Self-reported acute febrile illness, malaria and anemia among pregnant women in communities surrounding the Lagoon of Lagos, South-west Nigeria.

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Abstract

Background: Maternal febrile illness is often linked with undesirable adverse consequences of pregnancy and of fetal development.

Objective: The objective of this study was to assess the prevalence of malaria parasitemia and anemia among pregnant women who gave a self-report of febrile illness within 48 hours of presentation at antenatal clinics in semi-urban Lagoon communities in Lagos, Southwest Nigeria where malaria preventive strategies have been carried out.

Subjects and methods: A total of 113 pregnant women receiving antenatal care at two secondary-level health facilities in Ikorodu Local Government Area of Lagos State, were recruited into this cross-sectional. Relevant information such as age, gravidity, trimester of pregnancy, febrile illness within the past 48 hours and use of malaria commodities were extracted from them. Laboratory analysis was conducted for anemia and malaria parasitemia.

Results: In all, 32 (28.3%), 32 (28.3%) and 49 (43.4%) of the study subjects were pregnant for the first time, second time and many times respectively. The overall means (± sd) of age (years) and of PCV (%) were 29.9 (5.8) and 30.0 (6.3) respectively while the mean age of those in 1st 2nd and >2 pregnancies were 26.8 (5.2), 27.3 (3.7) and 33.7 (5.1) years respectively. Also, 38 (33.6%) of the 113 study subjects gave a self-report of febrile illness (SERFI) 48 hours prior to presentation at Antenatal clinic. Laboratory investigation showed that 22 (19.5%) of the study subjects were malaria parasite positive, whose mean Packed Cell Volume (26.8 ± 6.6%) was significantly lower (t=2.64, P-value=0.007) than that of the 91 (80.5%) without malaria parasitemia (30.8 ± 6.0%). The mean (± sd) PCV% of the 38 pregnant women who gave a SERFI (28.4 ± 5.2) was significantly lower (t=-2.13, P-value=0.018) than that of the 75 (66.4%) who did not (30.9 ± 6.6). Women in their first pregnancy were over 2½ times as likely to present with febrile illness than those in their second or more pregnancies (χ^2=5.36, P-value=0.02, OR=2.65, 995% CI: 1.15, 6.27). In all 36.8%, 27.8% and 40.0% of those in 1st, 2nd and 3rd trimester presented with febrile illness. Very few of the study subjects slept under Long-lasting Insecticide-treated nets (LLINs) night before the survey or used Sulphadoxine-pyrimethamine (SP) for Intermittent Preventive Treatment of malaria in pregnancy (IPTpp).

Conclusion: The prevalence of malaria and anemia among those who gave SERFI in pregnancy was moderately high in Ikorodu Local Government Area of Lagos State, Nigeria. More penetrating stronger health education should be given to pregnant women to report within 24-48 hours of any febrile illness in pregnancy. Efforts should also be intensified to identify cause(s) of maternal febrile illness to reduce maternal and neonatal morbidity and mortality in semi-urban settings of Lagos State specifically and throughout Nigeria in general.

Keywords: Self-report, Febrile illness, Pregnancy, Malaria, Anemia, Lagoon, Lagos, Nigeria.

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Introduction

Globally, febrile illness during pregnancy (FIDP) occurs as a common clinical problem and the feto-maternal risk is significantly elevated in pregnancy complicated by infection and fever [1]. Many cases of FIDP have atypical and uncommon presentation which may be problematic for clinicians in giving appropriate diagnosis and specific treatment [2]. Furthermore, in the pregnant state, maternal immune function is known to be altered and reduced consequent on regular functioning of the body in that state, protecting both the mother and the baby and this alone may predispose a pregnant woman to colds and fever. For this reason, many clinicians take caution in prescribing antibiotics due to the risk of teratogenicity [3,4]. Febrile illness in pregnancy may also occur due to infection. Pregnant women with febrile illness usually present with high temperature, sweating, shivering, headache, muscle ache, dehydration and

fatigue [5]. Fever is described as a body temperature exceeding 38.3°C [6], with the average normal oral body temperature taken as 36-37°C, giving a fluctuation by 0.5-1.0°C depending on the time of the day, with the lowest temperature being in the early morning and the highest in the evening. Biswas et al. [1] suggested that some febrile illnesses may revert to a more severe course during pregnancy and put the fetus in jeopardy. Others reported that intrapartum fever, without a laboratory diagnosis of infection, is associated with increased risk of neonatal hypoxic encephalopathy and unexplained neonatal seizures [7,8]. In the study of Goetz et al. [9], the fetus is exposed to various inflammatory mediators when there is maternal fever. Other studies submit that the underlying maternal cytokine polymorphism is strongly associated with both intrapartum fever and cerebral palsy at term [10,11]. Sustained fever of greater than 38.9°C for at least 24 hours has been shown to be associated with an increased risk of miscarriage and malformations including neural tube defects like spina bifida in early pregnancy [12] and possibly stillbirth in later pregnancy. Therefore, some febrile diseases may take a more severe course in pregnancy leading to transplacental transmission of infectious agents and fetal jeopardy.

