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The effect of intermittent preventive treatment using sulphadoxine pyrimethamine in control of malaria in pregnancy: A cross-sectional study in the Offinso district of Ghana

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Malaria infection during pregnancy causes maternal anaemia and placental parasitaemia both of which pose substantial risks to the mother, the foetus and the newborn. This study assessed the effects of intermittent preventive treatment (IPTp) using Sulphadoxine-Pyrimethamine (SP) to control malaria in pregnancy in the Offinso district, Ghana. Pregnant women attending antenatal clinics (ANC) between October 2005 and June 2006 in five health facilities in the District were studied. The effects of SP on parasitaemia, haemoglobin level and adverse effects on pregnant women were assessed. Of the 444 pregnant women studied, 190 (43%) took SP. The influence of SP intake on malaria infection was insignificant (r = 0.0008, p = 0.986). However, there was a tendency towards reduced parasitaemia as number of SP doses increased; one dose: 29/82 (35%), two doses: 18/57 (32%) and three doses: 11/57 (22%). The mean Hb level (10.4 ± 1.69 g/dl) for the SP group (all doses combined) was significantly higher than that (9.9 ± 1.64 g/dl) in the no SP group (p = 0.002). Further, there was a significant association between IPTp using SP and haemoglobin level (p = 0.01) with a dose-response relationship. SP usage had no significant adverse effects on the pregnant women. Effective implementation of IPTp using SP is an evidence-based measure for control of malaria-related anaemia in pregnancy.

Keywords: Malaria, intermittent preventive treatment, pregnant women, sulphadoxine-pyrimethamine.

INTRODUCTION

Malaria in pregnancy is a major public health problem in tropical and subtropical regions of the world. In Africa, millions of women living in malaria-endemic areas become pregnant each year and most live in areas of relatively stable malaria transmission (WHO, 2004; Tagbor et al., 2008). Malaria in pregnancy makes a significant contribution to maternal and perinatal morbidity and mortality. Each year more than 500, 000 women die during pregnancy or childbirth (WHO, 2004) and more than four million babies die in the first 28 days of life, accounting for 38% of mortality in children aged less than five worldwide (Lawn et al., 2005; Adam et al., 2005). In sub-Saharan Africa, the rate of maternal mortality is 2.5 times more than those in Asia, which are in turn more than 20 times those in developed countries (WHO/UNICEF, 2004).The main burden results from infection with *Plasmodium falciparum* (Sanders et al., 2005; Vallely et al., 2007). The effect of intermittent preventive treatment programme (IPTp) with sulphadoxine-pyrimethamine (SP) on malaria in pregnancy, is well documented and has been shown to reduce malaria

