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Research Article

Preventive and Curative treatment of malaria during pregnancy in Mali: Evaluation of the Healthcare Professionals based on the Malian National Malaria Control Program (NMCP) Guidelines

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Abstract

Malaria infections in pregnancy should be treated promptly with safe and efficacious antimalarial drugs to prevent harmful effects on the mother and fetus. To succeed, the Malian has developed NMCP guidelines for the management of malaria cases in pregnant women. The study aimed at the analysis of the prescription of antimalarial drugs based on the Mali's NMCP guidelines.

We conducted a cross-sectional study during malaria transmission season from June to August 2020. The sampling concerned all prescriptions for pregnant women containing at least one antimalarial drug.

The frequency of prescription of antimalarial drugs was 85%. 132 (74.16%) were preventive treatments and 46 (25.84%) curative treatments. 30 (90.91%) of pregnant women in the first trimester received one dose of Sulfadoxine-Pyrimethamine. 6 (12.5%) received three doses in the third trimester. Of the 46 antimalarial drugs prescribed for the treatment of uncomplicated malaria, 30 (65.22%) were Artemether-lumefantrine (tablet), 10 (21.74%) were Quinine (tablet). 29 (63.04%) were compliant with NMCP guidelines and 17 (36.96%) were not. The non-compliances concerned 3 prescriptions of Artemether-lumefantrine in the first trimester, 3 and 5 prescriptions of Quinine (tablet) in the second and third trimester respectively and at the end 2 and 4 non-compliances respectively for the prescription of injectable dosage forms of Quinine and Artesunate.

This study showed a great noncompliance with the Mali's NMCP guidelines in the prescription of antimalarial in pregnant women. Chemoprophylaxis should be prohibited in the first trimester.

Keywords: Curative and Preventive Treatment, Malaria in Pregnancy, Malaria Transmission, Mali

INTRODUCTION

Despite the progress made in the fight against malaria over the past decade, including a significant reduction in malaria-related morbidity and mortality in most sub-Saharan Africa countries, ~ 228 million cases and ~ 405'000 deaths were still recorded worldwide in 2018.[1] Children under 5 and pregnant women are the most vulnerable and therefore the most affected by malaria.[1] In 2018, there were an estimated 39 million pregnancies in sub-Saharan Africa, of which over 11 million (29%) were exposed to *P. falciparum*.[1] The majority of women residing in malaria-endemic areas of sub-Saharan Africa are partially immune and do not develop symptoms when infected with *P. falciparum* during pregnancy. However, even in the absence of symptomatic disease, malaria in pregnancy is associated with maternal anemia and adverse birth outcomes such as low birth weight, preterm delivery, and stillbirth.[2–4] Pregnancy is associated with various physiological changes that can alter the absorption, disposition, metabolism, and excretion of drugs.[5] These pregnancy-related changes in pharmacokinetic properties could result in overexposure or underexposure to antimalarial drugs. These pregnancy-related changes in pharmacokinetic properties could result in overexposure or underexposure to antimalarial drugs. Overexposure might lead to maternal and fetal toxicity and underexposure could cause therapeutic failures, resulting in poor pregnancy outcomes, maternal death, and increased risk of drug resistance.[5,6] Malaria infections in pregnancy should be treated promptly with safe and efficacious antimalarial drugs to prevent harmful effects on the mother and fetus.[7,8] For *P. falciparum* malaria infections during the first trimester, WHO recommends quinine with clindamycin for 7 days (or quinine alone if clindamycin is not available.[8] Guidelines for the treatment of *P falciparum* malaria in the second and third trimester are the same as for non-pregnant adults; this

means any ACTs that are recommended as first-line treatment—namely, artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, dihydroartemisinin-piperaquine, or artesunate plus sulfadoxine-pyrimethamine can be used in pregnancy.[8]

To control malaria in Mali, the National Malaria Control Programme (NMCP) recommends intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) in pregnant women and to use quinine (first trimester) and artemether – lumefantrine (AL) or artesunate-amodiaquine (second and third trimester) for the treatment of confirmed cases. The Malian has developed NMCP guidelines with protocols for the management of uncompleted and severe malaria cases in pregnant women.[9]

The prescriber's responsibility is to initiate properly an early antimalarial treatment for confirmed malaria cases. Chemoprophylaxis and curative treatment should comply with current standards and guidelines to reduce morbidity during pregnancy and adverse birth outcomes. The success of these recommendations in the treatment policy will depend on the adherence and compliance of healthcare professionals and their patients.[10]

METHODS

Our study took place in seven health centers of commune VI of district of Bamako in Mali, where malaria is endemic. We conducted a cross-sectional study during malaria transmission season from June to August 2020. The sampling concerned all prescriptions for pregnant women containing at least one antimalarial drug and recorded in a medical register in one of the seven health centers.

