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Research Article

Failing Sulphadoxine-Pyrimethamine May Increases the Risk of Fetal In-UteroSensitization and Neonatal Malaria: Systematic Review and Meta-Analysis

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Abstract

Background: Placental Malaria (PM) may lead to *in-utero*sensitization and neonatal malariawhich are both associated with increased malaria susceptibility in early childhood. Although the WHO recommend Sulphadoxine-Pyrimethamine (SP) to prevent malaria during pregnancy in endemic areas many pregnant women are still at risk of placental malaria.

Objectives: To assess the association of different SP dosing regimens with PM, and itseffectiveness in preventing placental malaria.

Results: Out of the 19 studies included, 7 studies reported no difference in the risk of placentalmalaria between the control and intervention groups. There were also no differences in the risk of placental malaria between women who took two doses of SP compared with those who took three of more doses (RR: 0.97, 95 % CI: 0.614-1.537).

Conclusion: The use of SP during pregnancy do not reduce the risk of PM, which increases the risk of fetal *in-utero* sensitization, making the child more susceptible to malaria and its accompanying complications. *In-utero* sensitization to malaria antigens may also affect malaria vaccine effectiveness, further complicating the efforts to achieving a potent and effective malaria vaccine.

Methods

Eligibility Criteria for Included Studies

Types of Studies: Randomized controlled trials, cohort, case control, and cross-sectional studies were included. Pregnant women of any gravidity and studies on different doses of SP prophylaxis for pregnant women were included. One trial had two arms: one comparing two doses of SP against a monthly regimen

in HIV positive women, and a second one comparing two doses of SP against a monthly regimen in HIV negative women. The two arms were treated as separate studies during the analysis [1]. Meta-analysis was done using only randomized controlled trials that compared three or more doses of SP to two doses. This systematic review was registered in the International prospective register of systematic reviews (PROSPERO; registration number CRD42016042774) in which the objectives, and inclusion criteria were specified in advance and documented (Supplementary Material I).Recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group were followed. (ATL and HA) conducted the actual searches in July 2016 independently. The search was conducted without language or time restrictions in the following online electronic databases; PubMed, Science Direct, MEDLINE, Google Scholar, and Africa Journals Online (AJOL) and was updated on 13thJuly, 2017 by ATL. The full search strategy is reported in Supplementary Material II. The search used both free text words and medical subject headings for 'Malaria' and 'Pregnancy', 'IPTp' and 'placenta malaria', 'Sulfadoxine-Pyrimethamine' and 'Malaria'. The search was conducted on 10thJuly, 2016 and 12th July, 2016 by the (ATL and LGT) independently. Studies reporting on malaria during pregnancy and use of SP during the period were retrieved. Bibliographies of selected studies were checked for additional publications. End-Note X7.4 (Thomson Reuters) was used to manage duplicates and screen the references for eligibility.

Data Extraction

The selection criteria were study population consisting of pregnant women. All types of original studies, including cross-sectional, case-control and cohort studies were included in the qualitative analysis. But only randomized controlled trials were used in the quantitative analysis.To determine the prevalence of placental malaria in the pregnant women, ATL and LGT independently assessed the eligibility of all the studies, by screening titles and abstracts of all articles. (ATL, LGT and MA) screened and selected relevant full-text articles. For quality control, (EDAO and BAB) randomly selected and reviewed 60% of the selected studies. Any disagreements in the selection process between reviewers were resolved in consultation with the senior authors (EDA and GOA). ATL extracted the following study characteristics: first author, year of publication, language, study site and setting, study design, objectives/measure of primary outcome, target population, selection criteria, total enrollment, sample size, diagnostic methods and clinical data. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Only published articles were included in this review and authors were not contacted for additional information. Publication bias though minimal, exist in this review due to our inability to add unpublished articles. Other biases were not investigated though substantial.

