Research Article ISSN 2639-9474

Nursing & Primary Care

Pregnancy Outcomes for Women Receiving and not Receiving Intermittent Preventive Treatment for Malaria in Pregnancy using Sulphadoxine-Pyrimethamine in Gokwe North, Midlands Province, 2011

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Received: 17 June 2018; **Accepted:** 08 August 2018

Citation: Muchekeza M, Chadambuka A, Tishmanga M, et al. Pregnancy Outcomes for Women Receiving and not Receiving Intermittent Preventive Treatment for Malaria in Pregnancy using Sulphadoxine-Pyrimethamine in Gokwe North, Midlands Province, 2011. Nur Primary Care. 2018; 2(4): 1-6.

ABSTRACT

Introduction: *Intermittent preventive treatment (IPT) for malaria in pregnancy has been implemented in Zimbabwe since 2004 but no pragmatic studies on its effectiveness have been done. This study investigated the operational effectiveness of IPT in Gokwe North, a malaria endemic district in Zimbabwe with IPT coverage of 43.8% for at least one dose of IPT.*

Methods: *A prospective cohort study was conducted in 2011. Pregnant women were recruited as they attended ANC at 34 weeks gestation and classified into whether they had received IPT or not. They were followed up until they delivered where different pregnancy outcomes (prematurity, low birth weight deliveries, still birth deliveries, maternal anaemia) were assessed for women in different IPT exposure groups.*

Results: *Three hundred women were recruited into the study. The prevalence of low birth weight and severe maternal anaemia was 35% and 25.3% respectively. No placental malaria was detected by microscopy on all 300 placental blood films. In multivariate analysis, IPT was protective for low birth weight deliveries (adjusted RR 0.31 (95%CI 0.17-0.56) and for developing severe maternal anaemia (adjusted RR 0.39 (95% CI 0.22- 0.67). A mean increase in birth weight of 229grams was observed for women who had received 1 dose compared to those who had not received any dose of IPT. IPT was also found to be protective for premature deliveries (adjusted RR 0.29 (95% CI 0.17-0.49) and for still birth deliveries (adjusted RR 0.42 (95% CI 0.16- 1.07).*

Discussion: *This study demonstrated that IPT with SP is effective in reducing LBW, prematurity, still births and severe maternal anaemia. It is therefore necessary to increase coverage, access and compliance to SP in Gokwe North district. A recommendation from this study to use community based IPT distributors as a way to improve IPT coverage was taken up for serious consideration by the National Malaria Control Programme. The results of this study are also to be presented at the National Malaria Conference in October 2011 so as to assist in ensuring the deployment of effective, well evaluated, documented and evidence based malaria prevention strategies in Zimbabwe.*

Keywords

IPT, malaria, pregnancy, Gokwe North.

Introduction

Overview of malaria in pregnancy

Malaria accounts for a large part of the disease burden of poor countries, causing over a million deaths and 300 to 500 million episodes of acute illness globally each year [1,2]. Malaria is a major cause of maternal and newborn illness and death in Africa causing 10,000 maternal deaths and 75,000-200,000 infant deaths each year [3]. Malaria contributes up to 15% of maternal anaemia, 14% of low birth weight deliveries, 36% of premature delivery and

8% of infant mortality [4-6].

The World Health Organization (WHO) recommends at least two doses of intermittent preventive treatment with Sulphadoxine-Pyrimethamine (IPT/SP) during the second and third trimesters of pregnancy to prevent poor pregnancy outcomes due to malaria in pregnancy [7].

The national malaria control programme (NMCP) for Zimbabwe aims to achieve IPT of malaria for at least 85% of pregnant women by 2012 [8]. National IPT-SP recommendations are that patients in high transmission areas should receive 3 doses of SP due to high prevalence of HIV in pregnant women (15.5%). First dose is to be given at quickening and subsequent doses at 26 -28 weeks then 32 -34 weeks [9].

Gokwe North is one of 33 districts with a high burden of malaria in Zimbabwe implementing IPT-SP since 2004 [8,9]. The IPT coverage for Gokwe North for the year 2009 was 43.8% for at least a single dose of IPT [10].

The proportion of LBW deliveries and neonatal deaths reported in Gokwe North for the period 2007-2009 are shown in the table below.