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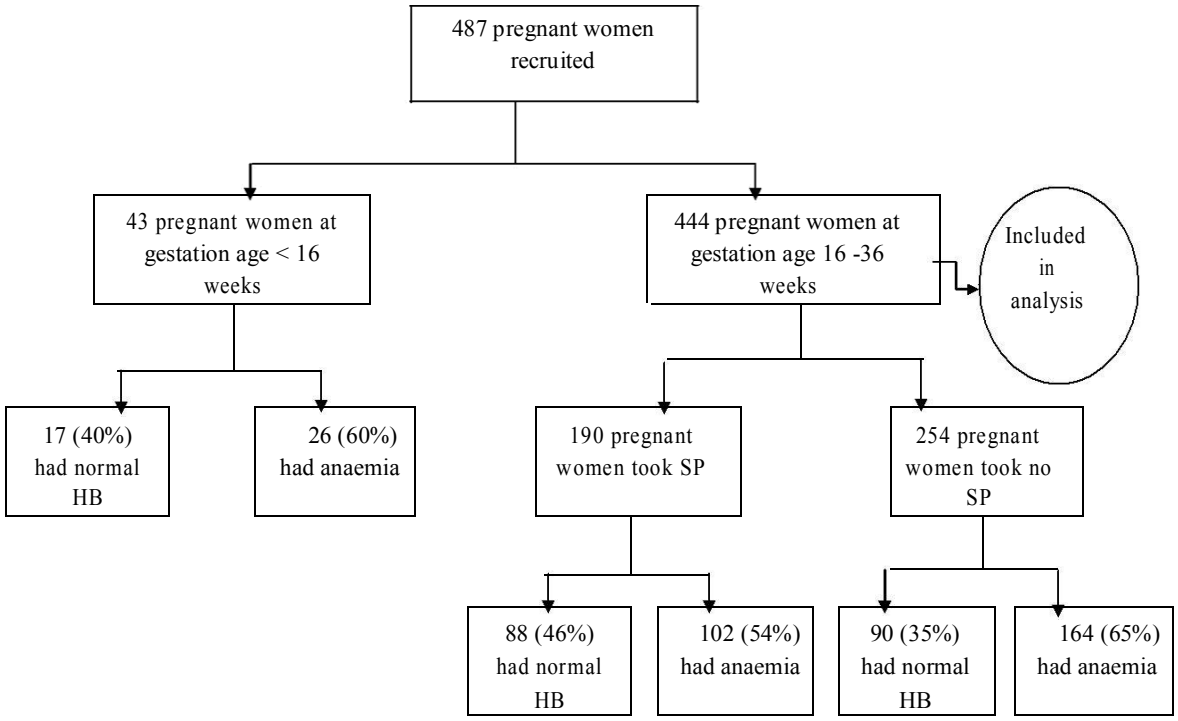

Figure 1. Trial profile of pregnant women recruited for the study.

episodes, maternal parasitaemia, malaria-related anaemia and incidence of low birth weight (LBW) (Parise et al., 1998; Shulman et al., 1999; WHO, 2004; Mbonye et al., 2008; Gies et al., 2009). However, in Ghana, IPTp coverage in pregnant women is less than 10% according to WHO (2005) report.

Malaria in Ghana is the leading cause of morbidity and accounts for nearly 40% of facilities, 30% of all health facility admissions and 10% of all officially reported deaths (GHS, 2007). Malaria during pregnancy is high among pregnant women and accounts for more than 2% of all malaria cases in the country (GHS, 2007). Moreover, in the studied district, malaria is the leading cause of morbidity and accounting for nearly 50% of outpatients' visits pregnantto womenhealthbelow16 weeksfacilitiesofgestation,WHO,2004)(Offin.The DHMT, 2007). The question arising is: Is the problem that of drug compliance or the drug is not effective in preventing malaria in pregnancy? This paper, therefore, assesses the effectiveness of using SP in intermittent preventive treatment of malaria in pregnancy (IPTp), in a routine programme setting in Offinso district, Ghana.

METHODOLOGY

Study site

The study was conducted in the Offinso District, one of the 27 administrative districts in the Ashanti Region of Ghana. It has an area of 1254 km^2, with 161 communities; most of them being small with population size of 50 - 300. In 2006, the district had a projected population of 169,842 with a growth rate of 3.4% (Offinso DHMT, 2007). The study was conducted in five health facilities that provide antenatal, delivery and postnatal services in the district, namely St. Patrick's Hospital Offinso, Nkenkaasu Government Hospital, Abofour Health Centre, Akomadan Health Centre and A.M.E Zion Clinic, Afrancho.

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Study design and population

The study was an analytical type with a cross-sectional design. Pregnant women attending antenatal clinic (ANC) at the five health facilities in the district were enrolled for the study. Forty three (9%) of the pregnant women enrolled were of gestational age < 16 weeks and were excluded from the analysis (SP is not to be given to **women whose pregnancies were between 16 and 36 weeks gestation were included in the study analysis as shown in Figure 1.**

Administration of questionnaires

After explanation of study procedures and collection of signed consent forms, standard questionnaires were administered to collect history of pregnancy, educational attainment, socio-economic status and drugs intake. Antenatal cards were checked to record gravida status, gestational age, height, attained weight and IPTp status, thus, taking SP at the health facility in the presence of a midwife or a nurse (that is, direct observed therapy, DOT). Adverse effects of taking SP, were also incorporated in the study questionnaire. The study covered the period of October 2005 to June 2006.