The nature of the antimalarial drugs, its dosage, the duration of treatment and the type of prescribed antimalarial combination according to the age of pregnant were analyzed based on the NMCP guidelines.[9] A non-compliant prescription was defined as any breach of one or more of the parameters listed above with respect to the NMCP guidelines. In the registries, we also collected information about biological diagnosis and the socio-demographic characteristics (age and sex of the patient). In addition, prescriber's qualification was reported.

Drug according to the age of pregnant, dosages and duration of treatment prescribed by the NMCP are shown below (**Table 1**).

Ethical aspects

The Faculty of Pharmacy of the University of Sciences, Techniques and Technologies of Bamako validated the protocol. Anonymity and confidentiality were respected.

Statistical analysis

Data were collected on a report form, entered into Excel and analyzed using the statistical software Epi info 6.04.

Table 1 : Drug, presentation, dosage, duration of treatment for uncomplicated malaria according to the age of pregnant by the NMCP.

<table>
<tr><td colspan="8">First trimester of pregnancy: Quinine salt tablet 10mg / kg every 8 hours for 7 days.</td></tr>
<tr><td colspan="8">Second and third trimester of pregnancy: Artemether 20 mg - Lumefantrine 120 mg</td></tr>
<tr><td>Age/weight</td><td>Presentation</td><td colspan="2">Day 1</td><td colspan="2">Day 2</td><td colspan="2">Day 3</td></tr>
<tr><td rowspan="2">≥ 35 Kg (≥13-years-old)</td><td rowspan="2">Tablet</td><td>Morning</td><td>Evening</td><td>Morning</td><td>Evening</td><td>Morning</td><td>Evening</td></tr>
<tr><td>4 tablets</td><td>4 tablets</td><td>4 tablets</td><td>4 tablets</td><td>4 tablets</td><td>4 tablets</td></tr>
<tr><td colspan="8">Second and third trimester of pregnancy: artesunate-amodiaquine</td></tr>
<tr><td>Age/weight</td><td colspan="3">Presentation</td><td>Day 1</td><td>Day 2</td><td colspan="2">Day 3</td></tr>
<tr><td>≥ 18kg to <36kg
(6 to 13 years-old)</td><td colspan="3">100mg/270 mg blister 3 tablets</td><td>1 tablet</td><td>1 tablet</td><td colspan="2">1 tablet</td></tr>
<tr><td>≥36kg
(≥14 years-old)</td><td colspan="3">100mg/270 mg blister 6 tablets</td><td>2 tablets</td><td>2 tablets</td><td colspan="2">2 tablets</td></tr>
<tr><td colspan="8">Note : Artesunate injection is the drug of choice for the treatment of severe malaria. In case of unavailability, artemether is preferable to quinine.</td></tr>
</table>

RESULTS

The study population consisted of 210 prescriptions given to 208 pregnant women seen in prenatal consultations.

Socio-demographic data and frequency of prescribing of antimalarials in pregnant women

Among the 210 prescriptions, 178 had an antimalarial, a frequency of 0.85 (85%). The most represented age group was 21-30 years with 58.43%. The average age was 24.16±5.83 years with extremes ranging from 13 to 37 years. Prenatal consultations were performed by midwives and matrons respectively 172 (96.63%) and 6 (3.37%). The Pregnant women were more in the second and third trimester with 53.98% and 27.27% respectively.

Type of treatment of malaria in pregnant women

Among the 178 prescriptions prescribed to 176 pregnant women, 132 (74.16%) were preventive treatment and 46 (25.84%) curative treatment (**Table 1**). Sulfadoxine purimethamine (SP) was the only molecule used in chemoprophalaxis. The international non-proprietary name prescription was respected in 16.85% and not respected in 83.15%. The tablet and injectable forms were the prescribed forms with 96.63% and 3.37% respectively. The dosage indication appeared on 88.77% of the prescriptions. Side effects occurred in 12 (6.82%) of 176 pregnant women (**Table 2**).

Table 2 : Evaluation of antimalarial prescription

Socio-demographic data		Effectifs	Pourcentage
Age ranges	13-20 years-old	30	16,85
	21-30 years-old	104	58,43
	31-37 years-old	44	24,72
	Total	178	100
Qualification	Physician	0	0
	Midewife	172	96,63
	Obstetric Nurse	6	3,37
	Total	178	100
Gestational age	1er Trimestre	33	18,75
	2ème Trimestre	95	53,98
	3ème Trimestre	48	27,27
	Total	176	100
Prescription in International Nonproprietary Name	Conform	30	16,85
	Non conform	148	83,15
	Total		
Galenic forms	Comprimé	172	96,63
	Injectable	6	3,37
	Total		
Types de traitement	Preventif	132	74,16
	Curatif	46	25,84
	Total		
Dosage indication	Yes	150	88,77
	No	28	15,73
	Total		
Onset of side effects	Yes	12	6,7
	No	166	93
	Total		
Malaria curative treatment duration	Conform	46	100
	Non conform	0	0
	Total		
Malaria diagnostic confirmed by RDT	Yes	46	100
	No	0	0
	Total		