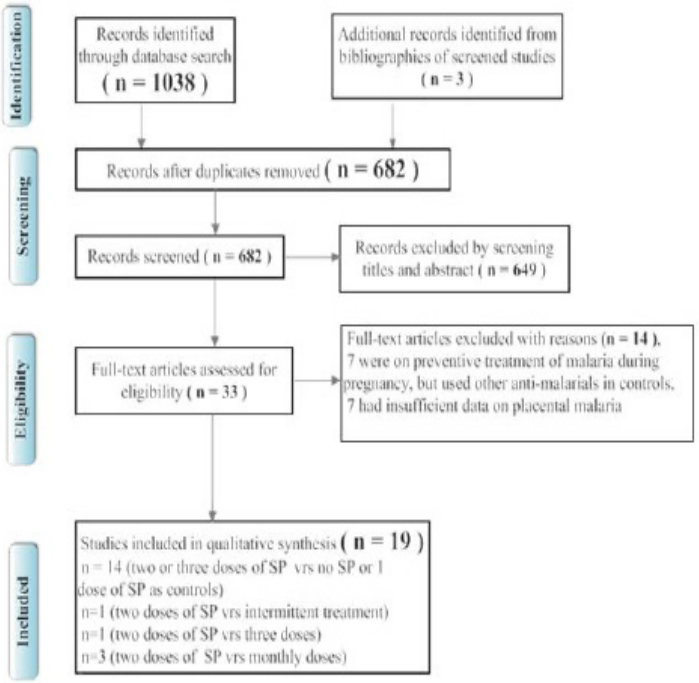

Figure 1: PRISMA flow diagram: selection of studies. Abbreviations: SP:Sulfadoxine-Pyrimethamine; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Missing Data

In some of the studies, not all enrolled participants' placentas were available for examination [2-6]. We did not contact the authors for additional information when placental malaria data from the studies were insufficient, unclear, or missing. Rather those studies were excluded. In six studies, data was presented as percentages, these were converted into absolute figures [1,5,7-9].

Results

This review and meta-analysis summarizes the results of studies on the protective efficacy of IPTp-SP to prevent placental malaria in pregnant women. Out of a total of 682 studies screened, 19 studies with a total of 12,623 pregnant women were included[1-19] (Table 1).

First Author	Year	Country	Study design	HIV status	No. of subjects
M.E. Aziken	2010	Nigeria	case-control	positives excluded	741
K. Challis	2004	Mozambique	case-control	not known	244
E. C. Inyang-Etoh	2011	Nigeria	case-control	not known	640

C. Mene´ndez	2008	Mozambique	case-control	included	845
A. M. van Eijk	2004	Kenya	cohort	included	1255
S. J. Rogerson	2000	Malawi	cohort	not known	969
F. H. Verhoeff	1998	Mali	cohort	included	560
D. Mosha	2014	Tanzania	cross sectional	included	350
F. J Mpogoro	2014	Tanzania	cross sectional	positives excluded	431
E. Serra-Casas	2011	Côte d'Ivoire	randomized controlled	included	313
O. A Toure	2014	Malawi	cross sectional	not known	1317
S. Gies	2009	Burkinafaso	cohort	not known	886
R. Ndeserua	2015	Mozambique	cross sectional	not known	350
I.U. Ezebialu	2012	Nigeria	cross sectional	included	347
D.H. Hamer	2007	Zambia	randomized-controlled	negatives excluded#	371
O.M. Maiga	2011	Gabon	randomized controlled	not known	738
S.J. Filler*(a),(b)	2006	Kenya	randomizedcontrolled	negative excluded#	608
M.E. Parise	1998	Kenya	randomized controlled	included	863
M. Luntamo	2010	Malawi	randomized controlled	included	796

*This study categorized subjects into two arms; HIV negative subjects (a) and HIV positive subjects (b)
#Studies involved only HIV positive subject: See above

Table 1: Characteristics of included studies.

Two studies [8,10] excluded HIV positive participants during enrollment, while in the other studies HIV positive participants were either included or participant's status not determined. Therefore, all pregnant women were included in the review or meta-analysis irrespective of their HIV status. Out of the nineteen (19) studies included, four (4) are cohort studies, five (5) cross sectional studies, four (4) case control studies and six (6) randomized controlled trials (Table 1). The selected studies were grouped into two; the first group compares two or more doses of SP (treated) against one or zero dose of SP (control), and the second group compares three or more doses (treated) against 2 doses of SP (control) (Table2).

