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FACTORS INFLUENCING SULFADOXINE-PYRIMETHAMINE RESISTANCE IN PLASMODIUM FALCIPARUM AMONG PREGNANT WOMEN IN ILORIN, NIGERIA

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ABSTRACT

Malaria remains a significant public health concern in sub-Saharan Africa, especially among pregnant women. Resistance to sulfadoxine-pyrimethamine (SP), a key drug for treatment and prevention, is rising. This study investigated the prevalence of SP resistance among pregnant women in Ilorin, Nigeria, across pregnancy trimesters and healthcare facility types, and identified influencing factors. A cross-sectional study was conducted among 764 pregnant women attending Primary, Secondary, Tertiary, and Private Health Facilities. Facilities were categorized as Primary (basic care), Secondary, Tertiary (advanced care), and Private (privately owned, with varying levels of specialisation). Resistance prevalence was defined as the percentage of pregnant women in each trimester exhibiting resistance to SP. Prevalence rates were 37.6% (first trimester), 28.9% (second trimester), 31.9% (third trimester), and 38.7% (at delivery). The highest prevalence occurred in Private Health Facilities during the first trimester (45.5%) and Secondary Health Facilities at delivery (66.7%). Multivariate regression analysis revealed that occupation, blood group, and IPTp use were the significant predictors of SP resistance. For instance, occupation was associated negatively with resistance in the first trimester: coefficient = -0.144, p = 0.027, whereas hypertension and proximity to stagnant water were significant at delivery, coefficients -0.342, p = 0.009 and -0.296, p = 0.035, respectively. These findings call for targeted malaria control strategies, considering trimester-specific risk factors and healthcare facility type. For example, improved access to IPTp and early detection of hypertension in the second and third trimesters may reduce resistance.

Keywords: Malaria, Sulfadoxine-pyrimethamine (SP) resistance, Risk factors, Pregnant women

INTRODUCTION

Malaria remains a major public health challenge in sub-Saharan Africa, with Nigeria accounting for a significant proportion of this burden due to Plasmodium falciparum. Pregnant women are at an increased risk of malaria infections, which can lead to severe complications: maternal anemia, low birth weight, and increased mortality rates in both mothers and infants (WHO, 2021). In Nigeria, IPTp-SP was adopted for the prevention of such adverse outcomes (Ogba et al., 2022). However, drug resistance, especially to SP, has been reported to be a major concern for IPTp-SP (Ajonina et al, 2024).

Resistance to SP in Plasmodium falciparum is driven chiefly by certain mutations in the genes encoding dihydrofolate reductase (Pfdhfr) and dihydropteroate synthase (Pfdhps) of the parasite. These enzymes are important in the biosynthetic pathway of folate, a pathway targeted by SP. These mutations in Pfdhfr decrease the binding affinity of pyrimethamine, while mutations in Pfdhps reduce the effectiveness of sulfadoxine. The accumulation of these mutations results in reduced susceptibility of the parasite to treatment with SP (Fagbemi et al., 2020).

Studies conducted in Benin and Uganda have documented increasing resistance to SP due to mutations in the Pfdhfr and Pfdhps genes, which are associated with treatment failure (Tuedom et al., 2021; Moussiliou et al., 2013). Resistance through the widespread dhps-431V mutation has been reported in Nigeria, particularly in Enugu State (Oguike et al., 2016). In Ogun State a study conducted by Fagbemi et al. (2020) among pregnant women with asymptomatic P. falciparum infection reported a high prevalence of Pfdhfr triple mutations (N51I, C59R, S108N) at 98%, and Pfdhps mutations A437G and A581G at 98% and 71%, respectively. The study further reported that 44% of the isolates had quintuple mutations with the CIRNI-SGKGA haplotype, indicating a very high resistance to SP. On the other hand, data from Ilorin, Kwara State, is scanty. However, a study on the utilization of SP for IPTp among parturients in Ilorin emphasized that SP is still being used for malaria prophylaxis. Specific data on the prevalence of Pfdhfr and Pfdhps mutations in this region were not provided, thus again emphasizing the need for localized studies to inform treatment policies (Adeniran et al., 2018).

Resistance and the spread of SP-resistant P. falciparum strains have major implications for public health, especially to the pregnant women population (Dosoo et al., 2022). SP is an established part of IPTp, designed to prevent malaria-associated adverse outcomes among mothers and infants. Resistance compromises the efficacy of this intervention and thus contributes to increased risk for maternal anemia, low birth weight, and perinatal mortality (Muthiani et al., 2023).

The rising SP resistance threatens the success of malaria prevention programs during pregnancy, especially in regions like Ilorin, North Central Nigeria. This study, therefore, attempts to determine the frequency of sulfadoxine-pyrimethamine among pregnant women attending ANC clinics in different health facilities in Ilorin, as well as factors that may be contributing to the development and spread of resistance. The study investigates these factors to generate data that can inform effective malaria control strategies and alternative treatments in the region.

MATERIALS AND METHODS

Study Area and Setting

The study was conducted in Ilorin, the capital of Kwara State, located in the North Central region of Nigeria. As of the year 2022, Ilorin remains an important cultural and economic link between the north and south, with an estimated population of over 900,000. The ethnically diverse city comprises Yoruba, Hausa, and Fulani, among others, with balanced religious affiliations between Islam and Christianity. Ilorin is characterized by a tropical savanna climate divided into wet and dry seasons. The wet season starts in April and lasts through October, with high levels of rainfall and humidity. From November to March is the dry season, with the addition of harmattan winds and less rain. The temperature in Ilorin annually ranges from 22°C to 34°C, with the hottest months being February and March and the coldest being December and January.

Various levels of healthcare facilities complement each other to show the well-developed health care in Ilorin. There are 40 PHCs spread across Ilorin West, Ilorin East, and Ilorin South local government areas. Secondary healthcare facilities include eight government-run hospitals: General Hospital Ilorin, Civil Service Hospital, among others. The tertiary healthcare service levels include the University of Ilorin Teaching Hospital and the Kwara State University Teaching Hospital, which offer specialist and advanced care. Finally, there are approximately 45 accredited health establishments; this adds to the choice of health care in the area. By these private hospitals and smaller clinics, a supplementation of the public health care will take place to offer a wide range of services to the populace.