Studies have shown that while pregnant, acute infections are linked to adverse outcomes such as miscarriage, pre-term labor, rupture of membranes, preterm birth and stillbirth [13-15]. However, some infectious diseases, such as Plasmodium falciparum, Listeria monocytogenes, hepatitis E virus (HEV), herpes simplex virus and influenza are more common but devastating to the pregnant woman and the fetus [16-20]. In sub-Saharan Africa, where malaria and other infectious diseases are endemic and may come as epidemic episodes, little evidence exists as to whether there is higher risk of disease or the severity of any disease in pregnancy and what the influences are on mothers and their offspring, by pathogens and gestational age [21-25]. Maternal infections with *P. falciparum* and *P. vivax* are well documented as the causative agents of adverse birth outcomes such as premature delivery, low birthweight and, at the extreme, maternal death [26-30].

There are epidemiological proofs which submit that infection during pregnancy may precipitate other devastating complications associated with pregnancy such as preeclampsia [31], and cardiovascular diseases, including the risk of first-time myocardial infarction and stroke [32]. Linthavong and colleagues also demonstrated the thorny issue of maternal infection with herpes simplex virus with the delivery of a live healthy baby [33] while Bello et al. showed how difficult it is to contain Lassa fever infection in pregnancy [34].

Maternal infection might lead to inflammation within the fetal tissue and the loss of vulnerable cell populations [35]. Bacterial and/or viral products could cross the placenta, enter the fetal circulation, bind specific cell-membrane receptors (i.e., CD-14 and toll-like receptors) on inflammatory cells within the systemic circulation, thus initiating a cascade of intracellular events, activating transcription factors such as nuclear factor κ-B and production of proinflammatory cytokines. These proinflammatory cytokines, such as granulocyte colony-stimulating factor, tumor necrosis factor-α, interleukin-1β, C-reactive protein and interferon γ, have a diversity of effects [35]. These include a direct toxic effect on neurones and vulnerable oligodendrocyte precursor populations, gliosis with release of nitric oxide and mitochondrial dysfunction, as well as microglial activation in the brain [35]. It has also been suggested that a maternal febrile episode can predispose to embryonic death, abortion, growth retardation, and defects of development and that these defects might be caused by metabolic changes in the mother due to the infection and fever, and not due to the associated elevation of temperature [35].

This study arose during the analysis phase of a larger study investigating the prevalence of malaria-induced anemia among pregnant women infected with Plasmodium parasites in two adjacent communities on the Lagoon front of Lagos Nigeria. There is paucity of data in the country on febrile illnesses among pregnant women by age, gravidity and trimester. There are also few studies reporting febrile illness among pregnant women within 48 hours prior to presentation. The aim of this current study is to ascertain the pregnancy-period prevalence of self-reported febrile illness 48 hour prior to presentation at antenatal clinic among women in different stages of pregnancy, those pregnant for the first second or more times, in different ages and different occupations.

Materials and Methods

Study site

This Study was carried out in between January and April 2009. This study was conducted at two sites Ijede General Hospital and Ikorodu General Hospital, both in Ikorodu Local Government area located within latitude 6037'N- 6045'N and longitude 303'East-305'East. Ijede is, eight kilometers from the semi urban town of Ikorodu which is in turn twenty kilometers from Lagos metropolis. Ijede has a homogeneous population of about 10,000 consisting primarily of peasant farmers, a few fishermen indigenes and increasingly non-indigenes that work in urban Lagos. It has three primary schools and one secondary school. The community is fed by a good access road, pipe borne water and relatively stable electric supply because of its proximity to Egbin thermal station, a major national electric grid. Ikorodu on the other hand is more urban with many more schools and hospitals. It has a population of about 700,000 and they are mostly traders with an increasing migrant population that go to work in Lagos.

This cross-sectional study was conducted in the antenatal clinic of two general hospitals in Ikorodu Local Government Area (LGA) in Lagos, Southwest Nigeria. Methods have been described in detail previously in a separate recent report of maternal activities during pregnancy [36]. Briefly, women who were attending antenatal clinics were approached by a trained researcher not involved in their medical care, to explain the purpose of the study and request for their approval to include them as participants. Women who were febrile or who had a history of fever in the 48 hours preceding presentation at the clinic were especially invited, but non-febrile volunteers were

not excluded. A short questionnaire was then administered to those that gave their consent to collect demographic data, history of drug use, participation in IPT, ITN possession and information on gestational age, history of febrile illness and other relevant data. The questionnaire used in this study was after review of the literature and discussion with clinical staff and was piloted prior to study commencement according to Lain et al. [32].

Sample Collection, Clinical Investigation and Diagnosis were done using 0.5 mL venous blood sample collected into labeled EDTA microtainer bottles. For purposes of treatment, the OptiMAL dipstick test (DiaMed, Cressier, Switzerland) with lot number 46110.36.01 was used to diagnose malaria according to manufacturer's instructions so that positive participants were treated according to the National Malaria Elimination Program guideline. Hematocrit was determined by measuring Packed Cell Volume (PCV) in microhematocrit tubes spun in hematocrit centrifuge at 12,000-15,000 rpm (xG) for 5 minutes and read using a hematocrit reader (Hawksley, England). Thick and thin blood films were made according to WHO specification [37] and the thin smears fixed with methanol. The slides were allowed to air dry until the next day when they were stained for 30 minutes using 3% Giemsa stain. The slides were examined under 100X oil immersion lenses and parasite density per µl was calculated by multiplying the number of parasites per HPF by 500, based on the assumptions that 5-8 µL of blood is used in making a thick blood films and that 0.002 µL of blood is in an HPF [38]. To declare a slide negative, at least 200 high powered fields were read.