RDT : rapid diagnostic test

Preventive treatment of malaria in pregnant women

75% of the 176 pregnant women received pyrimethamine sulfadoxine. 30 (90.91%) of first trimester pregnant women received one dose of Sulfadoxine-Pyrimethamine. Of those in the second trimester, 54.74% received one dose of Sulfadoxine-Pyrimethamine and 15.79% received two doses. 60.42% of those in the third trimester received two doses and 12.5% received three doses (Table 2).

Curative treatment of uncomplicated malaria according to pregnancy age and compliance with Mali NMCP guidelines

Out of the 46 antimalarials prescribed for the treatment of uncomplicated malaria, 30 (65.22%) were Artemether-lumefantrine (Tablet), 10 (21.74%) were Quinine (Tablet), Artesunate (Injectable) in third position with 8.69% and Quinine (Injectable) with 4.35%. 29 (63.04%) were compliant with NMCP guidelines and 17 (36.96%) were non-

compliant. The non-compliances concerned 3 prescriptions of Artemether-lumefantrine (Tablet) in the first trimester, 3 and 5 prescriptions of quinine (Tablet) respectively in the second and third trimester and at the end 2 and 4 non-compliances respectively for the prescription of injectable pharmaceutical forms of quinine and Artesunate. (**Table 3**)

Following the intake of Sulfadoxine-purimethamine by 7 pregnant women and the intake of quinine by 5 pregnant women, side effects such as dizziness, tinnitus, nausea and vomiting were reported. (**Table 2**).

Table 2 : Number of times the Sulfadoxine-Pyrimethamine has been taken depending on the age of pregnancy.

Number of doses of Sulfadoxine-Pyrimethamine	Pregnancy age in trimester		
	1er (n=33)	2ème (n=95)	3ème (n=48)
1	30 (90,91%)	52 (54,74%)	0
2	0	15 (15,79%)	29 (60,42%)
3	0	0	6 (12,5%)
TOTAL	30 (90,91%)	67 (70,53%)	35 (72,92%)

Table 3: Antimalarial prescribed for curative treatment of uncomplicated malaria according to age of pregnancy and compliance with Mali's NMCP guidelines.

Prescribed antimalarial	Pregnancy age in trimester (n=46)			Total
	1er	2ème	3ème	n (%)
Artemether-lumefantrine (Tablet)	3 (NC)	15 (C)	12 (C)	30 (65,22)
Quinine (Tablet)	2 (C)	3 (NC)	5 (NC)	10 (21,74)
Quinine (Injectable)	0	1 (NC)	1 (NC)	2 (4,35)
Artesunate (Injectable)	0	4 (NC)	0	4 (8,69)

NC: not compliant, C: compliant

All prescribed molecules according to the FDA risk category

A total of 506 drugs distributed among 14 molecules, including 5 fixed combinations, were identified out of 178 prescriptions containing an antimalarial drug. 35 (6.92%) drugs were unclassified by FDA risk category. Category C was the most prescribed and included 232 (45,85%) drugs; category B included 74 (14,62%) drugs and 165 (32,61%) drugs for category A. (**Table 4 and 5**).

Table 4: Frequency distribution of the medicines prescribed and FDA risk category

Drug name	Frequency	Percent	FDA risk category
Iron - Folic acid	161	31,82	A
Vitamin C	4	0,79	A
Paracetamol	53	10,47	B
Clotrimazole	7	1,38	B
Erythromycin	4	0,79	B
Metronidazole	10	1,98	B
Artemether-lumefantrine	30	5,93	C
Sulfadoxine-pyrimethamine	132	26,09	C
Hyoscine-butylbromide	30	5,93	C
Domperidone	28	5,53	C
Quinine	12	2,37	C
Phloroglucinol-Trimethylphloroglucinol	29	5,73	Unclassified
Artesunate	4	0,79	Unclassified
Metopimazine	2	0,40	Unclassified
Total	506	100,00	

Table 5 : FDA risk category and percent

FDA risk category	Frequency n (%)	FDA Categories are defined
A	165 (32,61)	Adequate clinical studies have shown no risk to fetus in any trimester
B	74 (14,62)	Animal studies have not shown adverse effect on the fetus and there are inadequate clinical studies
C	232 (45,85)	Animal studies have shown adverse effects, no adequate clinical studies. May be useful in pregnancy despite potential risks.
D	0	There is evidence of risk to human fetus, but potential benefits may be acceptable despite potential risks.
X	0	Animal/human studies show foetal abnormalities. Risks involved clearly outweigh benefits.
Unclassified	35 (6,92)	
Total	506 (100)	