Study design

A cross-sectional study among pregnant women in the second and third trimesters was conducted to evaluate the use of sulfadoxine-pyrimethamine. Informed consent was obtained, after which SP was provided as directly observed therapy according to WHO recommendations. Prenatal checks were carried out by qualified midwives. Blood samples were collected on three occasions for hemoglobin and parasitemia determination. Women in the first trimester were excluded because of confounding factors involving nausea, pregnancy losses, and risks from SP use during organogenesis. Women in the postpartum period were also excluded since the physiological condition is different, and the result will be biased. The focus was on SP administration during pregnancy to check for efficacy and safety.

The survey questionnaire went through three steps of validation: expert review by public health and malaria researchers regarding content validity, a pilot test with 50 pregnant women for clarity and reliability, and refinement based on feedback in order to address ambiguities. Cronbach's alpha of 0.85 confirmed internal consistency. All health facilities were given a standardized protocol manual detailing the administration of SP, collection of blood samples, and screening for malaria. Protocol adherence was ensured through the training of staff and routine supervision. The SP resistance test protocol was revised to reflect the current best practices, incorporating the latest WHO guidelines and studies such as Uwimana et al. (2022) for accuracy.

The design considered the seasonal trend in malaria and stratified the collection of data across seasons. Local usage of SP was investigated through interviews as well to contextualize findings within the local epidemiological setting.

Sampling

A total of 1,200 pregnant women were screened, and 437 were excluded: 290 in the first trimester, 87 postpartum, and 60 who refused or did not qualify. Through stratified sampling across health facilities, a total of 763 eligible women in their second and third trimesters were selected.

Total Pregnant Women Screened for Eligibility (N = 1,200)

- Excluded (N = 437)
  - Women in First Trimester (N = 290)
  - Postpartum Women (N = 87)
  - Declined Participation or Did Not Meet Other Criteria (N = 60)
- Eligible Pregnant Women in Second and Third Trimester (N = 763)

Stratified Sampling by Healthcare Facility Representation

Proportional Allocation of Participants to Selected Facilities

Final Participants Included in the Study (N = 763)

Stratified sampling guaranteed good representation of pregnant women across different healthcare facilities in Ilorin to achieve the total sample size targeted, which is 763, proportionately allocated to each facility. Of these, 162 subjects were assigned to Primary Healthcare Centers 21.2%, 200 to Secondary Healthcare Facilities 26.2%, and 201 to Tertiary Healthcare Facilities 26.3% to ensure due representation. Besides, 200 participants were sampled from private health facilities 26.2% to determine the contribution of private health to the region. This method of sampling emphasized care in secondary and tertiary facilities while indicating the contribution of private health.

Blood samples collection

Blood samples were collected in 10-ml EDTA Vacutainers and tested for malaria, hemoglobin levels, and HIV. Samples were also stored for genotyping. Thick blood smears were also prepared, stained with Giemsa, and used to count malaria parasites and assess parasitemia. The blood specimens were then transported in cool packs to storage at -20°C until further analysis. Data collection was through the use of a validated survey questionnaire adapted from the NMIS and pretested for its reliability. In addition, weight and height were measured using standard anthropometric methods to assess the nutritional status, with BMI being calculated for determining the levels of malnutrition.

Malaria screening

Malaria screening was performed using a Rapid Diagnostic Test. A sterile lancet pricked the fingertip, and a small drop of blood was collected using the sample collection device provided in the RDT kit. Take the blood specimen and place it onto the sample well or designated area on the RDT cassette, following the instructions in the kit. Added the specified number of drops of buffer solution to the buffer well or onto the test cassette, which helped the blood and reagents to move across the test strip. The test was then allowed to incubate for 15–20 minutes. A positive result was indicated if two lines appeared: one in the control line region (C) and one in the test line region (T).

Sulfadoxine-Pyrimethamine (SP) resistance determination

The susceptibility to sulfadoxine-pyrimethamine was determined by the schizont maturation inhibition technique of Koehne, (2022). The blood samples were diluted with RPMI 1640 medium to achieve a parasitemia of 0.5-1% and a hematocrit of 1.5-2%, and the parasites were synchronized at the ring stage by incubation for 12-24 hours at 37°C in a CO_2 incubator. Serial dilutions for sulfadoxine and pyrimethamine at concentrations ranging from 0.01 µg/mL to 10 µg/mL were prepared to measure the IC_{50} in inhibiting the growth of parasites. To a 96-well microtiter plate, 100 µL of parasite culture was aliquoted into each well, followed by the addition of 100 µL of drug solutions prepared at varying concentrations. Plates were incubated at 37°C with 5% CO_2 for 72 hours and parasite growth measured as above by Giemsa-stained thick blood films. Inhibitory effects of the drugs were estimated by comparing the parasite growth in treated and control wells.

Statistical analyses

Data were analyzed using SPSS version 25 for Windows. Comparisons of means and percentages were made by appropriate statistical tests, including chi-square. Statistical significance was considered at $p < 0.05$. Besides, a multivariate logistic regression analysis was conducted to determine the relation between the dependent and independent variables.

Ethical Approval

Approval for the study was obtained from the Kwara State Ministry of Health.

RESULTS AND DISCUSSION

Socio-demographic characteristics

Table 1: Socio-demographic characteristics of pregnant women in Ilorin, North Central Nigeria, by healthcare institution: Primary Health Care (PHC), Secondary Health Facility (HF), Tertiary Health Facility (HF), and Private Health Facility (HF). Participants surveyed were 764 across these institutions.

The age groups were between 21 and 30 years, representing the highest proportion of 33.0%; thus, the average age for all institutions falls between 27 and 28 years. Ethnicity was dominated by the Yoruba ethnic group, 91.9%, while Hausa, Fulani, Igbo, and others were a minority in the population. The religions were dominated by Muslims, 78.9%, while the remaining 21.1% professed to be Christians. Education level differed between facilities, with the Secondary HF having the highest proportion of women with no formal education, while the Private HF had the most women with tertiary education. The overall distribution of education was as follows: No formal education 8.9%, Primary 14.7%, Secondary 42.1%, and Tertiary 34.3%.