Ethical Approval

The study was conducted as a sub-study of another work "Characterization of molecular markers associated with plasmodium falciparum resistance to antimalarial drugs and evaluation of PCR methods for parasite density estimation in rural and semi-urban site in southwest Nigeria" for which ethical approval was obtained from the Nigerian Institute of Medical Research Institutional Review Board. All work was performed according to the guidelines for human experimentation in clinical research and Helsinki declaration

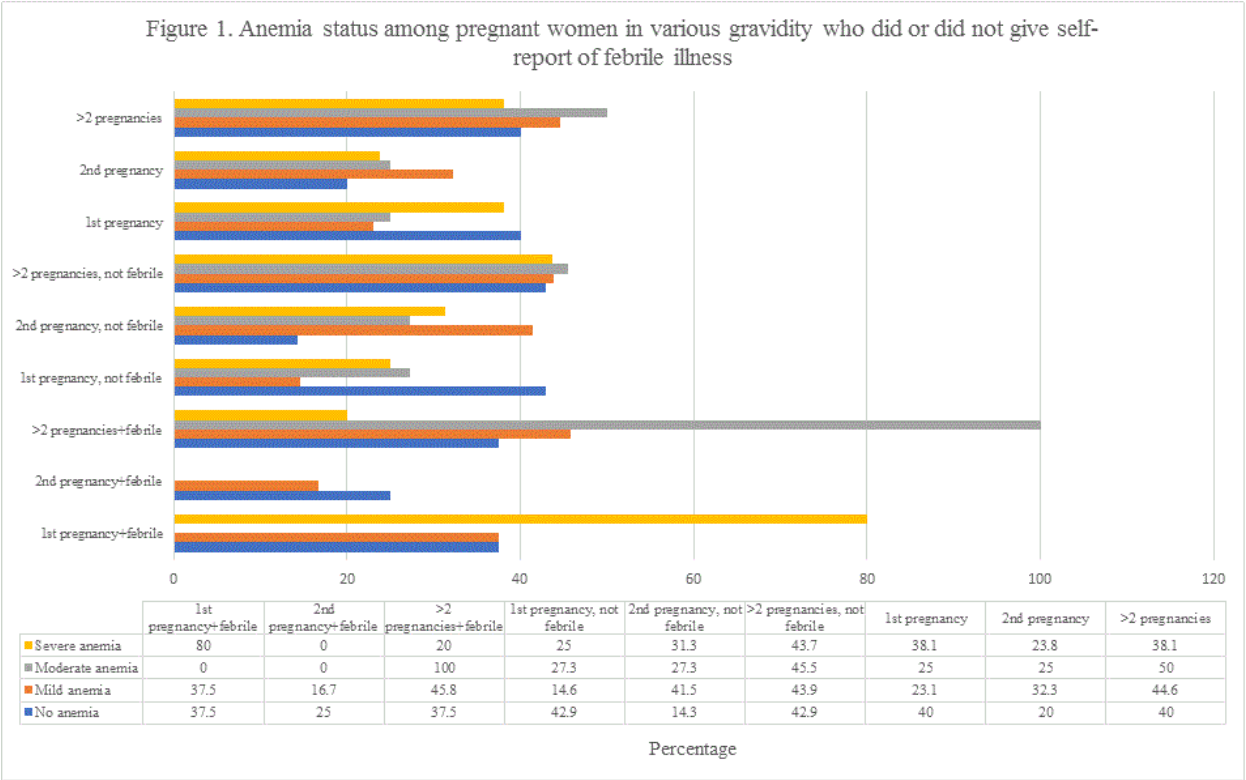
Results

A total of 113 pregnant women were recruited into the study. The highest proportion of these women (36, 31.9%) were in the age group of 26-30 years, were traders (54, 47.8%) and with secondary education (51, 45.1%). In all, 38 (33.6%) of them reported febrile illness 48 hours prior to presentation mostly in the age group 26-30 years (13, 34.2%), traders (20, 52.6%) and with secondary education (21, 55.3%). Of the 75 (66.4%) who did not report any febrile illness 48 hours prior to presentation, 46 (61.3%) were aged 26-35 years, 34 (45.3%) were traders, and 33 (75.0%) had attained tertiary education. History of their past pregnancies indicates that 32 (28.3%) of the study subjects were in their first pregnancy among whom 2 each (6.3%) were aged ≤ 20 years and 31-35 years respectively, and 13 (40.6%) were aged 26-30 years; 32 (28.3%) were in their second pregnancy among whom 2 (6.3%) were aged ≤ 20 years and 15 (46.9%) were aged 26-30 years; 49 were multigravida among whom 23 (46.9%) were aged 31-35 years and none was aged ≤ 20 years (Table 1).