Variable	2007	2008	2009
Total births	4469	4653	4164
% LBW deliveries	8	4	6
% neonatal deaths	2	3	2
% neonatal deaths in LBW babies	50	28.5	14

We hypothesised that these pregnancy outcomes could be attributed to malaria in pregnancy and could be averted if appropriate and effective malaria prophylaxis is taken during pregnancy. The operational effectiveness of IPT-SP has not been investigated in Gokwe North District and pragmatic studies to evaluate the effect of IPT- SP when delivered under 'real life conditions' have not been undertaken in Zimbabwe. We therefore investigated the pregnancy outcomes for women receiving and not receiving IPT using SP for malaria control in pregnancy in Gokwe North district.

Materials and Methods

We conducted a prospective cohort study at Mtora and Chireya mission hospitals in Gokwe north District among women attending antenatal care(ANC) clinic. Pregnant women were recruited at >= 34 weeks gestation. The women were categorized into groups depending on whether or not they had received IPT-SP and the number of doses received for those who had received IPT.

Those recruited at 34 weeks were followed up until the time of delivery to see the pregnancy outcomes. Only women aged 15 years and above with singleton pregnancies as detected by abdominal palpation were included. Women not consenting, those less than 15 years of age and having a multiple pregnancy as detected by abdominal palpation were excluded from the study. HIV positive pregnant women on Cotrimoxazole prophylaxis were excluded from the study. The effects of co-morbid pathologies among pregnant women were excluded and controlled for at multivariable analysis.

A minimum of 326 study participants was required. SP intake was confirmed by checking if the dose was ticked on the ANC card by the health worker who would have observed the woman take the medication. A structured interviewer administered questionnaire was used to collect information on socio-demographic characteristics, use of IPT, previous history of malaria/fever in current pregnancy, previous HIV test and result. ANC cards from all participants were reviewed to determine the gestational age at first visit, number of ANC visits and IPT doses given during the course of the pregnancy.

The recruited participants were then followed up until the time of delivery. At delivery the status (live birth versus still births) of the pregnancy outcome was recorded. The birth weight of the new born was also measured using a neonatal digital scale Two readings were made by two different observers with discordant readings being read by a third reader. Gestational age was calculated using the last menstrual period date as reported by the woman and also estimated by measuring the uterine fundal height.

A finger stick blood sample was drawn from the mother for hemoglobin measurement using a Hemocue hemoglobin detection system (Hemocue 201). This system measures hemoglobin from a drop of blood using a battery operated photometric device. The device easy to use and does not require specialized training. This system displays hemoglobin measurements in grams/dl within 15 to 60 seconds.

After delivery of the placenta the maternal side of the placenta was wiped and incised to collect pooled blood from the intervillous spaces using a micropipette. The blood was then dropped onto a slide to make a thick smear for microscopy to check for malaria parasites. Placental thick blood films were stained with Giemsa and examined under oil immersion for the presence of malaria parasites. Upon identification of malaria parasites in 100 microscopic fields, simultaneous counting of 200 white blood cells (WBCs) and the number of trophozoites in each field was done. Parasite densities were estimated using an assumed leukocyte count of 8000 leukocytes/L of blood. The number of parasites per microlitre (µl) of blood was then calculated as follows: (No. of parasites counted/200 WBC) x 8000 (standard constant) = parasites/µl.

Laboratory investigations were performed by two qualified microscopists. Discordant results were read by a laboratory technician in the district as a tie-breaker. A random10% of the specimens were read at the provincial hospital laboratory by a qualified laboratory scientist. EPI-INFO statistical software was used to generate frequencies of the key variables, proportions, and means of variables and contingency tables, relative risk (RR), 95% confidence intervals, do significance testing. Differences between

proportions of the treatment groups were tested using the z-statistic, chi-square test or Fisher's exact test. Stratified analysis was performed to assess for possible confounding. Logistic regression analysis was done to control for confounding. Variables that were significant in Univariate analysis or were known or suspected to be confounders or independent predictors in other literature were included in the logistic regression models. Treatment group (IPT versus no IPT) was maintained as a variable in each of the models regardless of statistical significance. Other variables were retained if the p value of the adjusted risk ratio was < 0.05.

Permission to carry out the study was obtained from the Health Studies Office, the Provincial Medical Director Midlands and the District Medical Officer- Gokwe North district. Informed written consent was obtained from all study participants. Health education was given to study participants after each interview. Ethical approval for the study protocol was obtained from the Medical Research Council of Zimbabwe.

Results

A total of 330 women were recruited from the 347 antenatal care attendees who were seen during the study period. A total of 300 women were however successfully recruited into the study. Of these, 210 (70%) had received some dose of IPT while 90 (30%) had not received any dose of IPT. Among women who received IPT, 57 (19%) had received full doses of IPT, 62 (20.7%) had received two doses of IPT and 91 (30.3%) had received a single dose of IPT.