Occupation-wise, the majority of them were business/self-employed 80.9%, although a large proportion was into farming/fishing 85.7% in the Private HF and civil servants in the Tertiary HF 47.5%. Unemployment in the Private HF was at 58.1%.

Table 1: Socio-demographic Characteristics of the pregnant women pregnant women in Ilorin North central Nigeria

Variables	Health Facilities				Total
	PHC	Secondary HF	Tertiary HF	Private HF	
Age Group					
≤20	0 (0.0)	13 (50.0)	1 (3.8)	12 (46.2)	26(3.4)
21-25	45 (17.9)	60 (23.8)	70 (27.8)	77 (30.6)	252(33.0)
26-30	90 (27.9)	88 (27.2)	64 (19.8)	81 (25.1)	323(42.3)
31-35	27 (22.5)	27 (22.5)	49 (40.8)	17 (14.2)	120(15.7)
36-40	0 (0.0)	9 (23.1)	17 (43.6)	13 (33.3)	39(5.1)
≥41	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	3(0.4)
Mean ±Std.	*27±4*	*27±5*	*28±5*	*27±5*	*28±4*
Ethnicity					
Yoruba	144 (20.5)	183 (26.1)	186 (26.5)	188 (26.8)	701(91.9)
Hausa	0 (0.0)	11 (61.1)	4 (22.2)	3 (16.7)	18(2.4)
Fulani	0 (0.0)	5 (33.3)	1 (6.7)	9 (60.0)	152.0)
Igbo	9 (45.0)	1 (5.0)	10 (50.0)	0 (0.0)	20(2.6)
Others	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	9(1,2)
Religion					
Christianity	36 (22.4)	42 (26.1)	49 (30.4)	34 (21.1)	161(21.1)
Islam	126 (20.9)	158 (26.2)	152 (25.2)	166 (27.6)	602(78.9)
Traditional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)
Educational Level					
No formal	21 (30.9)	12 (17.6)	5 (7.4)	30 (44.1)	68(8.9)
Primary	8 (7.1)	47 (42.0)	21 (18.8)	36 (32.1)	112(14.7)
Secondary	90 (28.0)	81 (25.2)	87 (27.1)	63 (19.6)	321(42.1)
Tertiary	43 (16.4)	60 (22.9)	88 (33.6)	71 (27.1)	262(34.3)

Occupation					
Farming/Fishing	0 (0.0)	0 (0.0)	2 (14.3)	12 (85.7)	14(1.8)
Business/Self Employed	144 (23.3)	185 (30.0)	145 (23.5)	143 (23.2)	617(80.9)
Civil Servants	18 (17.8)	8 (7.9)	48 (47.5)	27 (26.7)	101(13.2)
Unemployed	0 (0.0)	7 (22.6)	6 (19.4)	18 (58.1)	31(4.1)

Environmental care

Fig. 1 shows the kind of toilet facilities available for pregnant women attending health care institutions in Ilorin, Nigeria. The water closet WC is the most prevalent and utilized by 74.8% of respondents, especially in tertiary 31.3% and private health facilities 31.0%. Pit latrines are used by 12.5% of the total population; the highest usage was in Secondary HF at 28.4%. The bush is utilized by 77.9% at PHC and only 1.1% at Tertiary HF. 0.3% had no access to toilet facilities, which were found only in PHC.

Fig. 2 shows the distance of pregnant women from stagnant water. Very far is the highest for the modal, with 75.0%, where Tertiary HF leads at 28.8%. The second highest level is far at 23.2%, with Private HF leading at 34.5%. Only 1.8% of women are close to stagnant water, all located at Private HF. None reported "None," so they were all knowledgeable about stagnant water in their environment.