Table 1. *Socio-demographic characteristics of study subjects.*

				Past pregnancies						**Self-reported febrile illness**			
				Primigravida		**Secundigravida**		**Multigravida**					
				Mean (± sd) of age						**Yes**		**No**	
				26.8 (5.2)		**27.3 (3.7)**		**33.7 (5.1)**					
Variable	**Sub-variable**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**
Age	All	113	100	32	28.3	32	28.3	49	43	38	34	75	66.4
	≤ 20	4	3.5	2	6.3	2	6.3	0	0	2	5.3	2	2.7
	21-25	24	21.2	12	37.5	8	25	4	8.2	8	21	16	21.3
	26-30	36	31.9	13	40.6	15	46.9	7	14	13	34	23	30.7
	31-35	31	27.4	2	6.3	7	21.8	23	47	8	21	23	30.7
	>35	18	15.9	3	9.3	0	0	15	31	7	18	11	14.7
Occupation	Housewife	11	97	4	12.5	5	15.6	2	4.1	3	7.9	8	10.7
	Labour	6	5.3	2	6.3	2	6.3	2	4.1	2	5.3	4	5.3
	Office work	25	22.1	3	9.4	6	18.8	16	39	7	18	18	24
	Students	17	15	10	31.3	6	18.8	1	2	6	16	11	14.7
	Traders	54	47.8	13	40.6	13	40.6	28	57	20	53	34	45.3
Education	None	5	4.4	0	0	1	3.1	4	8.2	2	53	3	4
	Primary	13	11.5	2	6.3	2	6.3	9	18	4	11	9	12
	Secondary	51	45.1	15	46.9	16	50	20	41	21	55	30	40
	Tertiary	44	38.9	15	46.9	13	40.6	16	33	11	25	33	75

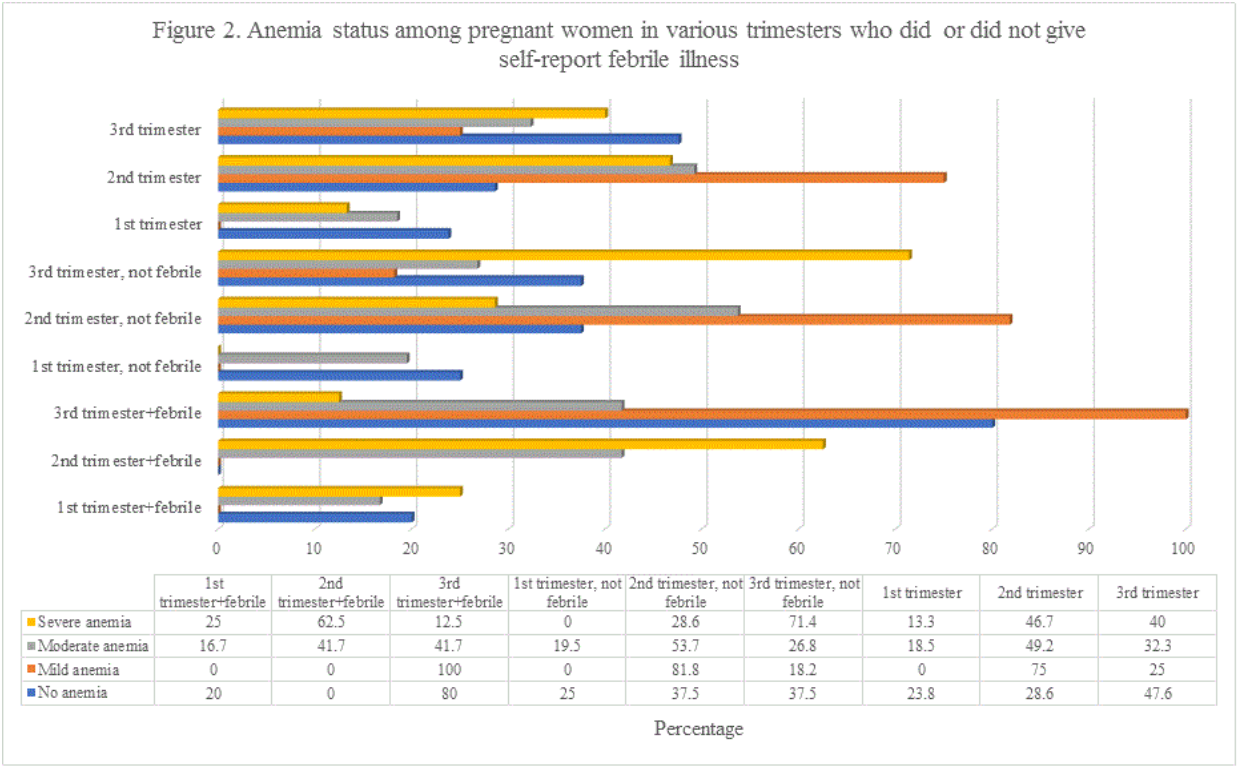
Figure 1 illustrates the anemia status of all the study subjects and relative to their gravidity as well as whether they gave a self-report of febrile illness or not. Overall, 80.0% of those with severe anemia were those who, in their first pregnancy, gave a report of febrile illness, while the remining 20% who reported febrile illness have had many pregnancies. There was a lower proportion (25.0%) of women with severe anemia who were in their first pregnancy but did not report febrile illness. Moderate anemia was found exclusively (100.0%) among multigravidas who gave self-report of febrile illness during pregnancy.