≥2 doses of SP versus <2 dose of SP (control)		2 doses doses (control) versus 3 or Monthly dose regimen
1	M.E. Aziken, et al. 2010 (Nigeria)	Hamer, et al.2007 (Zambia)
2	K. Challis, et al.2004 (Mozambique)	Filler, et al.2006 (a)(Malawi)
3	Inyang-Etoh, et al.2011 (Nigeria)	Maiga, et al.2011 (Mali)
4	C.Mene´ndez, et al.2008 (Mozambique)	Parise, et al.1998 (Kenya)
5	A. M. van Eijk,et al.2004 (Kenya)	Luntamo, et al.2010 (Malawi)
6	Verhoeff, et al.2004 (Malawi)	Filler, et al.2006 (b) (Malawi)
7	D. Mosha, et al.2014 (Tanzania)	
8	Serra-Casas, et al.2011 (Mozambique)	
9	Stephen J. Rogerson, et al.2000 (Malawi)	
10	Toure, et al.2014 (Côte d'Ivoire)	
11	S. Gies, et al.2009 (Burkina Faso)	
12	Mpogoro, et al.2014 (Tanzania)	
13	R. Ndeserua, et al.2015 (Tanzania	
14	I.U. Ezebialu, et al.2012 (Nigeria)	

Table 2: Selected studies into the two groups.

Heterogeneity

There was high heterogeneity among the studies in the group that compared two or more doses of SP (treated) against one or zero dose of SP (control) (Q=72.39, df=13, I2=82.04, P≤ 0.001), therefore, meta-analysis was not done for this group. But meta-analysis was performed in the group that compared 2 doses of SP against 3 doses or more doses (Q=8.99, df=5, I2=44.43, P=0.88). Heterogeneity was quantified with the I2statistic and $\chi 2$ test [20].

Qualitative Outcomes

Analysis of the individual studies showed that two or more doses of SP reduced the risk of placental malaria in some studies [2,3,5,6,8,10,11], but others [7,9,12,14,15,21,22] it did not (Table 3).

Author	Placental malaria prevalence		Statistics for each study				Main Findings Comment
	Treated	Controls	Risk Ratio	Lower limit	Upper limit	p- value	
A. van Eijk	15/157	160/1098	0.656	0.397	1.083	0.099	The prevalence of placental malaria was 13.8% and low birth weight (LBW) was 12.2%. IPT (≥1 dose of SP) was associated with a reduction in placental malaria and LBW [adjusted odds ratio (RR) 0.56, 95% confidence interval (CI) 0.39-0.83 and RR 0.65, 95% CI 0.45-0.95, respectively]. An adjusted mean increase in birth weight of 61 g was seen (95% CI 22-101 g) for each increment in number of SP doses (≥2 doses grouped together). IPT was associated with a reduction in placental malaria in HIV-seronegative women (OR 0.49, 95% CI 0.28-0.86) but this was not significant among HIV-seropositive women (RR 0.45, 95% CI 0.20-1.05). A significant effect on birth weight could not be detected among participants in the HIV-cohort. Conclusion: IPT with SP is effective in reducing placental malaria and LBW.
C. Mene´ndez	30/426	57/419	0.518	0.34	0.789	0.002	SP group showed a 40% reduction (95% CI, 7.40-61.20]; p = 0.020) in the incidence of clinical malaria during pregnancy, and reductions in the prevalence of peripheral parasitaemia (7.10% vs 15.15%) (p=0.001), and of actively infected placentas (7.04% vs 13.60%) (p = 0.002). Conclusions: Two-dose SP was associated with a reduction in some indicators, but these were not translated to significant improvement in other maternal or birth outcomes.
D. Mosha	15/181	21/169	0.667	0.356	1.25	0.207	Prevalence of placental parasitaemia was 16.6% (CI 11.4-22.9) in the high transmission area and 2.3% (CI 0.6-5.7) in the low transmission area. Being primigravida and residing in a high transmission area were significant risk factors for placental malaria (OR 2.4; CI 1.1-5.0; P = 0.025) and (OR 9.4; CI 3.2-27.7; P < 0.001), respectively. IPTp was associated with a lower risk of placental malaria (OR 0.3; CI 0.1-1.0; P = 0.044); the effect was more pronounced in the high transmission area (OR 0.2; CI 0.06-0.7; P = 0.015) than in the low transmission area (OR 0.4; CI 0.04-4.5; P = 0.478). IPTp use was not associated with reduced risk of maternal anaemia or low birth weight, regardless of transmission intensity. Conclusion: IPTp may have an effect on lowering the risk of placental malaria in areas of high transmission, but this effect did not translate into a benefit on risks of maternal anaemia or low birth weight.
E. Inyang-Etoh	38/358	32/282	0.935	0.600	1.458	0.768	The gross presence of placental malaria in the intermittent preventive treatment (IPT)-treated and the control groups was 10.6% and 11.3% respectively (P=0.76). Anemia occurred in 3.1% of the IPT-treated group compared to 11.7% among the control group (P=0.001). Only 7.9% of the IPT-treated women had moderate to severe placental parsitemia whereas as many as 53.2% of women in the control group had moderate to severe parasitemia (P=0.001). Conclusion: Intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine was associated with significant reduction in the degree of placental parasitemia among women in the IPT treated group, although it did not completely eradicate placental malaria in the treatment group.

