Prescriptions for uncomplicated malaria treatment among pregnant women in the Brazilian Amazon: evidences from the Mafalda Project

*Prescrições para tratamento de malária não complicada em gestantes na Amazônia Legal: evidências do Projeto Mafalda**

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Abstract

Aim: To evaluate antimalarial prescriptions according to quality indicators and to describe adverse events reports among pregnant women with uncomplicated malaria. **Methods:** Descriptive study of medical files of pregnant women 15 years and older, residents in high-risk municipalities in the Brazilian Amazon. Antimalarial medicines were characterized by frequency of prescription, type of plasmodium and health care facilities where prescribing took place, and by possible adverse events. Variables were compared by Pearson's chi-square. **Results:** A total of 262 medical files were evaluated. Most patients were diagnosed for *Plasmodium vivax* 71,2%. Chloroquine was the commonest prescribed antimalarial (65.6%). Of *P. vivax* prescriptions, 9.0%, and 16.2% of *P. falciparum* prescriptions presented antimalarials not recommended in the official protocol. Prescriptions for *P. falciparum*, in significantly higher proportion, did not adhere to the official protocol in regard to type of antimalarial and dose/duration of treatment (p = 0,001). They also lacked information on dose and dosing interval (p = 0,004). There were no significant differences among reference centers and basic health care units in respect to the prescribed antimalarials, to prescriptions containing antimalarials not recommended in the official protocol or in respect to lack of dosing information. Chloroquine was the antimalarial most related to the occurrence of adverse events. **Conclusion:** The findings indicate that there are flaws in antimalarial prescribing for pregnant women, especially in respect to their adequacy to the official protocol.

Keywords: Malaria. *Plasmodium falciparum*. *Plasmodium vivax*. Pregnant women. Drug prescriptions. Drug utilization.

Resumo

Objetivos: Avaliar prescrições de antimaláricos segundo indicadores de qualidade e descrever relatos de eventos adversos entre gestantes com malária não complicada. **Métodos:** Estudo descritivo de prontuários de gestantes maiores de 15 anos, residentes em municípios de alto risco na Amazônia Legal. Antimaláricos caracterizados segundo frequência de prescrição, tipo de plasmódio e de unidade de saúde de atendimento, e de possíveis eventos adversos. Para comparação das variáveis estudas utilizou-se o teste do qui-quadrado de Pearson. **Resultados:** Foram avaliados 262 prontuários de gestantes. A maioria das gestantes pesquisadas recebeu diagnóstico de infecção por *P. vivax* (71,2%). Cloroquina foi o fármaco mais prescrito (65,6%). Fármacos não recomendados foram encontrados em 9,0% e 16,2% das prescrições para *P. vivax* e *P. falciparum*, respectivamente. Prescrições para *P. falciparum*, em proporção significativamente maior, contiveram esquemas e posologia e/ou duração do tratamento não adequados ao protocolo oficial (p = 0,001), bem como sem especificação da posologia (p = 0,004). Não houve diferenças significativas entre hospitais de referência e unidades básicas de saúde quanto aos esquemas de tratamento, proporções de prescrições contendo esquemas de tratamento não adequados e sem especificação da posologia. Cloroquina foi o fármaco mais envolvido em ocorrências de eventos adversos. **Conclusões:** Os resultados mostraram deficiências na prescrição de antimaláricos para gestantes, especialmente quanto à adequação ao protocolo oficial.

Palavras-chave: Malária. *Plasmodium falciparum*. *Plasmodium vivax*. Gestantes. Prescrições de medicamentos. Uso de medicamentos.

Introduction

Malaria in pregnancy is a potentially severe condition. It is estimated that, every year, 50 million pregnant women are exposed to the risk of this infection in the world, which can affect the course of pregnancy and lead to several negative outcomes, such as anemia, prematurity, low birth weight, fetal loss and maternal death.[1,2]

In spite of the recognized impact of malaria on pregnancy, up to the moment the information on the real magnitude of the disease regarding this population is scarce in Brazil. It is known that almost all the cases registered in the country (more than 99%) are concentrated on the Amazon Region. In 2009, 308,453 cases were registered in this region. Of these, 257,530 (83.49%) were related to the species *Plasmodium vivax* and 50,816 (16.47%) to the species *Plasmodium falciparum*. Species like *Plasmodium malariae* and *Plasmodium ovale* accounted for 107 cases, corresponding to 0.03% of the total. Generally speaking, *P.vivax* causes the mild forms of malaria and *P. falciparum* is responsible for the severe clinical forms of the disease[3].