Determination of haemoglobin, parasitaemia and other anthropometrics

The finger-prick method was used to collect blood for determination of haemoglobin level (Hb) and parasitaemia. Test results of Hb levels were given to Maternal and Child Health (MCH) unit for management of severe anaemia.

Anthropometric measures including height and weight (for body mass index, BMI calculation,) temperature and systolic blood pressure were determined using appropriate equipment (including measuring rule, a balance, thermometer and sphygmomanometer respectively) in assessing the general health of the pregnant women with the assistance of the health staff. No remuneration was given to study participants.

Laboratory investigations

Thick and thin blood films were stained with 3% Giemsa for 30 min and examined for malaria parasites. Parasites were counted against 200 leukocytes to determine parasitaemia using tally counter. Ten percent of slides were randomly chosen and rechecked by a second microscopist blinded to the initial results. Parasite densities were estimated using an assumed leukocyte count of 8000 leukocytes/µl of blood (WHO, 2003). The limit of detection was approximately 10 parasites/µl of blood. A HemoCue® haemoglobin detection system (HemoCue AB, Angelholm, Sweden) was used to measure haemoglobin levels.

Ethical consideration

Permission to undertake the study was obtained from stakeholders including the District Health Administration, the District Assembly and the opinion leaders in the study communities. Ethical clearance was also sought and obtained from the Ghana Health Service and School of Medical Sciences (SMS) Ethics Committees. Each study participant after being briefed and offered the opportunity to ask questions about the study, was provided with individual informed written consent form to sign or thumbprint. The written consent forms and participant information forms were kept separately from the data collection tools.

Definitions and groupings

Parasitaemia (in peripheral blood) was defined as the presence of asexual stage parasites in thick smears. Women with haemoglobin levels (Hb < 11 g/dl) and (Hb < 7 g/dl) were considered to have moderate anaemia and severe anaemia, respectively. IPTp was defined as administration of a curative antimalarial treatment dose of SP at predefined intervals (between 16 - 36 weeks) to asymptomatic pregnant women during antenatal clinic (ANC), who are at risk of malaria, regardless of whether or not they are parasitaemic at the time of visit. Gravidity was categorized into primigravidae (women in their first pregnancies), secundigravidae (women in their second pregnancies) and multigravidae (women in their third, fourth or more pregnancies.

Statistical analysis

All study women were given an eight digit identification number, identifying village, house number, and a randomly computer generated digit. All answers were numerically coded on the questionnaire and responses and laboratory results entered into Microsoft Office Access, 2003 version. Data were analysed using Stata version 9.0 (Stata Corporation 4905, Lakeway Drive College Station, Texas 77845, USA). Averages and 95% confidence interval (CI) were used for summarizing of results. Frequencies and percentages were used to compare number of participants associated with the use of SP, parasitaemia, haemoglobin levels etc. Analyses of differences in proportions were done using Pearson's-squarechi test or Fisher's exact Analysis of variance (ANOVA) with Bonferroni and Sidak measure of comparisons were used to measure the differences in means and Pearson correlation coefficient used to determine the relations between variables. For all statistical tests in this IPTp study, $p < 0.05$ was considered significant.

RESULTS

Of the total of 487 pregnant women recruited (Figure 1), 281 (58.0%) were recruited in the dry season (November, 2005 –February, 2006) and 206 (42.0%) were in the wet season (October, 2005; March – June, 2006) with an average of 3.4 ± 1.4 (95% CI: 3.33 - 3.60) people living in a single room. Of the 444 (91%) of the pregnant women of gestational age 16 - 36 weeks included in the analysis, 190 (43%) took SP (Figure 1).