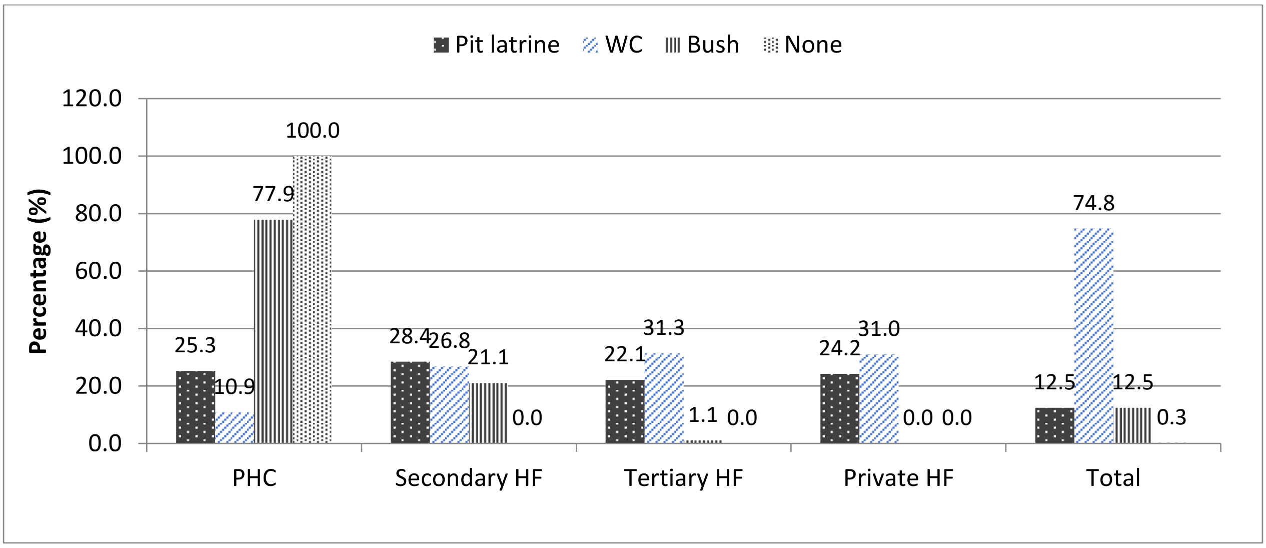

Figure 1: Use of toilet by the pregnant women in Ilorin North central Nigeria

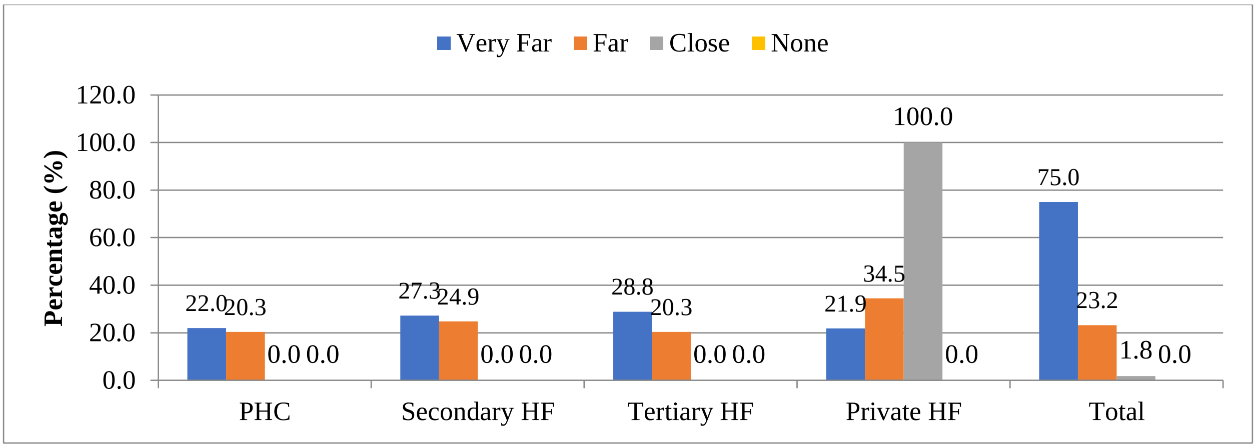

Figure 2: Proximity of water source to the household of pregnant women in Ilorin North central Nigeria

Health and Anthropometric indices

Table 2 presents the distribution of weight, mean height, blood pressure, and body mass index at different pregnancy visits: first, second, third, and delivery. The mean weight remained almost constant, with minor deviations: 68.9 ± 13.0 kg at the first visit, 69.3 ± 12.7 kg at the second, 69.0 ± 12.9 kg at the third and 68.8 ± 13.1 kg at delivery. The height remained the same, 1.6 ± 0.10 meters, throughout the visits. The systolic blood pressure was 114.4 ± 14.1 mmHg during the first visit, and it kept wavering up to 114.2 ± 14.3 mmHg at the time of delivery. The diastolic pressure was maintained within a similar range, starting from 70.8 ± 9.3 mmHg during the first visit to 70.5 ± 9.2 mmHg at delivery. BMI did not change either: 26.2 ± 5.8 kg/m² at the first visit compared to 26.1 ± 5.9 kg/m² at delivery. Distribution by categories of BMI was as follows: underweight, 4.7%; normal weight, 45.0%; overweight, 29.2%; and obese, 21.1% at the first visit. At delivery, the distribution was 4.8% underweight, 48.1% normal weight, 29.7% overweight and 17.4% obese. Hypertension decreased slightly from 19.7% at the first visit to 17.5% at delivery.

Table 2: Weight, Height, BP and BMI of the pregnant women in Ilorin North central Nigeria across trimester

Variables	First Visit	Second Visit	Third Visit	Delivery Visit
N	763	690	689	686
Weight (kg) [a]	68.9 ± 13.0	69.3 ± 12.7	69.0 ± 12.9	68.8 ± 13.1
Height (m) [a]	1.6 ± 0.10	1.6 ± 0.09	1.6 ± 0.10	1.6 ± 0.10
Systolic (mmHg) [a]	114.4 ± 14.1	115.0 ± 13.9	114.7 ± 14.0	114.2 ± 14.3
Diastolic (mmHg) [a]	70.8 ± 9.3	71.2 ± 9.1	70.9 ± 9.4	70.5 ± 9.2
BMI(Kg/m^2) [a]	26.2 ± 5.8	26.4 ± 5.7	26.3 ± 5.8	26.1 ± 5.9
BMI Group[1]				
- Underweight	36 (4.7%)	34 (4.9%)	35 (5.1%)	33 (4.8%)
- Normal	343 (45.0%)	326 (47.2%)	328 (47.6%)	330 (48.1%)
- Overweight	223 (29.2%)	201 (29.1%)	205 (29.8%)	204 (29.7%)
- Obese	161 (21.1%)	129 (18.7%)	121 (17.6%)	119 (17.4%)
Hypertension Group[1]				
- Normal	613 (80.3%)	574 (83.2%)	572 (83.0%)	566 (82.5%)
- Hypertensive	150 (19.7%)	116 (16.8%)	117 (17.0%)	120 (17.5%)

[a] Value is express as mean standard deviation, [1]The value is express in n(%)

Malaria Intervention

Table 3: Malaria prevention practices among pregnant women in Ilorin, North Central Nigeria. The table now shows the specific use of IPTp-SP in pregnancy. Indeed, out of the total, 610 women, which amounts to 79.6%, received IPTp-SP. The highest came from Secondary HF, 200 (32.8%), Tertiary HF, 201 (33.0%), and Private HF, 182 (29.8%). In contrast, IPTp-SP was received by only 27 women from PHC, which accounts for 4.4%, while 95.5% of PHC participants reported not having taken it. Another 11.4% (87 women) were unsure, mainly from PHC (82.8%, n=72). ITNs use was reported by 610 women, 80.0%; the highest usage was seen in Private HF with 188 women, 30.8%, while PHC had the lowest with 120 women, 19.7%. 353 women responded to sleeping under an ITN the previous night, and Private HF was the highest complying at 86.0% (n=172). Similarly, 46.2% stated that they have always slept under an ITN, with again the maximum compliance in Private HF at 80.0% (n=160). On the other hand, a relatively large proportion of participants in PHC (25.9%, n=42) and Secondary HF (25.0%, n=50) did not answer these questions at all. About IPTp use, the women reported consistent use at 70.0%, while 20.1% never used it.