This profile seems to apply to pregnant women. A study analyzed 13,308 cases of malaria notified to the *Sistema de Informação de Vigilância Epidemiológica* (SIVEP-Malária – Epidemiological Surveillance Information System) among women aged 10 to 49 years between 2003 and 2006. Among the registered cases, 6.1% occurred in pregnant women, and it was observed that 85% of the notifications were caused by *P. vivax*, 14.3% by *P. falciparum* and 0.6% were cases of mixed malaria infection[4].

One of the main strategies adopted by the Ministry of Health to control malaria is drug therapy, guided by means of an official protocol that is periodically revised. The protocol is organized by therapeutic regimens that vary according to the severity of the disease, the parasite species and the presence of pregnancy, among other factors[5-7].

To pregnant women with uncomplicated malaria caused by *P. vivax*, for example, chloroquine is recommended as the first-choice drug. The treatment lasts three days; 4 tablets must be taken on the first day and 3 on the other days. In infections caused by *P. falciparum* with the same severity, the recommendation is that 3 quinine sulphate tablets are taken per day during a period of 7 days. There is also the possibility of administrating 30mg/kg/day of quinine sulphate during 3 days, combined with 20mg/kg of clindamycin, four times a day, for a period of five days. In addition, from the second trimester of pregnancy onwards, the fixed combination of artemether and lumefantrine (8 tablets during three consecutive days) is recommended, or the use of mefloquine in a single dose of four tablets, which can be taken two tablets at a time. Neither primaquine nor doxycycline can be used by pregnant women; thus, the former cannot be combined with chloroquine for *P. vivax* and the latter cannot be combined with quinine for *P. falciparum*[5-7].

Independently of the type of infection, however, it is important that the use of antimalarials in pregnancy undergoes a thorough evaluation, as the risks for the mother and for the conceptus have not been completely established yet. In addition, treatment failures caused by the development of resistant forms of parasites have also been described in the literature[8,9].

As the prescription can be considered the final result of a process of diagnosis and decision that reflects both the availability of drugs and the information that is distributed about them – information that reaches the prescribing professional[10] -, the study of prescriptions of antimalarials for pregnant women is a useful tool.

The present study aims to assess the prescriptions of antimalarials according to quality indicators and to describe reports of adverse events related to the prescribed treatments for pregnant women with uncomplicated malaria living in the Brazilian Amazon Region.

Methodology

Area and data source

This study is part of the Mafalda Project (Model of Assessment for Pharmaceutical Care to Focal Endemics in the Amazon Region, Brazil: prescription, administration and adherence to the treatment of uncomplicated malaria caused by *P. vivax* and *P. falciparum* in high-risk cities), whose main objective was to investigate the utilization of antimalarials in the treatment of uncomplicated malaria caused by *P. vivax* or *P. falciparum* in adults and pregnant women[11,12].

The Amazon Region encompasses the following States: Acre, Amapá, Amazonas, Pará, Rondônia, Roraima and part of the States of Mato Grosso, Tocantins and Maranhão. Among the criteria to select the cities that participated in the research, established in the protocol of the Mafalda Project, the following were included: high-risk classification (Annual Parasite Index – API > 50) for uncomplicated malaria; existence of at least 7,000 annual cases of malaria; existence of prescriptions or written guidance about the treatment; and adoption, by the city, of the National Protocol, according to a report of the Municipal Health Department. These criteria determined the inclusion of 15 eligible cities, whose populations were stratified into three ranges: > 100,000 inhabitants, between 99,999 and 30,000 and < 29,999 inhabitants. The final choice was determined for convenience, in order to allow a better field logistics in the Amazon Region[11,12].

For the present investigation, the component "prescription of antimalarial drugs for pregnant women" of the Mafalda project was evaluated, in a descriptive study of the prescriptions. For this branch of the study, the cities that had health units that provide care for pregnant women were elected (Manaus, Careiro and Presidente Figueiredo in the State of Amazonas, and Porto Velho in the State of Rondônia). Units that were located less than 50 km from urban centers and which, in each city, concentrated the

highest number of assistances to pregnant women, according to information provided by the Municipal Health Departments, were elected. The heads of the municipal health departments and the managers of each unit authorized the conduction of the research by means of consent forms. Further details can be found in other publications[11,12].

In the selected cities, the visited units included reference centers for malaria and primary care units, totaling 8 units. All the medical files and prescriptions corresponding to pregnant women older than 15 years, with diagnosis of malaria by *P. vivax* and *P. falciparum,* who were present at the units at the moment of the visit, were revised. Additionally, the pregnant women's notification files were searched for within the SIVEP-Malária[13]. Due to logistic questions of the fieldwork of the Mafalda Project, data were collected in January and February 2007 and in January and February 2008 in the visited units, by a trained team, through a structured and pre-tested questionnaire[12]. The following information was collected: prescribed treatment (utilized drugs, dose and dosing interval, and treatment duration), diagnosis (whether it was a parasitological diagnostic test, type of malaria, time elapsed before delivering the results), adverse events related to treatment reported in the medical file (occurrence of an adverse event (yes or no), description of the event and information on the number of days that elapsed between the beginning of treatment and the occurrence of the event), prenatal data (type of pregnancy, number of consultations), data on the delivery and on the conceptus (type of delivery, report on complications, condition at birth, weight, Apgar index, report on adverse events in the newborn) [12].

