (41.6–41.8)	.58
Stillbirth	1.7 (.9–3.0)	99.4 (96.4–100.0)	98.0 (96.4–99.0)	.48
Delivery complications	26.8 (23.6–30.3)	70.8 (62.9–77.8)	73.8 (69.9–77.4)	.47
Physical abnormality[h]	1.2 (.5–2.3)	100.0 (97.6–100.0)	1.5 (.6–2.9)	.21

An increased number of doses of SP was associated with a small decrease in the rate of maternal blood smear positivity at delivery and a small but statistically significant decrease in the prevalence of LBW among infants. There was no effect on other maternal or infant outcomes, including maternal Hb level, placental infection, stillbirth, or mean birth weight. Data are proportion of those with the outcome (%) and 95% CIl or, where noted, mean and 95% CI.

Abbreviations: CI, confidence interval; Hb, hemoglobin; LBW, low birth weight; SGA, small for gestational age.

[a] Calculated by the χ^2 test or Fisher exact test, for categorical variables, and the Student *t* test or Wilcoxon rank sum test, for continuous variables.

[b] No histopathologic data were available for 1 woman from the group that received ≥2 SP doses.

[c] Defined as a Hb level of <11 g/dL.

[d] Defined as a Hb level of <8 g/dL.

[e] Data were missing for 13 infants, 12 of whom were stillborn.

[f] Data on birth weight were missing for 1 stillborn infant.

[g] Defined as SGA, LBW, and/or preterm delivery.

[h] Data were missing for 11 infants, 10 of whom were stillborn.

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Table 3

Maternal and Infant Outcomes, by Gravidity and Number of Sulfadoxine-Pyrimethamine (SP) Doses

	Primigravid, by No. of SP Doses			Multigravid, by No. of SP Doses		
Outcome	**0–1 (n = 42)**	**≥2 (n = 194)**	***P***	**0–1 (n = 114)**	**≥2 (n = 360)**	***P*[a]**
Placental infection[b]						
Any	61.9 (45.6–76.4)	61.6 (54.3–68.5)	>.999	20.5 (13.5–29.2)	15.9 (12.3–20.1)	.25
Active	4.8 (.6–16.2)	5.3 (2.6–9.5)	>.999	7.1 (3.1–13.6)	3.1 (1.5–5.4)	.09
Chronic	7.1 (1.5–19.5)	9.5 (5.7–14.6)	.77	3.6 (1.0–8.9)	1.4 (.5–3.2)	.23
Past	50.0 (34.2–65.8)	46.8 (39.6–54.2)	.74	9.8 (5.0–16.9)	11.4 (8.3–15.2)	.73
Smear positivity, by blood source						
Peripheral	4.8 (.6–16.2)	11.0 (6.9–16.3)	.39	0.9 (0–4.9)	3.6 (1.9–6.1)	.20
Placenta	7.1 (1.5–19.5)	8.4 (4.9–13.2)	>.999	2.7 (.6–7.6)	4.5 (2.6–7.1)	.58
Cord	0 (0–8.4)	2.1 (.6–5.3)	>.999	0 (0–3.2)	0.6 (.1–2.0)	>.999
Maternal Hb level, g/dL, mean (95% CI)	10.4 (9.8–11.1)	10.8 (10.5–11.0)	.26	11.2 (10.8–11.5)	11.2 (11.0–11.4)	>.999
Maternal anemia[c]	54.8 (38.7–70.2)	48.2 (40.9–55.5)	.50	42.9 (33.5–52.6)	42.9 (37.7–48.2)	>.999
Severe maternal anemia[d]	11.9 (4.0–25.6)	6.3 (3.3–10.7)	.20	7.1 (3.1–13.6)	4.7 (2.8–7.5)	.34
Secondary outcome[e]						
Composite[f,g]	47.6 (32.0–63.6)	26.5 (20.3–33.3)	.01	21.6 (14.4–30.4)	19.5 (15.5–24.0)	.68
SGA[f]	47.6 (32.0–63.6)	25.9 (19.8–32.8)	.01	21.6 (14.4–30.4)	19.5 (15.5–24.0)	.68
LBW	4.8 (0.6–16.2)	3.1 (1.2–6.7)	.64	7.1 (3.1–13.6)	1.4 (.5–3.2)	.004
Preterm delivery	0 (0–8.4)	0.5 (0–2.9)	>.999	0.9 (0–4.9)	0.6 (.1–2.1)	.56

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Outcome	Primigravid, by No. of SP Doses			Multigravid, by No. of SP Doses		
	0–1 (n = 42)	≥2 (n = 194)	*P*	0–1 (n = 114)	≥2 (n = 360)	*P*[a]
Birth weight, g, mean[f]	3044 (2906–3183)	3178 (3122–3235)	.05	3286 (3186–3385)	3295 (3252–3337)	.87
Gestational age, wk, mean[e]	41.4 (41.1–41.8)	41.5 (41.3–41.7)	.72	41.7 (41.4–42.0)	41.8 (41.7–41.9)	.54
Stillbirth	0 (0–8.4)	0.1 (.01–3.7)	>.999	0.9 (0–4.9)	2.5 (1.2–4.7)	.46
Delivery complications	33.3 (19.6–49.5)	27.7 (21.5–34.7)	.46	27.7 (19.6–36.9)	25.3 (20.9–30.2)	.62
Physical abnormality[h]	0 (0–8.4)	1.1 (.1–3.8)	>.999	0 (0–3.3)	1.7 (.6–3.7)	.34

Data shown are proportion of women with each outcome (%) and 95% CI or mean and 95% CI.