Pregnant women who received IPT were significantly different from women who did not receive IPT with regards to employment status, proportion of booked pregnancies, proportion of HIV tests and proportion of houses sprayed for malaria prevention. The two groups were however similar in all other socio-demographic characteristics such as level of education, median age, parity and median number of ANC visits attended.

Pregnant women in Gokwe North were knowledgeable on the symptoms of malaria since more than 85% in both groups (IPT versus No IPT) correctly reported on the symptoms of malaria. The least reported symptom of malaria was joint weakness which was reported by 66.7% of women who had received IPT and 81.8% of women who had not received IPT.

The most commonly reported effects of malaria in pregnancy were premature deliveries, delivering low birth weight babies and still births as reported by more than 65% of women in both groups. Less than 50% of women in both groups reported maternal anaemia and maternal deaths as effects of malaria in pregnancy.

The prevalence of Insecticide treated net (ITN) use among pregnant women who had received and not received IPT was 58.6% and 58.9% respectively. Seventy six percent of women who received IPT had their houses sprayed in the last IRS season for malaria prevention while 61.1% of women who did not receive IPT had their houses sprayed. Twenty percent of women who had not received IPT 20% reported having experienced 2 or more fever episodes in the current pregnancy compared to 8.6% in the IPT group. A larger proportion (16.7%) of women who had not received IPT was treated for malaria during the current pregnancy compared to 11.9% who had received IPT who were treated for malaria in the current pregnancy. Eighty three percent (83%) of the women in the on IPT exposure group had booked pregnancies.

There were a greater proportion of still births (13.3%versus 4.8%), low birth weight deliveries (56.7% versus 24.3%), premature deliveries (50% versus 23.8%) and women who developed severe maternal anaemia (38.9% versus 19.5%) in women who did not receive IPT compared to those who received IPT and this was statistically significant. There was a mean birth weight increase of 229g for women who had received 1 dose of IPT compared to those who had no exposure to IPT.

Receiving IPT was significantly protective low birth weight deliveries, premature deliveries, still births and severe maternal anaemia as shown in table 1.

Parameter	IPT-SP vs No IPT- SP		
	RR 95% CI p- value		
Clinical malaria	0.71	0.39- 1.28	0.27
2 or more fever episodes in pregnancy	0.82	0.52- 1.28	0.38
Maternal anaemia (Hb< 11 g/dl)	0.94	0.79- 1.13	0.5
Severe maternal anaemia (Hb<8g/dl)	0.50	*0.34- 0.73	0.0004
Premature delivery	0.47	*0.35- 0.65	0.00001
LBW delivery	0.42	*0.32- 0.58	0.000001
Still birth delivery	0.36	*0.16- 0.80	0.009

Table 1: The risk of clinical malaria, fever episodes and poor pregnancy outcomes for women who received and did not receive IPT, Gokwe North, 2011. *statistically significant.

All exposures to IPT were significantly protective of poor pregnancy outcomes (LBW, prematurity, still births, severe maternal anaemia) in Gokwe North District. Having received 2 or more doses of IPT however conferred the greatest protection against these poor pregnancy outcomes compared to single or no IPT exposure as shown in table 2.

Pregnancy Outcomes	No IPT RR 95% CI		0 dose IPT RR 95% CI		>=2 doses IPT RR 95% CI	
Still births	Reference	-	0.41	0.15-1.12	0.32	*0.12-0.86
Low birth weight	Reference	-	0.52	*0.36-0.75	0.36	*0.24-0.53
Premature delivery	Reference	-	0.55	*0.37-0.81	0.42	*0.28-0.63
Severe maternal anaemia	Reference	-	0.62	*0.40-0.97	0.41	*0.25-0.67

Table 2: The risk of poor pregnancy outcomes for women in different IPT exposure groups, Gokwe North, 2011.

No placental malaria was detected from microscopy of blood films of all 300 participants regardless of whether they had received IPT or not. As a result the risk of placental malaria in women receiving

and not receiving IPT in Gokwe North could not be determined.

In multivariate analysis IPT remained significantly protective of low birth weight deliveries, prematurity and severe maternal anaemia as shown in table 3. The preventive fraction of IPT against delivering LBW babies, prematurity and still birth deliveries was above 50%. The preventive fraction of IPT against severe maternal anaemia was 5.7%.