	1st pregnancy+febrile	2nd pregnancy+febrile	>2 pregnancies+febrile	1st pregnancy, not febrile	2nd pregnancy, not febrile	>2 pregnancies, not febrile	1st pregnancy	2nd pregnancy	>2 pregnancies
Severe anemia	80	0	20	25	31.3	43.7	38.1	23.8	38.1
Moderate anemia	0	0	100	27.3	27.3	45.5	25	25	50
Mild anemia	37.5	16.7	45.8	14.6	41.5	43.9	23.1	32.3	44.6
No anemia	37.5	25	37.5	42.9	14.3	42.9	40	20	40

Figure 1. *Anemia status among pregnant women in various gravidity who did or did not give self-report of febrile illness.*

Figure 2 indicates anemia status among the study subjects in various trimester of pregnancy and whether they provided a self-report of febrile illness or not. Severe anemia was more prominent (62.5%) among women in their second trimester of pregnancy, who gave a history of febrile illness and among those in the third trimester (71.4%) who did not give a self-report of febrile illness. Moderate anemia was equally distributed among women in the 2nd and 3rd trimester who reported febrile illness but more (53.7%) who were in the 2nd trimester but did not report febrile illness.



	1st trimester+febrile	2nd trimester+febrile	3rd trimester+febrile	1st trimester, not febrile	2nd trimester, not febrile	3rd trimester, not febrile	1st trimester	2nd trimester	3rd trimester
Severe anemia	25	62.5	12.5	0	28.6	71.4	13.3	46.7	40
Moderate anemia	16.7	41.7	41.7	19.5	53.7	26.8	18.5	49.2	32.3
Mild anemia	0	0	100	0	81.8	18.2	0	75	25
No anemia	20	0	80	25	37.5	37.5	23.8	28.6	47.6

Figure 2. *Anemia status among pregnant women in various trimesters who did or did not give self-report febrile illness.*

There was a significant difference (t=-2.13, P-value=0.018) in the mean (± sd) PCV (28.4 ± 5.2%) of pregnant women who reported febrile illness (38, 33.6%) compared to those who did not report any febrile illness (30.9 ± 6.6%) as shown in Table 2. There was also a noteworthy variance (t=2.64, P-value=0.007) in the mean (± sd) PCV% of pregnant women who had malaria parasitemia (26.8 ± 6.6) compared to those who did not (30.8 ± 6.0). Those who reported or did not report febrile illness were then segregated into two groups – those who were parasite positive and those who were parasite negative. There was no remarkable alteration (t=0.22, P-value=0.41) in the PCV% of pregnant women who reported febrile illness and were parasite-positive (28.8 ± 7.0) and those who reported febrile illness and were parasite-negative (28.3 ± 4.3). Surprisingly, a notable variance (t=-3.96, P-value= 0.0008) was observed in the PCV% of pregnant women who did not report any febrile illness but were parasite positive (24.4 ± 5.4) compared to those who did not report any febrile illness but were parasite-negative (31.9 ± 6.3). When all parasite-negative women were considered, the mean (± sd) PCV% (28.3 ± 4.3) of those who reported febrile illness (n=26, 28.6%) was significantly lower (t=-3.11, P-value=0.004) than that (31.9 ± 6.3) of women who did not report febrile illness (n=65, 71.4%). When all parasite-positive pregnant women were considered, the mean (± sd) PCV% (28.8 ± 7.0) of those who reported febrile illness (n=12, 54.5%) was significantly higher (t=1.64, P-value=0.05) than that (24.4 ± 5.4) of women who did not report febrile illness (n=10, 45.5%). Overall, pregnant women with malaria parasitemia were three times more likely to give a report of febrile illness within 48 hours than pregnant women who were not infected with malaria parasites (χ^2=5.36, P-value=0.02, OR=3.00, 95% CI:1.15, 7.79)

Table 2. *Mean Packed Cell Volume (%) and prevalence of malaria parasitemia with self-reported febrile illness.*

Variable	Item	Freq.	%	χ^2	P-value	OR	95% CI	Packed Cell Volume		t-test	P-value
								Mean	± sd		
Self-report febrile	Yes	38	33.6					28	5.2		
	No	75	66.4					31	6.6	-2.1	0.02
Malaria parasite	Yes	22	19.5	-	-	-	-	27	6.6		
	No	91	80.5					31	6	2.64	0.01
Self-report febrile =Yes	MP +ve	12	31.6					29	7		
	MP -ve	26	68.4					28	4.3	0.22	0.41
Self-report febrile =No	MP +ve	10	13.3	5.36	0.02	3	1.15, 7.79	24	5.4		
	MP -ve	65	86.7					32	6.3	-4	0
Self-report febrile =Yes	MP +ve	12	54.5	5.36	0.02	3	1.15, 7.79	29	7	1.64	0.05
Self-report febrile =No		10	45.5					24	5.4		
Self-report febrile =Yes		26	28.6					28	4.3		
Self-report febrile =No	MP -ve	65	71.4					32	6.3	-3.1	0