Abbreviations: CI, confidence interval; Hb, hemoglobin; LBW, low birth weight; SGA, small for gestational age.

[a] Calculated by the χ^2 test or Fisher exact test, for categorical variables, and the Student *t* test or Wilcoxon rank sum test, for continuous variables.

[b] No histopathologic data were available for 1 woman from the group that received ≥2 SP doses.

[c] Defined as a Hb level of <11 g/dL.

[d] Defined as a Hb level of <8 g/dL.

[e] Data were missing for 13 infants, 12 of whom were stillborn.

[f] Data on birth weight were missing for 1 stillborn infant.

[g] Defined as SGA, LBW, and/or preterm delivery.

[h] Data were missing for 11 infants, 10 of whom were stillborn.

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Table 4

Factors Affecting the Prevalence of Placental Infection With Malarial Parasites

Factor	Prevalence,%	Prevalence Ratio (95% CI)[a]	*P*
SP doses, no., by gravidity			
Primigravid			
≥2	61.9 (54.6–68.9)	0.94 (.72–1.21)	.62
<2	61.9 (45.6–76.4)	Reference	
Multigravid			
≥2	15.9 (12.3–20.1)	0.77 (.50–1.19)	.24
<2	20.5 (13.5–29.2)	Reference	
Maternal age, y			
≥25	11.7 (8.1–16.1)	0.48 (.32–.71)	.0002
<25	44.0 (39.3–48.8)	Reference	
ITN use last night			
Yes	28.5 (23.0–34.4)	0.84 (.68–1.04)	.12
No	33.6 (29.3–38.2)	Reference	

Receipt of ≥2 doses of sulfadoxine-pyrimethamine was not significantly associated with protection from placental infection in either primigravid or secundigravid women, after adjustment for maternal age, ITN use, or month of delivery, where month was modeled as a categorical variable. Only increasing maternal age and gravidity remained significant protective factors. Data were not significantly different when we looked at active, past, or chronic placental infection or positive maternal peripheral smear. Data shown are the prevalence of each outcome stratified by number of SP doses and additional factor shown. The 95% CI appers in column 1 and prevalence ratio and 95% CI appear in column 2.

Abbreviations: CI, confidence interval; ITN, insecticide-treated net.

[a] Calculated using a Poisson regression model with robust standard errors.

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Table 5

Factors Affecting the Prevalence of Composite Birth Outcome Among Infants

Factor	Prevalence,%	Prevalence Ratio (95% CI)	P^a
SP doses, no., by gravidity			
Primigravid			
≥2	26.1 (19.9–33.0)	0.55 (.37–.81)	.003
<2	47.6 (32.0–63.6)	Reference	
Multigravid			
≥2	19.5 (15.5–24.0)	0.95 (.62–1.45)	.80
<2	21.6 (14.4–30.4)	Reference	
Maternal age, y			
≥25	18.8 (14.3–24.1)	0.87 (.61–1.24)	.43
<25	26.0 (22.0–30.5)	Reference	
ITN use last night			
Yes	17.6 (13.1–22.9)	0.67 (.49–.92)	.01
No	26.6 (22.5–31.0)	Reference	

Receipt of ≥2 doses of SP was significantly associated with protection from the composite birth outcome of SGA, low birth weight, or preterm in primigravidae but not multigravidae, after adjustment for maternal age, ITN use, or month of delivery, where month was modeled as a categorical variable; this was driven by a significant protection against an SGA infant (data not shown). Although there was no significant effect of SP, multigravidae were at lower risk of delivering a baby with the composite birth outcome. Use of an ITN last night was also associated with lower risk for the composite birth outcome. Data shown are the prevalence of each outcome stratified by number of SP doses and additional factor shown. The 95% CI appers in column 1 and prevalence ratio and 95% CI appear in column 2.

Abbreviations: CI, confidence interval; ITN, insecticide-treated net; SGA, small for gestational age; SP, sulfadoxine-pyrimethamine.

[a] Calculated using a Poisson regression model with robust standard errors.

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Table 6

Effect of Increasing Number of Sulfadoxine-Pyrimethamine (SP) Doses

	Placental Infection		Composite Birth Outcome		Composite Birth Outcome Among Primigravidae	
Variable	**PR (95% CI)[a]**	***P***	**PR (95% CI)[a]**	***P***	**PR (95% CI)[a]**	***P***
SP effect, by no. of doses						
1	0.80 (.80–.51)	.33	0.77 (.77–.40)	.43	0.50 (.50–.30)	.01
2	0.71 (.71–.47)	.10	0.61 (.61–.33)	.13	0.30 (.30–.19)	<.0001
≥3	0.61 (.61–.33)	.10	0.22 (.22–.05)	.04	0.18 (.18–.05)	.01
Multigravid	0.37 (.37–.29)	<.0001	0.68 (.68–.50)	.02		
Maternal age ≥25 y	0.48 (.32–.71)	.0002	0.88 (.62–1.25)	.47	0.66 (.11–4.08)	.65
Used ITN last night	0.84 (.84–.68)	.12	0.68 (.68–.50)	.02	0.67 (.67–.42)	.10

In an adjusted analysis that controlled for maternal age, ITN use, or month of delivery, where month was modeled as a categorical variable, an increasing number of doses of SP was a associated with a trend toward a lower risk of placental infection, although this was not statistically significant. There was a dose-dependent trend to a decreased risk of a composite birth outcome among all women, with a statistically significant effect of ≥3 doses, compared with 0 doses. Among primigravidae, there was a clear dose-dependent effect, with a significant effect of each dose increase.

Abbreviations: CI, confidence interval; ITN, insecticide-treated net.

[a]Calculated using a Poisson regression model with robust standard errors.