Fifty four or 12.0% of the pregnant women used traditional medicine including herbs and bark of trees which they added to foods they ate or used for enemata and which they reported to be helpful as diuretics, for control of nausea and prevention of constipations. However, these herbs had no antimalarial effects. The educational level among the pregnant women was low with less than 50% completing Senior Secondary and Middle/Junior Secondary Schools (Table 1). Educational level of the pregnant women had a significant association with Hb level, ($p = 0.032$). The socioeconomic statuses of the pregnant women were generally low with few owning properties as shown in Table 2. Over 50% of the pregnant women were farmers; traders and artisans (dressmakers, hairdressers, potters etc) were less than 40%. The "others" underedthose occ unemployed and students who were pregnant. Radio usage was very high among pregnant women as compared to television use. Only 36% of the women slept in insecticide treated nets (ITNs) (Table 2). The mean age of the participants was 26.0 ± 6.2 years. The youngest participant was 14 years and the oldest was 45 years of age. Other anthropometric indicators showed that they were less at risk of complications during delivery since they attained normal height and weight during pregnancy with relatively no hypertensions and obesities (Table 3). In the SP group, 82 (43%) of the pregnant women took first dose only, 57 (30%) and 51(27%) respectively took second and third doses of SP (Table 4).

The effect of SP use on parasitaemia in pregnancy

Of the 123 pregnant women with parasitaemia, 65 (53%) took no dose of SP, 29 (24%), 18 (15%) and 11 (9%), respectively, took 1, 2 and 3 doses of SP. Pearson

Table 1. Background characteristics of study subjects.

Characteristics	N (444) (%)
Age	
≤19	66 (15.0)
20-29	237 (53.0)
30-39	125 (28.0)
≥40	16 (4.0)
Parity	
Primigravidae	87 (19.59)
Secundigravidae	91 (20.5)
Multigravidae	266 (59.91)
Marital status	
Married	317 (71.0)
Single	127 (29.0)
Educational level	
None	157 (35.4)
Primary	86 (19.4)
Middle/J.S.S	185 (41.7)
Secondary	14 (3.1)
Tertiary	2 (0.4)
Religion	
Christian	333 (75.0)
Muslem	80 (18.0)
Free thinkers	26 (6.0)
Traditionalist	5 (1.0)

Table 2. Socioeconomic status of study subjects.

Socioeconomic status	N (444) (%)
Occupation	
Farmer	241 (54.0)
Trader	96 (22.0)
Artisan	62 (14.0)
Others	45 (10.0)
Ownership of property	
Car	76 (16.0)
Motorbikes	45 (10.0)
Bicycles	182 (41.0)
Radio	336 (76.0)
Television	163 (37.0)
Sleep on bed	349 (79.0)
Windows netted	157 (35.0)
Sleep in ITNs	158 (36.0)
Latrine at home	165 (37.0)
Source of drinking water	
Pipe borne water	153 (34.0)
Well water	55 (12.0)
Bore hole water	151 (34.0)
River water	80 (18.0)
Animals kept at home	
Goats	96 (22.0)
Sheep	119 (27.0)
Poultry	274 (62.0)

correlation showed poor relation of SP doses with malaria infection (r = 0.0008, p = 0.986); thus there was no significant association between SP and parasitaemia (Pearson χ^2 =1.32, p = 0.25). Parasitaemia in the no SP group by proportion was higher than those who took SP 65/123 (53%) as against 58/123 (47%). Moreover, the proportion of parasitaemia in those who took one dose of SP, 29/82 (35%) as against those who took doses two and three, 18/57 (32%) and 11/57 (22%), respectively, was higher (Table 4). Intriguingly, very few, 7/108 (6%) pregnant women who took 2 and 3 doses were found to have high parasitaemia (parasite density ≥ 5000 per µl of blood) as compared to those who took one dose of SP (Table 4).

Primigravidae were found to have the highest mean parasite density (1699 per microlitre of blood) as compared to secundigravidae (338 per microlitre of blood) and the multigravidae (195 per microlitre of blood); the differences among them were significant (p = 0.001). Occupation of the pregnant women did have a significant association with their parasite densities (Pearson χ^2 = 18.09, p = 0.034). Farmers were found to have increased parasitaemia as compared to the other occupation groups. Parasitaemia in ITN users (36/123 - 29%) were few as compared to non-ITN users (87/123 - 71%). Parasitaemia did not show any significant seasonal variation in pregnant women (p = 0.22) and seasonal differences were not significant (r = -0.02, p = 0.72).