DISCUSSION

This study assessed compliance with the national malaria control program guidelines in pregnant women. The frequency of prescription of antimalarials was 85%. This percentage is higher than the 38% obtained by Eze et al.,[11]. This difference is explained by the fact that this study was conducted in community health centers while a university hospital was part of their study site. The majority of the pregnant women (58.43%) were between 21 and 30 years of age. The mean age was 24.16±5.83 years with extremes ranging from 13 to 37 years. This result is similar to that of Alemu BK.et al.,[12] with 26.5 years as the mean age of the gestating females and the age range of 25 and 34 years was in majority. The majority of pregnant women were in the second trimester with 53.98% in contrast to the study of Alemu et al.,[12] where 63.2% of pregnant women were in the third trimester.

Among the 178 prescriptions given to 176 pregnant women, 132 (74.16%) were for preventive treatment with sulfadoxine purimethamine and 46 (25.84%) for curative treatment. The prevalence of 62.4% in pregnant women reported by Idowu et al.,[13] is higher. Indeed, malaria chemoprophylaxis is known to reduce parasite levels during pregnancy.[14] This would explain the low prevalence of malaria in pregnant women.

16.85% of the drugs were prescribed in international non-proprietary names. However, the value obtained (43%) by Eze et al.,[11] was higher. This means that prescribers were not fully complying with the WHO recommendation that drugs should be prescribed using their international non-proprietary names.[15] This very low prescription of generic names leads to an increase in the direct and indirect cost of medicines due to the unavailability of non-branded medicines at the community health center.

75% of the 176 pregnant women received pyrimethamine sulfadoxine. This is higher than the 36% reported in the 2011 Mali Health Information and Management System survey.[16] This difference is explained by the low attendance of health centers in several localities. In addition, the 20.3% obtained by Eze et al.,[11] is much lower because their study concerned all prescriptions. 90.91% of women in the first trimester received a dose of sulfadoxine-pyrimethamine, which confirms the inconsistency or lack of clarity of Mali's guidelines on malaria in pregnancy compared to the WHO recommendations that sulfadoxine-pyrimethamine be administered under direct observation as early as possible in the second trimester of pregnancy and at each prenatal visit at least one month apart.[16,17] Of those in the second trimester, 54.74% received a single dose of sulfadoxine-pyrimethamine and 15.79% received two doses. 60.42% of those in the third trimester received two doses and 12.5% received three doses. These results show that second and third trimester pregnant women did not receive even one dose of sulfadoxine-pyrimethamine. They are clearly below the WHO target of at least three doses during pregnancy.[18]

Regarding the treatment of uncomplicated malaria, of the 46 antimalarial drugs prescribed 65.22% was artemether-lumefantrine (Tablet), 21.74% was quinine (Tablet), artesunate (Injectable) in third position with 8.69% and Quinine (Injectable) with 4.35%. These values are higher than those of Luz et al.,[19] who found a prescription frequency of 16.2% for artemeter-lumefantrine, 10.8% for quinine sulphate and 1% for artesunate.This difference could be explained by the application of therapeutic regimens prescribed according to the type of plasmodium in their study

Treatment of uncomplicated malaria was 63.04% compliant with Mali's NMCP guidelines and 36.96% non-compliant.

The non-compliances concerned 3 prescriptions of Artemether-lumefantrine (Tablet) in the first trimester, 3 and 5 prescriptions of quinine (Tablet) respectively in the second and third trimester and at the end 2 and 4 non-compliances respectively for the prescription of injectable pharmaceutical forms of quinine and Artesunate which are reserved for the treatment of severe malaria by the guidelines of the NMCP of Mali and WHO.[8,9]

The most prescribed drugs were in category C of the FDA drug classification for fetal risk, followed by those in category A. Animal studies have shown adverse effects with category C drugs, no adequate clinical studies. These drugs such as Artemether-lumefantrine, Sulfadoxine-pyrimethamine, Quinine can be used according to the age of the pregnancy and thus minimize the potential risks.[5,11] Phloroglucinol-trimethylphloroglucinol, artesunate and metopimazine have not been classified by the FDA as a risk category. Other studies have shown that these molecules are probably safe.[7,20]

CONCLUSION

This study showed a great non compliance with the Mali's NMCP guidelines in the prescription of antimalarial drugs during the treatment of uncomplicated malaria to the detriment of pregnant women and their fetus. Chemoprophylaxis with sulfadoxine-pyrimethamine should

be prohibited in the first trimester. We suggest improving the Mali's NMCP guidelines for chemoprophylaxis.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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