Parameter	IPT-SP vs No IPT-SP		
	Adjusted RR 95% CI	p-value	
Still birth delivery	0.42	0.16- 1.07	0.07
Premature delivery	0.29	*0.17- 0.49	0.0001
Severe maternal anaemia	0.39	*0.22- 0.67	0.007
LBW delivery	0.31	*0.17- 0.56	0.0001

Table 3: Risk of poor pregnancy outcomes for women receiving and not receiving IPT in multivariate analysis, Gokwe North, 2011. *statistically significant.

Discussion

Our study has revealed that IPT is effective in preventing poor pregnancy outcomes associated with malaria in pregnancy in Gokwe North District when delivered under real life conditions. The protective effect of IPT was observed regardless of the number of doses received even though the proportion of women who had received full IPT doses was low (19%).

Similar findings were reported in studies done in Malawi, Nigeria and Mali where IPT was found to be protective of delivering low birth weight babies, premature deliveries and developing maternal anaemia regardless of the dose received [11-13]. The IPT coverage for Gokwe North for at least 1 dose was 43.8%. This point to one of the major challenges of IPT provision in Zimbabwe, where this service is largely health worker provided and hence depends on pregnant women booking at health facilities for them to access it. The proportion of pregnant women who would access IPT could be possibly increased if this service were to be decentralized to the community by utilization of community health workers.

A study done in Uganda to assess the effect of new IPT delivery approaches by the use of drug-shop vendors, traditional birth attendants, community health workers and adolescent peer mobilisers to administer IPT has also shown an improvement in the uptake, access and compliance to IPT [14]. With the new approaches, 92.4% of women received IPT during the second trimester as recommended by policy compared to 76.1% at health units (p-value< 0.0001).

Eighty three (83.3%) of women in the no IPT exposure group had booked pregnancies. This means that these women should have at least received a single dose of IPT but they did not. The reasons for their failure to receive IPT are unclear and have not been fully explored but may relate to poor antenatal attendance, late booking, health workers forgetting to give IPT, IPT drug stock outs and the strict time limits of the provision of IPT according to the Zimbabwe National Malaria Prevention and Control Guidelines [9].

Women in both IPT exposure groups (IPT vs No IPT) exhibited good knowledge on malaria and its effects in pregnancy by reporting correctly on malaria symptoms and on its effects in pregnancy. This knowledge was however not being translated into action by the women in the no IPT exposure as shown by failure to take up IPT for prevention of poor pregnancy outcomes. This was probably because this group of women had a poorer perception of their susceptibility to these poor pregnancy outcomes compared to their counterparts who had received IPT.

Thirteen percent of women who did not receive IPT had still birth deliveries compared to 4.8% of women exposed to IPT who had the same pregnancy outcome. Several studies done in Kenya, southern Ghana, Malawi and Nigeria have also demonstrated a significantly greater proportion of still birth deliveries among women who had no IPT exposure compared to those who had this exposure [12,13,15,16].

The proportion of LBW deliveries was greater in those women who were not exposed to IPT compared to those exposed. This is also similar to findings by Hommerich et al., 2007 in their study in southern Ghana where the prevalence of LBW deliveries among women who had no IPT exposure was reported to be 15.4% compared to 10% and 9.3% for women who had received one and three doses of IPT respectively [16]. Several studies done in Africa have also reported similar findings of the prevalence of LBW deliveries among pregnant women with different exposures to IPT [12,13,17,18].

A greater proportion of women who did not receive IPT developed severe maternal anaemia compared to those who had received IPT developing the same outcome. Rogerson et al., 2000 in their study to evaluate the effectiveness of IPT in reducing malaria morbidity found out that maternal haemoglobin concentrations were higher in the SP group compared to the non-SP group with effects more marked in first and second pregnancies12. Similar findings were also reported by two separate studies done in Nigeria to evaluate the use IPT in malaria endemic areas [17,18].

An increase in the mean birth weight of 229 grams was observed for women who had received 1 dose of IPT compared to those who had no exposure to IPT. This is supported by findings from a study by van Eijk et al., 2004 in a large observational study conducted in Western Kenya. In this study IPT was found to be protective of delivering a LBW baby with a dose response relationship being observed with a mean increase in birth weight of 61grams for each increment in the number of SP doses [15].

In our study, receiving IPT was observed to be protective of developing clinical malaria although this finding was not statistically significant. This finding seems to support the hypothesis that IPT has a prophylactic effect for the development of new malaria infections on the mother apart from its protective effect against placental malaria [19].

In a study done in Ibadan, Nigeria, Falade et al., 2007 reported that IPT was effective in reducing the prevalence of maternal malaria parasitaemia [20]. Similar findings were also reported by Kayentao et al., 2005 in their study to compare intermittent preventive treatment with Chemoprophylaxis for the prevention of malaria during pregnancy in Mali [11].