E. Serra-Casas	18/167	32/146	0.492	0.289	0.838	0.009	Risk of postpartum infection was lower in older women (odds ratio [OR] =0.34, 95% Confidence Interval [CI] =0.15 to 0.81) and higher in women with a placental infection at delivery (OR 4.20, 95% CI _ 2.19 to 8.08)
F. Verhoeff	46/287	40/273	1.094	0.741	1.616	0.652	There was no significant difference in parasite prevalence in peripheral or placental blood between women who had received one or two antenatal doses of SP. The multigravidae who had received two doses of SP had higher mean haemoglobin concentrations than those who had received just one (P = 0.009) [this difference was not seen in the primigravidae (P = 0.92)]. The mean birthweights were higher, and incidence of LBW lower in babies born to primi- and multi-gravidae who had received two or three doses of SP treatment than those seen in babies born to women who had had just one dose (P, 0.03 for each). The odds ratio for LBW in primigravidae compared with multigravidae decreased from 3.2 to 1.0 as the number of SP doses increased from one to three.
F. J Mpogoro	37/130	124/301	0.691	0.51	0.936	0.017	The uptake of ≥ three doses of SP was associated with reduced odds of having placental malaria (adjusted odds ratio (AOR) = 0.31, p = 0.039) compared to < three doses. Women with placental parasitaemia were five times more likely to have delivered pre-term (AOR = 4.67, p = 0.002) and had lower mean birth weight infants than their uninfected counterparts (mean difference = 82 g, p = 0.039). Conclusions: Receipt of ≥ three doses of IPTp-SP reduced the odds of placental parasitaemia.
I. U. Ezebialu	137/249	76/98	0.709	0.608	0.828	0.001	Histological evidence of placental malaria was most common in the age range 25-29 years (n = 95, 37.4%), followed by age ranges 30-34 (n = 78, 30.7%), 35-39 (n = 44, 17.3%), 20-24 (n = 29, 11.4%), and 40 years and above (n = 8, 3.1%).
K. Challis	3/124	16/120	0.181	0.054	0.607	0.006	Enrolment malaria parasitaemia was 35.3% in the placebo group and 30.6% in the SP group. At the second dose, the prevalence of malaria parasitaemia in the placebo group and SP group was 19.7% and 8.7%, respectively. This implies a relative risk (RR) of 2.24 with 95% CI (1.34, 3.75). And in placenta 13.3% and 2.4% with an RR of 4.87 (1.58, 15.0). The mean birthweight in the SP group was 3077 g and in the placebo group 2926 g.
M. E. Aziken	42/370	84/371	0.501	0.356	0.705	0.001	SP reduced the odds of placental parasitemia by 37% (RR 0.501; 95% CI, 0.48- 0.81). Peripheral (P=0.002) and placental (P=0.001) parasitemia were significantly reduced in the subgroup of women who took 2 or 3 doses of SP. Anemia at delivery was significantly lower in the IPT-SP group (10.8 vs 1.6%). The risk of low birth weight was also significantly lower in the IPT-SP group. Conclusion: IPT-SP is effective in preventing placental parasitemia, and reduces rates of malaria, maternal anemia, abortion, preterm delivery and low birth weight among pregnant women.
O. A Toure	57/570	60/747	1.245	0.881	1.759	0.214	LBW infants 18.8% (22/107) were born to women with placental malaria and 8.5% (103/1097) to women without placental malaria. Conclusion: LBW was associated with placental malaria.