Considering various states and history of pregnancy, women in the third trimester (16, 42.1%) were 1.55 more likely to report febrile illness 48 hours prior to presentation that those in first or second trimester (χ^2=1.13, P-value=0.29, OR=1.55, 95% CI: 0.69, 3.46), as illustrated in Table 3. Those having their first pregnancy (16, 42.1%) were about 3 times as likely to report febrile illness (χ^2=5.36, P-value=0.02, OR=2.68, 95% CI:1.15, 6.27) than those having their second or more pregnancy. Of the 38 pregnant women who reported febrile illness, very few (9, 23.7%) possessed Long-Lasting Insecticide-treated Nets (LLINs), and only 6 (15.8%) of them slept under LLIN night before survey, 24 (63.2%) went for orthodox treatment for malaria, 11 (29.0%) were using Sulphadoxine-pyrimethamine (SP) for intermittent prevention therapy in pregnancy (IPTp), 2 (53%) were combining IPTp with sleeping under LLIN and 4 (10.5%) were sleeping under LLIN and also taking herbal tea for malaria prevention.

Table 3. *Self-reported febrile illness among women in different gestational ages, gravidity and utilization of malaria prevention commodities.*

		Self-report of febrile illness 48 hours prior to presentation							
						χ^2	**P-value**	**OR**	**95% CI**
Variable	**Sub-variable**	**Yes**		**No**					
		Freq.	**%**	**Freq.**	**%**				
Gestational age	First trimester	7	18	12	16	0.11	0.7	1.19	0.42, 3.31
	Second trimester	15	40	39	52	1.59	0.2	0.6	0.27, 1.33
	Third trimester	16	42	24	32	1.13	0.3	1.55	0.69, 3.46
Gravidity	Primigravida	16	42	16	21.3	5.36	0	2.68	1.15, 6.27
	Secundigravida	6	16	26	34.7	4.42	0	0.35	0.13, 0.95
	Multigravida	16	42	33	44	0.04	0.9	0.93	0.42, 2.04
Possess LLIN	Yes	9	24	19	25.3	0.04	0.9	0.91	0.36, 2.27
	No	29	76	56	74.7				
Slept under LLIN	Yes	6	16	9	12	0.31	0.6	1.37	0.45, 4.20
	No	32	84	66	88				
Treated for malaria	Yes	24	63	31	41.3	4.81	0	2.43	1.09, 5.43
	No	14	37	44	58.7				
Used SP for IPTp	Yes	11	29	21	28	0.01	0.9	1.05	0.44, 2.48
	No	27	71	54	72				
IPTp + LLIN	Yes	2	5.3	2	2.7	0.03*	0.9	2.03	0.27, 14.99
	No	36	95	73	97.3				
LLIN + Herbal tea	Yes	4	11	5	6.7	0.12*	0.7	1.65	0.42, 6.53
	No	34	90	70	93.3				

***Fisher's Exact Test**

Table 4 shows that only very few women in their first pregnancy and who reported febrile illness possessed LLIN (1, 6.2%), used LLIN (1, 6.2%), used SP for IPTp (6, 37.5%) compared to those who were in their first pregnancy, did not report febrile illness but possessed LLIN (2, 12.5%) used LLIN (1, 6.2%) and used SP (3, 18.7%) respectively. The Table also shows that, of those who reported febrile illness, the ownership (5, 33.3%) and use (4, 267%) of LLIN were highest among those in the second trimester of pregnancy while use of SP was highest (9, 562%) among those in the third trimester. No pregnant woman who reported febrile illness used LLIN or SP for IPTp. Among those who did not report febrile illness, possession of LLIN was highest among women in their second pregnancy (8, 30.88%), but use of LLIN was highest (6, 18.2%) and use of SP for IPTp (11, 33.3%) were highest in those who were multigravidas. In the group that did not report

febrile illness, possession of LLINs was highest (12, 30.8%) in the second trimester, use was highest (2, 16.7%) in the first trimester and SP for IPTp was highest (9, 37.5%) was highest in the third trimester.

Table 4. *Frequency distribution of possession and use of anti-malaria commodities among pregnant women in different gravidity and different trimester who did or did not present with febrile illness.*

Variable	All		Gravidity						Trimester							
			Primigravida		Secundigravida		Multigravida		All		First		Second		Third	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Reported febrile illness																
Possessed LLIN	9	23.7	1	6.2	2	33	6	37.5	9	24	1	14	5	33.3	3	19
Did not possess LLIN	29	76.3	15	93.8	4	67	10	62.5	29	763	6	86	10	66.7	13	81
Used LLIN	6	15.8	1	6.2	0	0	5	31.2	6	16	0	0	4	26.7	2	13
Did not use LLIN	32	84.2	15	93.8	6	100	11	68.8	32	84	7	100	11	73.3	14	88
Used SP	11	28.9	6	37.5	1	17	4	25	11	29	0	0	2	13.3	9	56
Did not use SP	27	71.1	10	62.5	5	83	12	75	27	71	7	100	13	86.7	7	44
Used LLIN +SP	2	5.3	1	6.2	0	0	1	6.2	2	5.3	0	0	0	0	2	13
Did not use LLIN +SP	36	94.7	15	93.8	6	100	15	93.8	36	95	7	100	15	100	14	88
Used LLIN +Herbal tea	4	10.5	2	12.5	0	0	2	12.5	4	11	0	0	2	13.3	2	13
Did not use LLIN +Herbal tea	34	89.5	14	87.5	6	100	14	87.5	34	90	7	100	13	86.7	14	88
Used SP + Herbal Tea	3	7.9	2	12.5	0	0	1	6.2	3	7.9	0	0	1	6.7	2	13
Did not use SP+ Herbal tea	35	92.1	14	87.5	6	100	15	93.8	35	92	7	100	14	93.3	14	88
Did not report febrile illness																
Possessed LLIN	19	33.9	2	12.5	8	31	9	27.3	19	34	3	25	12	30.8	4	17
Did not possess LLIN	56	66.1	14	87.5	18	69	24	72.7	56	66	9	75	27	69.2	20	83