Malaria Screening

Table 4 is a presentation of malaria screening result in pregnant women by trimester. In the first visit, out of 763 women tested, 156, 20.4% were positive for malaria by RDT, and 162, 21.2% by microscopy, with the mean number of parasites being 189.79 ± 23.10 parasites/µL. In the second trimester, out of 690 women tested, 128, 18.6% tested positive by RDT, while 125, 18.1% were positive by microscopy with a mean parasite count of 185.63 ± 27.92 parasites/µL. In the third trimester, 155 out of 689 tested women were positive by RDT and 159 by microscopy, respectively. Mean parasite count was 184.16 ± 26.12 parasites/µL. At delivery among 686 women, 92 tested positive by RDT whereas 108 were positive by microscopy with the mean parasite count of 188.61 ± 30.71 parasites/µL.

Table 3: Malaria preventive measure of the pregnant women in Ilorin North central Nigeria according health facility

Variables	PHC (n=162)	Secondary HF (n=200)	Tertiary HF (n=201)	Private HF(n=200)	Total (n=763)
IPTp-SP During Pregnancy					
No	63 (95.5)	0 (0.0)	0 (0.0)	3 (4.5)	66 (8.6)
Not Sure	72 (82.8)	0 (0.0)	0 (0.0)	15 (17.2)	87 (11.4)
Yes	27 (4.4)	200 (32.8)	201 (33.0)	182 (29.8)	610 (79.6)
Insecticide-Treated Net (ITN)					
No	42 (27.5)	50 (32.7)	49 (32.0)	12 (7.8)	153 (20.0)
Yes	120 (19.7)	150 (24.6)	152 (24.9)	188 (30.8)	610 (80.0)
Slept Under ITN Last Night					
No	71 (43.8)	91 (45.5)	77 (38.3)	16 (8.0)	255 (33.4)
Yes	49 (30.2)	59 (29.5)	73 (36.3)	172 (86.0)	353 (46.2)
None Response	42 (25.9)	50 (25.0)	51 (25.4)	12 (6.0)	155 (20.4)
Always Sleep Under ITN					
No	66 (40.7)	83 (41.5)	78 (38.8)	28 (14.0)	255 (33.4)
Yes	54 (33.3)	67 (33.5)	72 (35.8)	160 (80.0)	353 (46.2)
None Response	42 (25.9)	50 (25.0)	51 (25.4)	12 (6.0)	155 (20.4)

Table 4: Malaria screening across trimester

Visit	Total Number Tested (N)	Positive by RDT (n(%))	Positive by Microscopy (n(%))	No. Parasite (parasites/µL)
First	763	156 (20.4%)	162 (21.2%)	189.79 ± 23.10
Second	690	128 (18.6%)	125 (18.1%)	185.63 ± 27.92
Third	689	155 (22.5%)	159 (23.1%)	184.16 ± 26.12
Delivery	686	92 (13.4%)	108 (15.7%)	188.61 ± 30.71

Prevalence of SP Resistance by Trimester

Table 5 present the prevalence of sulfadoxine-pyrimethamine resistance in pregnancy among pregnant women in Ilorin, North Central Nigeria. Cumulatively, resistance to SP was detected in 53 of 141, amounting to 37.6%, while for 88 women, amounting to 62.4%, resistance was not detected during the first trimester. In the second trimester, 33 out of 114 women had a resistance accounting for 28.9%, while for 81 women, accounting for 71.1%, no resistance was detected. For the third trimester, 36 out of 113 women, amounting to 31.9%, showed SP resistance, while for 77 women, amounting to 68.1%, SP resistance was not evident. The resistance of SP at delivery among 75 women was 29 (38.7%), while the same number of women did not have this resistance, which is 46 (61.3%). The differences among the trimesters are statistically significant in SP resistance, giving a p-value of 0.013, and hence the variation of SP resistance prevalence across trimesters cannot be due to chance.

Prevalence of SP Resistance by Healthcare Facility Type

Table 6 is the presentation of the prevalence of sulfadoxine-pyrimethamine (SP) resistance among pregnant women in Ilorin, North Central Nigeria, by health facility across different trimesters. In the first trimester, the prevalence of SP resistance varied by health facility: 11 (25.6%) at the Primary Health Care (PHC) centers, 9 (37.5%) at Secondary Health Facilities (HF), 13 (43.3%) at Tertiary Health Facilities, and 20 (45.5%) at Private Health Facilities. For the second trimester, the rates were 9 (21.4%) at PHC, 5 (26.3%) at Secondary HF, 7 (38.9%) at Tertiary HF, and 12 (34.3%) at Private HF. In the third trimester, the prevalence was 5 (23.8%) at PHC, 9 (22.5%) at Secondary HF, 19 (43.2%) at Tertiary HF, and 3 (37.5%) at Private HF. At delivery, the prevalence was 9 (25.7%) at PHC, 4 (66.7%) at Secondary HF, 3 (50.0%) at Tertiary HF, and 13 (46.4%) at Private HF. In all the prevalence of SP resistance across all health facilities was 53 (37.6%) in the first trimester, 33 (28.9%) in the second trimester, 36 (31.9%) in the third trimester, and 29 (38.7%) at delivery.