R. Ndeserua	10/184	18/166	0.501	0.238	1.055	0.069	Use of at least 2 doses of SP for IPTp during pregnancy was insignificantly associated with reducing the risk PM (P=0.08), low birth weight (P=0.73) and maternal anemia (P=0.71). But associated significantly with reducing the risk of preterm birth (P<0.001). Conclusion: Two doses of SP for IPTp regime are ineffective in preventing and treating PM and adverse pregnancy outcome.
S. Gies	61/617	93/269	0.286	0.214	0.382	0.001	Two or more doses of SP significantly reduced the risk of placental parasitaemia [Adjusted Odds Ratio (AOR) = 0.04, 95%CI = 0.003-0.60, P = 0.023] and anaemia at delivery (AOR = 0.31, 95%CI = 0.18-0.52, P < 0.001). IPTp was associated with reduced risk of LBW in primigravidae (AOR = 0.11, 95%CI = 0.07-0.17, P < 0.001), but not in secundigravidae (AOR = 0.70, 95%CI = 0.26-1.91, P = 0.452). For each increment in number of SP doses mean PCV increased by 1.0% (95%CI = 0.4-1.7, P = 0.005) at 32 weeks' gestation, by 1.2% (95%CI = 0.2-2.2, P = 0.025) at delivery and mean birth weight by 220 g (95%CI = 134-306 P < 0.001) in primigravidae and by 102 g (95%CI = 55-148, P = 0.001) in secundigravidae. Conclusion: The risk of malaria infection was significantly reduced by IPTp with SP in primi- and secundigravidae in rural Burkina Faso.
S.J. Rogerson	69/303	182/666	0.833	0.655	1.061	0.139	SP prescription was associated with a decrease in placental malaria prevalence (from 31.9% with no SP prescription to 22.8% with 22 doses SP) and density, decreased prevalence of low birthweight (from 23% in women not receiving SP to 10.3% in women given ≥ 2 doses), and higher maternal haemoglobin concentrations. These effects were most marked in first and second pregnancies, in which malaria prevalence was highest.

Table 3: Selected studies comparing two doses of SP to control (no or one dose of SP).

Quantitative Synthesis

Out of the six studies included in the quantitative analysis, only two studies observed significant reduction in placental malaria prevalence among the two groups; one in HIV positive women (36b) using monthly dose(p=0.029), and the other in HIV negative women using three doses of SP (p>0.001). The remaining four studies [1,17,19,23] observed insignificant reduction in the risk of placental malaria between the two groups.The summary effect from the meta-analysis (Figure 2) of five randomized controlled trials showed that, women who received 3 or more doses of SP had a similar risk of placental malaria (RR= 0.97, 95 % CI: 0.614-1.537) when compared to those who received two doses of SP (Figure 2 and 3).

But women who took 3 or more doses had a slight reduction in risk of Low Birth Weight compared to those who took only two doses of SP, though this reduction was not statistically significant (RR: 0.823, 95% CI: 0.636-1.066, p= 0.14) (Figure 3). The summary risk ratios at 95 % confidence intervals were calculated using the random effect model [20]. One trial had two arms: one comparing two doses of SP against a monthly regimen in HIV positive women, and a second one comparing two doses of SP against a monthly regimen in HIV negative women. The two arms were treated as separate studies during the analysis [1].