Used LLIN	9	12	1	6.2	2	7.7	6	18.2	9	12	2	17	4	10.3	3	13
Did not use LLIN	66	88	15	93.8	24	92	27	81.8	66	88	10	83	35	89.7	21	88
Used SP	21	28	3	18.7	7	27	11	33.3	21	28	0	0	12	30.8	9	38
Did not use SP	54	72	13	81.3	19	73	22	66.7	54	72	12	100	27	69.2	15	63
Used LLIN +SP	2	2.7	1	6.2	0	0	1	3	2	2.7	0	0	1	2.6	1	4.2
Did not use LLIN +SP	73	97.3	15	93.8	26	100	32	96.7	73	97	12	100	38	97.4	23	96
Used LLIN +Herbal tea	5	6.7	0	0	2	7.7	3	9.1	5	6.7	0	0	3	7.7	2	8.3
Did not use LLIN +Herbal tea	70	93.3	16	100	24	92	30	90.9	70	93	12	100	36	92.3	22	92
Used SP+ Herbal Tea	7	9.3	0	0	2	7.7	5	15.1	7	9.3	0	0	4	10.3	3	13
Did not use SP+ Herbal tea	68	90.7	16	100	24	92	28	84.9	68	91	2	100	35	89.7	21	88

Discussion

A stable human body temperature above normal level, which normally lies between 37.0 to 37.5°C, with diurnal variations, is regarded as fever. In disease state, disorders of temperature regulation may be explained by alterations in body's aquatic fluid, insufficient hydration, and fluctuations in metabolism [36]. Maharaj [35] added that febrile illnesses may be classified as intermittent, if they fall to normal each day; remittent, if they fall each day, but still remaining above the normal; sustained, if they are without significant diurnal variation; or relapsing, when they alternate with periods of one to several days of normal temperatures. The underlying sequence of events seems to be the removal of endotoxins from the circulation by fixed phagocytes of the reticuloendothelial system, followed by margination of polymorphonuclear leukocytes along the margins of the vessels.

This study has some key findings, one of which is that approximately a third (33.6%) of pregnant women reported febrile illness within 48 hours of presentation, which accords with the opinions reported in other studies [1,2] that acute febrile illness is a common clinical problem worldwide. In sub-Saharan Africa, pregnancy puts women in high-risk group because they are often challenged with acute infections such as Plasmodium falciparum presenting with severe anemia, hypoglycemia and acute pulmonary edema [39]. Left untreated, Plasmodium falciparum infection in pregnant women may be complicated by cerebral malaria, metabolic acidosis, acute kidney injury (AKI), convulsions, disseminated intravascular coagulation (DIC), shock and hyperpyrexia. Other common infections in pregnancy in sub-Saharan Africa include, but are not limited to vaginal infections, sexually transmitted diseases including HIV, intra-amniotic infection, skin and soft tissue infection [40]; hepatitis, pneumonia and urinary tract infection causing pyelonephritis [41]. In pregnancy, there are increases in urinary progestins and estrogens which may lead to diminished capacity of the lower urinary tract to counter-attack invading bacteria. In addition, the combination of enlarged bladder volume, reduced bladder tone, and decreased ureteral tone, play major roles in increased urinary stasis and uretero-vesical reflux.

The second key finding in this study is that high proportions of those who reported febrile illness were in their 2nd (39.5%), and 3rd (42.1%) trimester and only 18.4% were in the 1st trimester, figures that are lower than the 48.6% for the 2nd trimester, higher than the 37.4% for the 3rd trimester and almost the same (19.0%) for the 1st trimester as reported by Nath and Mahajan [2]. Furthermore, 16 (50.0%) of 32 women pregnant for the first time, 6 (18.7%) of the 32 pregnant for the second time and 16 (32.6%) of the 49 who had been severally pregnant presented with febrile illness. This finding accords with what previous studies reported that nulliparous women were more likely to exhibit intrapartum fever than parous women [42-44]. Febrile illness in early pregnancy may be deleterious to the fetus. The fetal body temperature is mostly regulated by utero-placental hemodynamics and heat exchange at the amniotic fluid interface [1,2]. In the early stages of pregnancy, the development of the fetus depends, almost completely depends on protein activity which is sensitive to temperature. An increase in body temperature from the normal 37.5°C (99.6°F) to 38.9°C (102°F) hinders the functioning of proteins and can lead to miscarriage. Furthermore, fever in early pregnancy has been reported to increase the risk of congenital birth defects such as cranio-facial clefts, abnormal

arch artery anatomy, aortico-pulmonary septation and conotruncal heart defects through neural crest cell dysfunction in babies [45,46]. The effects of increased body temperature on pregnancy are contingent on how much the temperature rises, indicating that trifling rise in temperature during preimplantation period and severe exposures during embryonic and fetal development might result in miscarriage, preterm birth, intrauterine growth restriction and still birth [1].