Study variables

The variables used in this study included the type of healthcare unit (reference center for the treatment of malaria or primary care unit); diagnosis of malaria by type of plasmodium (*P. vivax* or *P. falciparum*); gestational age (in weeks); the prescribed treatment (antimalarial(s), dose/dosing interval and treatment duration); occurrence and description of adverse events. The treatment studied in this paper was the initial treatment for the episode that led the pregnant woman to seek for assistance in the healthcare system. Treatments for prophylaxis or relapses in pregnant women were not investigated.

For analysis purposes, the following quality indicators of the prescription of antimalarials were constructed, based on the prescription indicators proposed by the Mafalda Project[14] and according to the provisions of the pertinent sanitary legislation[15] and to the guidelines of the National Malaria Control Program[5-7]:

- proportion of prescriptions whose treatment regimens do not comply with the official protocol: estimated by the number of inadequate prescriptions concerning the medication(s) prescribed and the gestational trimester/total of prescriptions. To construct this indicator, each prescribed treatment regimen was evaluated according to the guidelines established in the official protocol for the treatment of pregnant women[5-7]. The therapeutic regimens were classified as compliant if they were prescribed taking into account the plasmodium species (*P. vivax* ou *P. falciparum*), as well as the ongoing gestational trimester. The therapeutic regimens that diverged from these recommendations were classified as non-compliant;
- proportion of prescriptions whose information on dose/dosing interval and/or treatment duration does not comply with the official protocol: estimated by the number of prescriptions with dose or duration different from what is recommended in the official protocol/total of prescriptions. To construct this indicator, each treatment regimen was evaluated according to the guidelines established in the official protocol for the treatment of pregnant women[5-7]. The regimens were considered compliant if the information on dose and treatment

duration coincided with the recommendations of the official protocol;
- Proportion of prescriptions without specifications for dose/dosing interval: estimated by the number of prescriptions without dosing information/total of prescriptions;
- Proportion of prescriptions without specifications for the duration of the treatment: estimated by the number of prescriptions without information on treatment duration/total of prescriptions.

Data analysis

The antimalarials prescribed to the pregnant women were identified, and their frequency distribution was described. The prescribed regimens were also characterized according to type of plasmodium and type of healthcare unit.

The quality indicators of the prescription of antimalarials were compared according to type of plasmodium and healthcare unit by means of Pearson's chi-square test, and p-values below 0.05 were considered significant.

In addition, the antimalarials were described according to the frequency of possible adverse events, in relation to the involved medication, the affected system and the reported symptoms.

The statistical analysis was performed using the software SPSS, version 13.0 for Windows (IBM Corporation, United States).

Ethical Considerations and Conflict of Interests: The Mafalda Project was approved by the Ethics Research Committee of the Sérgio Arouca National School of Public Health (ENSP/Fiocruz)[12]. The authors state that there were no conflicts of interests.

Results

Of the 273 medical files of pregnant women with diagnosis of malaria by *P. vivax* ou *P. falciparum* that were found in the researched healthcare units, 11 (4.03%) were excluded because it was not possible to identify the prescribed therapeutic regimen. In the remaining 262 files, the most frequent type of infection was by *P. vivax* (71.2%), verified by means of a parasitological diagnostic test (99.6%). Gestational age was located in 209 files (79.8%) and varied between 1 and 44 weeks (mean = 23.0 weeks; [SD = 9.61]). The majority of the pregnant women were in the second trimester of gestation (45.0%).

Considering the consulted files, a total of 308 antimalarials was found, which corresponded to 10 active principles (two medicines composed a fixed-dose combination therapy). Chloroquine was the most prescribed medication (65.6%), followed by mefloquine (11.4%) and quinine sulphate (9.1%) (Table 1).

Table 1 - Distribution of prescribed antimalarials. Mafalda Project, 2007/2008.
***Tabela 1** - Distribuição dos antimaláricos prescritos. Projeto Mafalda, 2007/2008.*

Drug	Frequency n (%)
chloroquine	202 (65.6)
mefloquine	35 (11.4)
quinine sulphate	28 (9.1)
artemether-lumefantrine	16 (5.2)
clyndamicine	15 (4.9)
primaquine	6 (1.9)
artesunate	3 (1.0)
doxycycline	2 (0.6)
artemether	1 (0.3)
Total	308

In the majority of the prescriptions (n = 220; 84.1%), the treatment was characterized as monotherapy, that is, the use of isolated medications; 15.2% (n = 40) of the prescriptions contained combinations of two medications; in the remaining prescriptions, combinations of three medications were used. The prescriptions considered to be non-compliant with the official protocol totaled 13.3% (n = 35).