Placental Malaria

In the sub-Saharan Africa, about 25% of the over 25 million women who become pregnant develop PM [24,25]. PM is characterized by placental sequestration of malaria parasites [26] and carries a substantial risk for the mother, her foetus and the neonate, which include maternal anaemia, low birth weight and still birth [27]. P. falciparumsequester in the placenta using a VAR2CSA protein on infected erythrocytes, to interact with Chondroitin SulphateA (CSA) on syncytiotrophoblast and intervillous space [28-30]. This triggers a local inflammation and infiltration of monocytes into the intervillousspace [31] resulting in the release of pro-inflammatory cytokines such a Tumour Necrosis Factor (TNF) and gamma interferon (IFNγ) [31] leading to the inflammation of the placental [32]. This affects the integrity of the placenta resulting in leakage of pathogens and/or their antigens into the fetal circulation [33-35].

FoetalIn-uteroSensitization by Malaria Parasite and Increased Risk of Childhood Malaria

Infants born to mothers with PM are themselves at an increased risk of malaria during the early years of life [36,37]. This may be due to similar levels of exposure of mothers and their infants to infected mosquitoes, but current studies suggest, tolerance

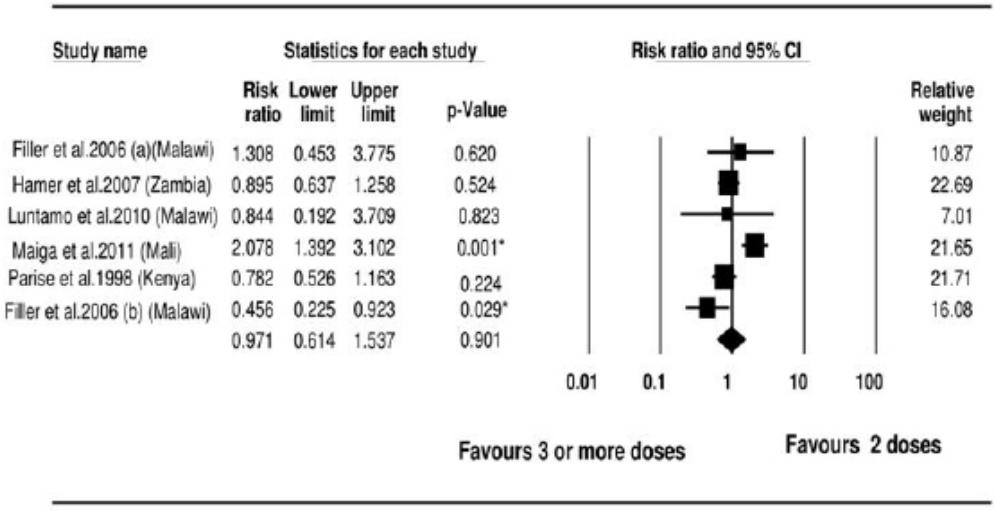

Figure 2: Two doses of SP against three or more doses, and risk of Placental Malaria (PM). Each study is displayed as a square and horizontal line, representing the odd ratio, together with its confidence interval. The area of the square represents the weight that the study contributes to the meta-analysis. The combined Risk Ratio and its confidence interval are represented by the diamond. The P value after I^2 represents chi-square test for heterogeneity. Values with (*) are statistically significant ($p \leq 0.05$).