The pregnant women with parasitaemia, 2 (2.0%) had severe anaemia, 83 (67.0%) moderate anaemia and 38 (31.0%) had normal haemoglobin (Hb ≥ 11 g/dl). However, there was a negative poor correlation of haemoglobin with parasitaemia (r = -0.035, p = 0.477).

The effect of SP on haemoglobin level in pregnancy

The mean Hb level was 10.1 ± 1.8 g/dl with the lowest being 6 g/dl and highest 17 g/dl. Anaemia was found in 266/444 (60%) of the study subjects. There was a significant positive association between the use of SP in IPTp and Hb level (Pearson χ^2 = 17.0; p = 0.01). The proportion of those who took SP and had moderate anaemia was 102/190 (54%) as compared to those who took no SP 164/254 (65%). The mean Hb level (10.4 ± 1.69 g/dl) for the SP group was significantly higher than that (9.9 ± 1.64 g/dl) in the no SP group (p = 0.002). Among the primigravidae 59/87 (68.0%) were anaemic;

Table 3. Characteristics of pregnant women.

Characteristics	Mean (SD)	95% CI
Age (yrs)	26.0 ± 6.2	25.4- 26.6
Haemoglobin level (g/dl)	10.1 ± 1.7	10.0- 10.3
Body mass index (kg/m^2)	22.7 ± 3.7	22.3- 23.0
Height (cm)	160.2 ± 9.2	159.3- 161.1
Weight (kg)	58.3 ± 8.4	57.5- 59.1
Systolic blood pressure (mmHg)	109 ± 11.6	107.9- 110.3
Temperature (°C)	36.5 ± 0.6	36.4- 36.6

Table 4. Parasitaemia in pregnant women taking SP.

Parasite density (per µl of blood)	Doses of SP				
	0	1	2	3	Total
None	189	53	39	40	321
Percentage (%)	74.41	64.63	68.42	78.43	72.30
1-1999	54	24	13	7	98
Percentage (%)	21.26	29.27	22.81	13.73	22.07
2000-4999	6	5	2	0	13
Percentage (%)	2.36	6.10	3.51	0.00	2.93
≥ 5000	5	0	3	4	12
Percentage (%)	1.97	0.00	5.26	7.84	2.70
Total	254	82	57	51	444

Table 5. Relationship between doses of SP (0 - 3) and mean Hb level in pregnant women.

SP doses taken	Hb mean(SD) g/dl	95% CI
0	9.9 ± 1.64	9.7 - 10.1
1	10.1 ± 1.61	9.8 - 10.5
2	10.4 ± 1.93	9.9 - 10.9
3	10.9 ± 1.43	10.5 - 11.4

60/91 (66.0%) were anaemic in the secundigravidae whilst 147/266 (55.0%) were anaemic in the multigravidae. There was a significant association of haemoglobin with gravidity (Pearson χ^2 = 9.4; p = 0.05). Mean Hb levels increased with increasing doses of SP and increasing gravidity. Primigravidae who took 3 doses of SP (Hb = 11.2 g/dl) as against doses 0, 1 and 2 (Hb = 9.3 g/dl, 9.0 g/dl, 9.7 g/dl, respectively) had the highest mean Hb level. Analysis of variance showed significant difference in mean Hb level by gravidity (p = 0.0001); Primigravidae had the lowest mean Hb level of 9.4 g/dl, with secundigravidae and multigravidae women attaining mean Hb level of 10.1 g/dl and 10.4 g/dl, respectively. Thus, multigravid women were found to have mean increase of Hb level (Hb = 0.92 g/dl, p = 0.001; Hb = 0.32 g/dl, p = 0.37) over primigavid and secundigravid women, Respectively using Bonferroni Thirty six comparisonpregnantwomen,19%. complainedBySidak'sofadverse measure of comparison, the mean Hb level for those who took 3 doses of SP increased by 1.02 g/dl, (p = 0.001) over those who did not take SP, increasing by 0.78 g/dl, p = 0.075, 0.53 g/dl, p = 0.55 over doses 1 and 2 of SP, respectively (Table 5). There was a weak relationship between Hb level and the use of insecticide treated nets (ITNs) (correlation coefficient, r = 0.004, p = 0.90). There was a mean increase of Hb level with increased age of study women but the difference was not significant (p = 0.19). Seasonal variations did not show significant association with Hb level (p = 0.3).