Table 5: Prevalence of SP Resistance by Trimester of the pregnant women in Ilorin North central Nigeria

Trimester	Number of Women (n)	SP Resistance Present (n)	SP Resistance Absent (n)	SP Resistance (%)	p-value
First	141	53	88	37.6	0.013*
Second	114	33	81	28.9	
Third	113	36	77	31.9	
At Delivery	75	29	46	38.7	

** Chi-square test Significant at the 0.05 level*

Table 6: Prevalence of SP Resistance by Health facility of the pregnant women in Ilorin North central Nigeria

Institution	First Trimester	Second Trimester	Third Trimester	Delivery
PHC	11 (25.6%)	9 (21.4%)	5 (23.8%)	9 (25.7%)
Secondary HF	9 (37.5%)	5 (26.3%)	9 (22.5%)	4 (66.7%)
Tertiary HF	13 (43.3%)	7 (38.9%)	19 (43.2%)	3 (50.0%)
Private HF	20 (45.5%)	12 (34.3%)	3 (37.5%)	13 (46.4%)
Total	53 (37.6%)	33 (28.9%)	36 (31.9%)	29 (38.7%)

Factors that influence SP Resistance

Factors that influence SP Resistance In first Trimester

Multiple regression analysis for the factors influencing SP resistance in the first trimester, it can be seen from Table 7. Model 1 includes age, ethnicity, educational level, and occupation, indicating that occupation is significant, coefficient = -0.144, 95% CI: -0.298 to -0.024, p = 0.027, indicating certain occupations that contribute to low SP resistance. Adding blood group in Model 2 increases the predictive power of the model, and blood group is now significant with a coefficient of -0.142, 95% CI: -0.070 to -0.006, p = 0.023. R-square increased to 0.25, p = 0.050. Model 3 includes additional factors selected, wherein occupation, blood group, and IPTp use came out as significant predictors, with an increased R-square of 0.34, p = 0.040.

Factors that influence SP Resistance in Second Trimester

The multiple regression analysis in the second trimester, as shown in Table 8, reveals striking findings across different models. Model 1, with the inclusion of age, ethnicity, education, and occupation, presented no significant association with SP resistance (R-square = 0.024, p = 0.612). Adding weight to Model 2 presented a coefficient of 0.347 (p = 0.046), and a better fit at R-square = 0.44, p = 0.019. Model 3, which added hypertension, toilet facility use, proximity to stagnant water, and IPTp use, had significant predictors for hypertension (-0.266, p = 0.007) and toilet facility use (-0.255, p = 0.009), with an improved R-square of 0.32 (p = 0.042).

Factors that influence SP Resistance in Third Trimester

Regarding the third trimester, the multiple regression analysis presents mixed results, as shown in Table 9. Model 1 (with age, ethnicity, education, and occupation) yields a negative coefficient of age with a coefficient = -0.141, 95% CI: -0.037 to 0.005. However, with an R-square of only 0.11 and a p-value of 0.058, this model is poorly fitted. Model 2 (Adding weight and height) within the model, both weight is a significant predictor (coefficient = 0.376, p = 0.038) and education level (coefficient = 0.166, p = 0.032). In this model, R-square is increased up to 0.158 (p = 0.09). Model 3 adds hypertension, toilet facility use, stagnant water, mosquito net use, and IPTp use. Stagnant water and mosquito net use are significant at coefficients: -0.185, p = 0.042; -0.168, p = 0.039, respectively. This model explains 24% of the variability, at R-square = 0.24, p = 0.049.

Factors that influence SP Resistance at delivery

Table 10 presents SP resistance at delivery, as shown in In Model 1, which consists of the variables age, ethnicity, education, and occupation, the coefficient for ethnicity is -0.136 (95% CI: -0.312 to 0.086). This model is relatively weak, with an R-squared value of 0.049 and a p-value of 0.463. Model 2, with added weight, height, and BMI, reports hypertension as a significant predictor-coefficient = -0.342 (95% CI: -0.754 to -0.060; p = 0.009)-and proximity to stagnant water-significant: coefficient = -0.296; 95% CI: -0.544 to -0.035; p = 0.035. This model improves, with an R-square of 0.19 (p = 0.049). Model 3 includes all factors and retains hypertension and proximity to stagnant water as significant predictors, accounting for 28% of the variance in SP resistance (R-square = 0.28, p = 0.019).

Table 7: multiple regression analysis of the factors influencing SP (Sulfadoxine-Pyrimethamine) resistance in the first trimester

Predictors	Model 1	Model 2	Model 3
AGE	-0.016 (-0.025, 0.021)	-0.002 (-0.024, 0.023)	-0.001 (-0.026, 0.025)
Ethnicity	-0.137 (-0.268, 0.030)	-0.145 (-0.282, 0.028)	-0.112 (-0.264, 0.069)
Educational Level	-0.122 (-0.191, 0.033)	-0.107 (-0.185, 0.046)	-0.103 (-0.184, 0.050)
Occupation	-0.144 (-0.298, -0.024)*	-0.160 (-0.318, -0.014)*	-0.180 (-0.340, -0.003)**
Blood Group		-0.142 (-0.070, -0.006)*	-0.127 (-0.068, 0.010)
Weight(kg)		0.025 (-0.020, 0.022)	0.016 (-0.021, 0.023)
Height (m)		0.005 (-1.522, 1.568)	-0.013 (-1.646, 1.525)
BMI (kg/m^2)		0.116 (-0.205, 0.355)	0.096 (-0.226, 0.351)
Hypertension(mmHg)		0.007 (-0.229, 0.249)	0.008 (-0.229, 0.251)
Toilet Facility use			0.064 (-0.111, 0.222)
Close to Stagnant Water			-0.061 (-0.217, 0.106)
Use of Mosquito Nets			0.014 (-0.102, 0.119)
Use of IPTp			-0.149 (-0.189, 0.028)
F	1.252	1.519	2.287
R-square	0.07	0.25	0.34
p-value	0.063	0.050*	0.040*

** Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).*

Table 8: Multiple regression analysis of the factors influencing SP (Sulfadoxine-Pyrimethamine) resistance in the second trimester