Clinicians are often left with a dilemma concerning malaria parasitemia as 54.5% of those who were positive for malaria parasites in this study reported febrile illness whereas 45.5% of them did not report febrile illness. This indicates that even when there is no report of a febrile illness, clinicians should still check for malaria parasitemia either by microscopy or Rapid Diagnostic Test (RDT) kits. (What does WHO say about this?) Among those who were negative for malaria parasites, 28.6% reported febrile illness indicating that febrile illness is not cause by malaria parasites alone. Clinicians should thus look for underlying causes of fever and not assume that, in endemic settings, malaria is the sole cause of maternal fever.

Ownership and utilization of anti-malaria commodities were found to be very low as only 9 (23.7%) of those who reported febrile illness and 19 (33.9%) of those who did not report febrile illness possessed LLINs and even fewer (6 or 15.8% among those who reported and 9 or 12.0% among those who did not report febrile illness) used LLINs, that is slept under LLIN during pregnancy. This accords with the finding of another study in Southwest Nigeria that, despite the fact that replacement of LLINs took place on a large scale, its utilization, especially among the at-risk groups, was still low [47]. It must be mentioned also that the use of first dose of Sulphadoxine-pyrimethamine (SP) for intermittent preventive therapy in pregnancy (IPTp), as advised by WHO [48], was still low as only 32 or 23.3% (11 or 28.9% of those who reported and 21 or 28.0% of those who did not report febrile illness in pregnancy) used SP for IPTp. This figure is similar to the 21.3% reported in Ghana [49]. Use of SP as IPTp seems to be advantageous as a recent systematic review showed that 2 doses of IPTp with SP retained activity to reduce placental malaria and low birth weight in areas with 1%-26% in vivo resistance in children [50].

This study focused on subjective report of febrile illness during antenatal period. The majority of our study subjects were multigravidas. It is speculated that febrile illness among our study subjects could have been the outcome of inflammatory reactions as a result of infectious agents or effect of toxins from infection or inflammatory reactions which may be compounded by maternal complication and produce profound adverse effect on the fetus. Based on a previous study [1], this study postulates that pregnancy-related febrile illness progressing to hyperthermia may cause changes in the uterine environment that may be fatal to the well-being of the developing fetus.

Conclusion

Febrile illness in pregnancy is a clinical entity that could be more widespread than reported in Nigeria and other sub-Saharan countries. This clinical entity probably results in an array of antenatal, intrapartum and post-partum medical and gynecological complications as well as fetal and neonatal problems. In this study, 32 (28.3%) of study subjects were pregnant for the first time and 16 (50.0%) of them reported febrile illness within 48 hours of presentation at Antenatal clinic. Only 3 (9.4%) of these 32 primigravidas possessed LLIN and only 2 (66.7%) of these 3 slept under LLIN night before survey. Use of SP for IPTp was still low. The mean PCV of pregnant women with malaria parasites was significantly lower than that of malaria-free pregnant women and that of those who gave a self-report of febrile illness was also significantly lower than the mean PCV of those who did not give a report of febrile illness in pregnancy. Pyrexia from various etiologies that range from preventable infections like malaria, dengue, typhoid and hepatitis result in adverse feto-maternal outcome. Therefore, standard methods of infection control in homes, communities and health-care settings, improving health education and awareness will go a long way in preventing such adverse feto-maternal outcomes. Multi-center studies with larger sample size and longer duration of time are urgently needed to address this important issue in order to reduce both maternal morbidity and mortality as well as neonatal morbidity and mortality. Data from such studies are essential for policy formulation in maternal and child health.

Limitations: This study has some limitations that need clarification. First, women were allowed to give a subjective report of febrile illness they experience during pregnancy. This was not further investigated because, the fever could have gone down either by itself or with the use of analgesic. Measuring fever at consultation may have been misleading in accessing subjective febrile illness in this group of pregnant women. Be that as it may, body temperature of pregnant women should be taken at presentation and a history of fever should be elicited by the attending clinician. Secondly, the cause or causes of fever was not probed in this study, apart from laboratory examination for malaria parasitemia. The direction of the study was to investigate the proportion of pregnant women who presented with fever during pregnancy. However, it would have been more robust to further examine bacterial or viral cause of the febrile illness among the two groups of women or to investigate any systemic disease or pro-inflammatory products such as granulocyte colony-stimulating factor, tumor necrosis factor-α, interleukin-1β, C-reactive protein and interferon γ. However, this was beyond the scope of the study. Also, the study did not investigate the outcome of pregnancy among the women with febrile illness in comparison with those without febrile illness. It would have been preferable to have had a post-partum study (i) birth weight, (ii) placenta weight (iii) Apgar score (iv) congenital anomaly and other variables in the babies of those with febrile illness in pregnancy and those without febrile illness in pregnancy. It would have been better to follow up the babies to observe any hidden congenital anomaly which would have been obvious within the first or

second year of life, such as congenital heart defect. This is the focus of another upcoming study.

Conflict of Interest

None.

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