Effect of use of SP in pregnant women

One hundred and ninety (190) or 39.0% of the pregnant women took SP as aforementioned; however, the number of pregnant women taking increasing doses decreased. effects from taking SP as against 154 or 81% who had no complaints. The adverse effects included general

malaise, body weakness, nausea, vomiting, palpitations and itching. However, there was no significant difference in the adverse effects among those who took the first, second and third doses of SP (p = 0.401).

DISCUSSION

The results of the present study showed significant increase in Hb levels of pregnant women who took SP compared to the no SP group (p = 0.002). Increased doses of SP were found to be associated with higher Hb levels in the pregnant women, with no significant adverse reactions. Parasitaemia was more prevalent in the no SP group compared to the SP group (53% vs. 47%). This reduction of maternal anaemia and parasitaemia in relation to the number of SP taken, thus, confirm the beneficial impact of the drug as reported by WHO, 2004 and in other studies (Parise et al., 1998; Verhoeff et al., 1998; Shulman et al., 1999; van Eijk et al., 2004; Kayentao et al., 2005; Schellenberg et al., 2005; Tagbor et al., 2006).

Findings from this study confirm findings from previous studies, which showed that pregnant women, particularly primigravidae were highly susceptible to *P. falciparum* infection and to clinical malaria which could result in maternal anaemia, low birth weight, and preterm delivery (Sullivan et al., 1999; Menendez et al., 2000; Glover – Amenyor, 2005; Tagbor et al., 2006). We showed that primigravidae had the highest mean parasite density and higher proportion of anaemia.

Given that over 50% of the pregnant women studied were farmers and traders who had little or no formal education, it is possible that most of them had little or no knowledge on malaria and/or malaria-related anaemia. The low socioeconomic status and poor housing of most pregnant women (75%) were indicative of poor living conditions which contribute to increased exposure to female anopheline mosquito bites.

The high parasite density (≥ 5000 parasites per microlitre of blood) in very few (7/108) of the pregnant women who took high doses of SP could be as a result of possible development of resistance of the parasite to SP or its active principle.

STUDY LIMITATIONS

Although determinants of anaemia were not part of this study, it is likely that a combination of factors such as malnutrition, helminth infection and other disease conditions in addition to malaria contributed significantly to anaemia in pregnancy. This inference is supported by other studies (van den Broek, 1996; Steketee, 2003; Agyei, 2005; Glover-Amenyor et al., 2005). Seventy two percent (72%) of the pregnant women had BMI below 19 kg/m^2 and were anaemic, suggesting that malnutrition is a possible major cause of anaemia in pregnancy. Additional negative effects of malnutrition in pregnancy include low birth weight and preterm delivery (Ogunyemi et al., 1998; Ehrenberg et al., 2003; Neggers and Goldenberg, 2003; Helgstrand and Andersen, 2005).

For the purpose of this study, SP doses were obtained from the ANC cards, and possible non-recording of doses might have led to an underestimation of doses received but this is not expected to significantly influence the observed findings.

CONCLUSION AND RECOMMENDATIONS

Results of the present study, thus, suggest that effective implementation of the IPTp using SP is an evidence-based measure for control of malaria-related anaemia in pregnancy. Reduction in maternal anaemia impacts positively on both maternal and neonatal health. The Ghana Health Service should design and implement interventions to increase the proportion of pregnant women (especially primigravid women) who take the recommended three doses of SP during pregnancy, paying attention to improved face-to-face health education, focussed antenatal care and better social mobilisation. Again, effective monitoring of the use of the SP in IPTp should be done to avoid possible development of resistance as other alternative drugs drugs are being looked at.

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