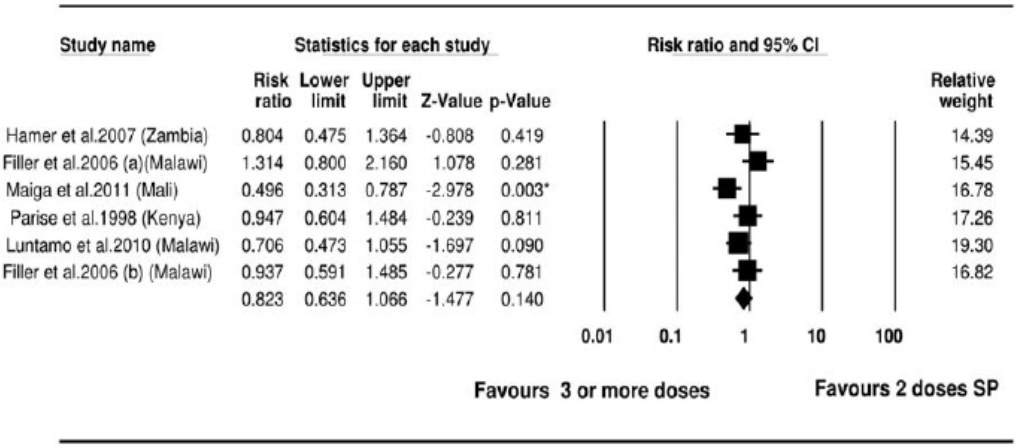

Figure 3: Two doses of SP against three or more doses, and risk of Low Birth Weight (LBW). Each study is displayed as a square and horizontal line, representing the odd ratio, together with its confidence interval. The area of the square represents the weight that the study contributes to the meta-analysis. The combined Risk Ratio and its confidence interval are represented by the diamond. The P value after I^2 represents chi-square test for heterogeneity. Values with (*) are statistically significant ($p \leq 0.05$).

due to in uteroexposure to blood stage malaria antigens could be the reason [38-41]. Many infants in malaria-endemic areas experience their first exposure to malaria antigens in-utero, sometimes during a critical period of foetal immune (T-cell) development. Some studiessuggest the presence of malaria antigens in the foetal circulation in early foetal life (below 13weeks), the period of foetal T-cell development, may lead to tolerance to malaria antigens [41], making the infant more susceptible to malaria in early childhood. Another possible factor that can lead to foetal tolerance is exposure to minute-quantities of soluble antigens in-utero [42,43]. Malhotra and colleagues in Kenya [44] were able to show that, a subset of children exposed to malaria antigensin-utero,acquired a tolerant T-cell phenotype to malaria blood-stage antigens. This T-cell phenotype persisted in infants up to childhood (36 months of age) and was associated with an increased susceptibility to malaria infection and anaemia. Another group in Gabon [36] reported that, infants of mothers with placental malaria had a significantly higher risk of clinical malaria during the first 30 months of life (adjusted hazard ratio, 2.1; 95% Confidence Interval [CI], 1.2- 3.7).

Induction of Specific T-Regulatory Cells and Vaccine Effectiveness

Developing specific tolerant T-cellsor T-regulatory cells (Tregs) to antigens of the malaria parasites in-uteromay also affect the efficacy of a malaria vaccine in these children. CD4+ CD25+ regulatory T cells (Treg) are a specialized subpopulation of T cells responsible for the maintenance of immunological tolerance by actively suppressing immune responses to specific antigens suchas self or foreign antigens [45].Therefore, induction of plasmodium specific Treg cells in a child due to in-utero exposure could negatively affect their immune responses to plasmodial antigenslater on in life [44].Such children may either fail to generate protective immune responses to a malaria vaccine or may need more doses to the said antigens, due to the negative feedback of these specific Tregs.

Congenital Malaria

Congenital malaria is said to occur when asexual parasites are detected in the cord blood or in the peripheral blood during the first week of life [46,47]. Majority of these congenital malaria cases are as a result of transplacental transmission of the parasite to the foetus[48-50], when the pregnant woman develops PM. Several studies observed a correlation between PM and neonatal malaria [51-53]. Though some newborns who are parasitaemic at birth, spontaneously clear their parasites without becoming ill, others experience the consequences of malaria [49,54].

Strengths and limitations

In some of the studies [7,11], the researchers used a questionnaire to gather the evidence of SP usage. The researchers relied on what the pregnant women said, if there was no evidence of SP use in the antenatal records, this is subjective and prone to false information which could affect our results. Also, some studies excluded HIV positive pregnant women [8,10] whilst others did not test for HIV in participants [2,5,12-15]. This could also affect our summary results, because HIV-infected pregnant women are immune-compromised and therefore have reduced antimalarial immunity [55] and therefore higher prevalence of malaria [56,57].

Conclusion

The use of SP during pregnancy do not reduce the risk of PM which increases the risk of fetal in-utero sensitization, making the child more susceptible to malaria and its accompanying complications. In-utero sensitization to malaria antigens may also affect malaria vaccine effectiveness, further complicating the efforts to achieving a potent and effective malaria vaccine. All these points to the fact that, the consequences of placental malaria go beyond low birth weight, therefore more and efficient measures are needed to prevent placental malaria and its associated complications.

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