In both our bivariate and multivariate analysis, receiving IPT was found to be significantly protective of delivering LBW babies with an adjusted risk ratio of 0.31 (p- value= 0.0001).

Studies done in other African countries also demonstrated this effect of IPT on the risk of delivering LBW babies among pregnant women in areas of both low and high malaria transmission [11-13,15,16,19].

We also found the receipt of IPT to be significantly protective of premature deliveries with an adjusted risk ratio of 0.29 (95% CI 0.17-0.49). These findings are similar to those obtained in studies done by Rogerson et al 2000, in Malawi where those women who had received IPT were reported to be less likely to deliver premature babies than those who had not received IPT [12].

In Gokwe North, women who had received IPT were also found to be 58% less likely to deliver stillbirths than those who had not received IPT. This protective effect of IPT was also reported in other studies [11,13,17] including in randomized controlled trials [22] which had less limitations such as exposure misclassification which is often inherent in observational studies like the one we conducted.

The protective effect of IPT against developing severe maternal anaemia was also observed in this study with an adjusted risk ratio of 0.42 (p-value= 0.007). A study done in Ghana by Hommerich et al., 2007 demonstrated a substantial decline in maternal anaemia was the receipt of IPT among pregnant women16. Several other studies done in Africa in areas of both high and low malaria transmission have demonstrated a significant protective effect of IPT against maternal anaemia [11-13,15,17,18,21,22].

No placental malaria was detected in both the IPT exposure and non-exposure group. This could mean that the level of malaria transmission in Gokwe North was not high enough to cause detectable placental parasitaemia by microscopy. Microscopy has been reported by some authors to often miss placental parasitaemia which may be picked up by other methods such as placental histology [24].

Even in higher malaria transmission settings, pathologically significant placental sequestration has been reported to take long since the placenta selectively accumulates parasites that bind to certain proteolglycans [19].

A study done in southern Ghana found out that histidine rich protein -2 capture test was able to detect submicroscopic infections in seemingly aparasitaemic women [25]. This study also concluded that placental malaria was often missed by standard microscopy and that the gold standard for placental malaria diagnosis was histology.

The absence of placental malaria for both groups of women in Gokwe North could also be attributed to the success of other malaria preventive strategies such as the use ITNs and Indoor Residual Spraying (IRS) for malaria prevention. Over the past three years the district has constantly recorded lower numbers of malaria cases compared to previous years 10. The success of additional malaria preventive methods could have conferred protection against developing placental malaria to both IPT exposure groups making it impossible to exhibit any significant differences with regards to this outcome.

Contrary to our findings with regards to the detection of placental malaria in the different IPT exposure groups, several studies have demonstrated a significant protective effect of IPT against placental malaria infections with higher placental malaria densities being observed in those women who had not received IPT compared to those who had received it [11-13,15,17,18,21-23].

The protective effect of IPT was more pronounced for women who had received 2 or more doses of IPT compared to a single dose or no IPT exposure for all pregnancy outcomes (LBW, prematurity, still births, severe maternal anaemia) [12,15,16,18,21]. The preventive fraction of IPT against still birth deliveries, low birth weight deliveries and premature deliveries was above 50%. This means that more that 50% of these poor pregnancy outcomes were averted by giving IPT to pregnant women in Gokwe North District.

The reduction of such outcomes to this extent could contribute greatly to child health by reducing neonatal and infant morbidity and mortality. These effects of IPT could be further increased by improving coverage and adherence to treatment in Gokwe North District.

Intermittent Preventive Treatment using SP in pregnant women is therefore still highly effective in improving pregnancy outcomes as evidenced by a lower prevalence of clinical malaria, premature deliveries, low birth weight deliveries, still births and severe maternal anaemia among women who had received IPT compared to those who had not. IPT in Gokwe North District still holds great benefits for pregnant women despite the escalating global resistance to Sulphadoxine-Pyrimethamine.

The National Malaria Control Programme in Zimbabwe therefore needs to ensure a constant supply of SP to all health facilities in malaria endemic areas in order to increase IPT coverage in antenatal care. The use of community based IPT distributors should be evaluated for consideration as an option to improve IPT coverage. As a result of this study, The Ministry of Health and Child Welfare Zimbabwe is seriously considering the use of community based IPT-SP distributors to improve coverage. Further research however may need to be conducted to determine the anti-parasitic effect of IPT-SP in an area of high malaria transmission in Zimbabwe.

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