Predictor	Model 1	Model 2	Model 3
AGE	0.04 (-0.018, 0.03)	0.005 (-0.025, 0.026)	0.014 (-0.025, 0.02)
Ethnicity	-0.11 (-0.256, 0.06)	-0.096 (-0.238, 0.081)	-0.104 (-0.247, 0.07)
Educational Level	-0.07 (-0.142, 0.05)	0.005 (-0.101, 0.106)	0.005 (-0.098, 0.10)
Occupation	0.03 (-0.141, 0.21)	-0.009 (-0.205, 0.187)	0.010 (-0.182, 0.20)
Blood Group		-0.025 (-0.048, 0.037)	-0.005 (-0.045, 0.04)
Weight(kg)		0.347 (-0.005, -0.03)*	0.383 (-0.003, 0.04)*
Height (m)		0.165 (-1.370, 2.858)	0.207 (-1.149, 3.02)
BMI (kg/m^2)		-0.102 (-0.396, 0.289)	-0.106 (-0.396, 0.28)
Hypertension(mmHg)			-0.266 (-0.711, -0.04)**
Toilet Facility Use			-0.255 (-0.347, -0.04)**
Close to Stagnant Water			-0.115 (-0.284, 0.06)
Use of Mosquito Nets			0.121 (-0.039, 0.17)
Use of IPTp			0.188 (-0.012,- 0.19)*
F	0.621	1.971	2.192
R-Square	0.024	0.44	0.32
p-value	0.612	0.019*	0.042*

** Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).*

Table 9: Multiple regression analysis of the factors influencing SP (Sulfadoxine-Pyrimethamine) resistance in the third trimester

Predictors	Model 1	Model 2	Model 3
AGE	-0.141 (-0.037, 0.005)	-0.110 (-0.036, 0.011)	-0.084 (-0.033, 0.014)
Ethnicity	-0.117 (-0.257, 0.060)	-0.131 (-0.276, 0.055)	-0.129 (-0.284, 0.067)
Educational Level	0.166 (-0.017, 0.254)*	0.191 (-0.005, 0.27)*	0.160 (-0.029, 0.257)
Occupation	-0.024 (-0.206, 0.160)	-0.020 (-0.206, 0.167)	-0.040 (-0.232, 0.155)
Blood Group		-0.016 (-0.048, 0.041)	-0.001 (-0.048, 0.048)
Weight(kg)		0.376 (-0.003, 0.023)	0.330 (-0.004, 0.022)
Height (m)		-0.227 (-2.492, 0.457)	-0.192 (-2.335, 0.615)
BMI (kg/m^2)		-0.276 (-0.387, 0.124)	-0.259 (-0.380, 0.132)
Hypertension(mmHg)		-0.103 (-0.360, 0.13)	-0.141 (-0.40, 0.09)
Toilet Facility Use			-0.129 (-0.299, 0.072)
Close to Stagnant Water			-0.185 (-0.453, 0.018)*

Use of Mosquito Nets			-0.168 (-0.220, 0.020)*
Use of IPTp			-0.054 (-0.183, 0.115)
F	1.132	1.227	2.117
R-Square	0.11	0.158	0.24
p-value	0.058	0.09	0.049*

** Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).*

Table 10: Multiple regression analysis of the factors influencing SP (Sulfadoxine-Pyrimethamine) resistance at delivery

Variables	Model 1	Model 2	Model 3
AGE	0.029 (-0.028, 0.036)	-0.043 (-0.04, 0.03)	0.027 (-0.039, 0.047)
Ethnicity	-0.136 (-0.312, 0.086)	-0.206 (-0.38, 0.039)	-0.206 (-0.390, 0.048)
Educational Level	-0.160 (-0.222, 0.048)	0.059 (-0.11, 0.183)	0.054 (-0.120, 0.178)
Occupation	-0.001 (-0.199, 0.197)	-0.009 (-0.20, 0.187)	-0.058 (-0.247, 0.150)
Blood Group		-0.132 (-0.08, 0.025)	-0.149 (-0.088, 0.022)
Weight(kg)		0.038 (-0.02, 0.032)	0.320 (-0.018, 0.047)
Height (m)		0.212 (-1.54, 3.787)	0.066 (-2.545, 3.243)
BMI (kg/m^2)		0.462 (-0.21, 0.732)	0.034 (-0.509, 0.548)
Hypertension(mmHg)		-0.342 (-0.75, -0.060)**	-0.317 (-0.763, -0.009)*
Toilet Facility			-0.208 (-0.398, 0.058)
Close to Stagnant Water			-0.296 (-0.544, -0.035)*
Use of Mosquito Nets			0.031 (-0.190, 0.232)
Use of IPTp			-0.118 (-0.227, 0.097)
F	0.91	2.669	2.181
R-Square	0.049	0.19	0.28
p-value	0.463	0.049*	0.019*

** Significant at the 0.05 level (2-tailed). ** Significant at the 0.01 level (2-tailed).*

Discussion

The socio-demographic profile of pregnant women attending health facilities in Ilorin, North Central Nigeria, was significantly different across facility categories. This study has shown a high prevalence of younger women in Secondary and Private Health Facilities; there were no women under 20 years in the PHC category. This could mean that young women have limited access to health and have lower levels of education, hence being susceptible to poor health conditions during pregnancy (Gontie et al., 2020; Yola et al., 2018). Specifically, most of the women working within Secondary Health Facilities do not have formal education, which is associated with poor health and increased susceptibility to infections such as malaria (Ouzennou et al., 2019; Fana et al., 2015).

The ethnic and religious makeup reflects their cultural backgrounds, the majority being Yoruba, in coherence with the regional demographic. There is a suggestion in some literature that ethnicity might affect health-seeking behavior and accessibility to healthcare (Yola et al., 2018; Kasso et al., 2020). Furthermore, the high proportion of Muslim participants may influence health practices and beliefs on malaria prevention since religious doctrines can affect health behavior (Kimbi et al., 2014; Sabin et al., 2018).

Blood pressure, weight, and body mass index among pregnant women are alarming. This is suggestive that the average weight and BMI actually changed so little between visits. The high prevalence observed in some studies (Nyanga et al., 2020; Garba et al., 2023) entails possible health risks which, with co-presence of hypertension and malaria resistance, make the health environment even more complicated and worsen the vulnerability toward adverse pregnancy outcomes. This findings are important , most especially in the context of malaria prevalence and the efficacy of malaria prevention measures like IPTp-SP and ITNs. A relatively high proportion of women received IPTp-SP from Secondary and Tertiary Health Facilities, this is inline with the various studies that found that ANC to be an important platform for malaria prevention (Kalu et al., 2023; Mpogoro et al., 2014; Hill et al., 2015). However, the low ITNs uptake at PHCs raise concerns on the accessibility and education regarding malaria prevention strategies. This is indicated by Orish et al. (2016) and Kasso et al. (2020).

The high prevalence of SP resistance in Plasmodium falciparum infections in this study, especially among pregnant women in Ilorin, is a concern because this has implications for malaria treatment and maternal health. Overall, the SP resistance among pregnant women was 37.6%, although there was significant variation by trimester of pregnancy: first, second, and third trimesters had 37.6%, 28.9%, and 31.9% resistance rates, respectively. In other studies reporting on SP resistance among pregnant women and its correlation with low birth weight, the rates at delivery were 38.7% (Desai et al., 2016). A significant difference (p = 0.013) obtained across the trimesters indicate that SP resistance may vary based on conditions such as immunity and exposure at different stages in pregnancy, hence proving the research hypotheses of Emmanuel et al. (2024). In the first trimester, private health facilities had a 45.5 percent resistance rate, in comparison to 25.6 percent in the PHCs and 37.5 percent in the Secondary Health Facilities (Gleave et al., 2023). This trend persisted across trimesters, suggesting that the type of healthcare facility may affect exposure to SP and the development of resistance. These variations thus call for targeted interventions in higher-risk settings.

SP resistance in P. falciparum results from mutations in the pfdhfr and pfdhps genes, reducing SP effectiveness by altering the folate biosynthesis pathway (wang et al., 2022). Key mutations in pfdhfr (codons 16, 51, 59, 108, 164) and pfdhps (codons 431, 436, 437, 540, 581, 613) have been strongly associated with resistance (Adebobola, 2021). Studies such as the one done in Angola by Rosillo et al. (2023) on the prevalence of these mutations have called for continued monitoring. Monitoring genetic markers is an important component in assessing SP efficacy, guiding policy adjustments, and exploring alternative treatments for malaria in endemic regions.

The multiple regression analyses also identified several factors associated with SP resistance. Occupation in the first trimester emerged as a significant predictor with a coefficient: -0.144 and a p-value: 0.027, suggesting the fact that some occupations reduce the likelihood of resistance to SP, most likely because of different exposures to malaria or health care (Vandy et al., 2019). Blood group became another significant predictor of SP resistance with a coefficient of -0.142 and a p-value of 0.023. Grais et al. (2018) showed that occupation and blood group remained significant predictors of SP resistance in subsequent models, as did IPTp use, with a coefficient of -0.149 and a p-value of 0.035. Mlugu et al. (2021) also found weight and IPTp use to be significant predictors of SP resistance in the second trimester. Greater resistance was associated with higher weight (coefficient = 0.347, p = 0.046), whereas IPTp use had a positive effect on reducing resistance (coefficient = 0.188, p = 0.045). The model explained 44% of the variability within SP resistance (R-square = 0.44, p = 0.019). Apart from that, in this trimester, hypertension and the use of toilet facilities significantly predicted SP resistance with a coefficient: -0.266, p-value: 0.007, and coefficient: -0.255, p-value: 0.009, respectively, with an R-square value of 0.32, p = 0.042, reflecting a moderate explanatory power.

From the third trimester analysis, weight and educational level had a significant predicted SP resistance with coefficients of 0.376 (p = 0.038) and 0.166 (p = 0.032), respectively. Other significant predictors were proximity to stagnant water and mosquito net use with coefficients -0.185 (p = 0.042) and -0.168 (p = 0.039). The study has pointed to environmental factors and personal health practices in combating malaria in pregnancy. The model accounted for 24% of the variance in SP resistance at delivery, with an R-square of 0.24, p = 0.049, hence its moderate explanatory power as shown by Gikunju et al., (2020).

Overall, hypertension and proximity to stagnant water were significant predictors of SP resistance at delivery: hypertension, coefficient = -0.342, p = 0.009; environmental factors such as proximity to stagnant water and access to sanitation facilities. For example, proximity to stagnant water had a negative coefficient (-0.296, p = 0.035), with an R-square value of 0.28 (p = 0.019) emphasizing its role in exposure to malaria. Such factors may be minimized by improved environmental sanitation and proper water drainage. These results emphasize the need for addressing health conditions alongside environmental concerns in managing malaria resistance in pregnant women. Results are similar to observations in other studies (Nayebare et al., 2020).

CONCLUSION

The pregnant women in Ilorin were predominantly young, self-employed, and from the Yoruba ethnic group. Although IPTp-SP acceptance and ITN usage were high in this area, it was especially high in secondary and tertiary healthcare facilities, yet uptake was significantly lower in primary healthcare centers. The cumulated SP resistance rate for all women was found to be 37.6%, with huge variations across trimesters and healthcare facilities, hence posing a critical challenge to its prophylactic efficacy. Such variability in the resistance rates can be due to a variety of factors, including the differently developed healthcare infrastructures, varied access to medical resources, and also differently implemented preventive strategies in the three trimesters. Occupational status, educational attainment, body weight, hypertension, and proximity to stagnant water were the key determinants for SP resistance during different pregnancy stages. These results also indicate possible cross-resistance with other antimalarial drugs, further complicating the treatment regimens. Therefore, the control of malaria policies in Nigeria should adopt both environmental and socio-economic approaches in a bid to curbing the menace, while research into genetic markers of SP resistance in Plasmodium falciparum may provide better information necessary for treatment protocols and malaria prevention strategies.

The higher barriers to access, poorly developed infrastructure, and lack of knowledge about malaria prevention at the primary healthcare level impede higher uptake of ITNs and IPTp-SP. Improving accessibility therefore calls for policies that will ensure an increase in healthcare workers' training, resources distribution, and more engagement with communities to help raise awareness of these preventive measures.. These findings emphasize the need for an intensified effort in malaria prevention, particularly at the primary healthcare level, and addressing socio-economic and environmental determinants of SP resistance. Further, the integration of genetic research into malaria control strategies, along with the improvement of public health interventions, may lead to better overall pregnancy outcomes and reduce the overall burden of malaria in pregnant women.

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