Table 2 contains the proportion of prescriptions written in accordance with the type of Plasmodium. Overall, 188 therapeutic regimens were prescribed for infection by *P. vivax* and 74 for *P. falciparum*. Among these treatments, 9.0% of the prescriptions for *P. vivax* and 16.2% of the prescriptions for *P. falciparum* contained medications that were not indicated for this type of Plasmodium.

Significant differences regarding the quality indicators for prescription of antimalarials were found in the prescriptions for *P. vivax* and *P. falciparum* (Table 3). Compared to the prescriptions for *P. vivax*, the prescriptions for *P. falciparum* containing treatment regimens that did not comply with the official protocol occurred with a frequency that was almost three times higher (p = 0.001). The prescriptions with information on dose and/or treatment duration that did not comply with the official protocol and those without specification for dose/dosing interval occurred with a frequency that was almost two times higher.

Table 4 shows the result of the comparison of prescriptions written at reference centers for the treatment of malaria and at primary care units. No significant differences were observed, neither concerning the treatment regimens chosen at the centers and at the units, nor regarding the proportions of prescriptions containing first-choice antimalarials according to the official protocol. The proportions of prescriptions containing treatment regimens that were not compliant with the official protocol and without specifications for dose/dosing interval also did not differ between the researched healthcare facilities. On the other hand, proportions of prescriptions without specification for treatment duration were almost four times higher at the reference centers compared to the primary care units (p = 0.004). Likewise, in

Table 2 - Therapeutic regimens prescribed according to plasmodium type. Mafalda Project, 2007/2008.
***Tabela 2** - Esquemas prescritos segundo tipo de plasmódio. Projeto Mafalda, 2007/2008.*

Plasmodium species	Treatment	Frequency n(%)
P. vivax	isolated chloroquine	171 (91%)
	chloroquine in combination	5 (2.7%)
	mefloquine	5 (2.7%)
	quinine sulphate	4 (2.1%)
	artemether-lumefantrine	3 (1.6%)
P. falciparum	mefloquine	28 (37.8%)
	mefloquine in combination	2 (2.7%)
	artemeter-lumefantrine	12 (16.2%)
	quinine sulphate	8 (10.8%)
	quinine sulphate and clyndamicine	14 (18.9%)
	quinine sulphate in another combination	2 (2.7%)
	chloroquine	5 (6.8%)
	chloroquine in combination	1 (1.4%)
	artemether	1 (1.4%)
	clyndamicine	1 (1.4%)

Table 3 - Antimalarial prescriptions quality according to plasmodium type. Mafalda Project, 2007/2008.
***Tabela 3** - Qualidade das prescrições de antimaláricos para gestantes segundo tipo de plasmódio. Projeto Mafalda, 2007/2008.*

Indicators	*P. falciparum*	*P. vivax*	p-value*
Proportion of prescriptions with therapeutic regimens not compliant with the official protocol	25.0	9.0	0.001
Proportion of prescriptions with information on dose and/or treatment duration not compliant with the official protocol	45.7	17.0	0.000
Proportion of prescriptions without specifications for dose/dosing interval	44.6	26.1	0.004
Proportion of prescriptions without specifications for treatment duration	29.7	25.0	0.434

* p-value from Pearson chi-square test
** Teste do qui-quadrado de Pearson*

these centers, there were more prescriptions with two or more antimalarials (p = 0.022). Furthermore, it was observed that both in the reference centers and in the primary care units the proportion of diagnoses for *P.vivax* and *P. falciparum* was the same (data not shown on tables).

Table 5 shows the list of antimalarials that were possibly involved in occurrences of adverse events, totaling 19 therapeutic regimens (5.0% of the prescriptions). Chloroquine was the medication most involved in such occurrences, which affected mainly the gastrointestinal system. The symptoms were nausea, vomiting, epigastric pain, abdominal pain and indigestion. Other possible adverse events that were reported were: irritation, insomnia and itching related to artemether-lumefantrine. For combinations containing quinine sulphate, the possible occurrences that were reported were vertigo and vomiting.

Discussion

The adequate and opportune treatment

Table 4 - Antimalarials prescribed to pregnant women according to health care facility type. Mafalda Project, 2007/2008.
***Tabela 4** - Prescrições de antimaláricos para gestantes segundo tipo de unidade de atendimento. Projeto Mafalda, 2007/2008.*

Indicators	Reference Center	Primary Care Unit	p-value*
Proportion of prescriptions containing			
chloroquine	70.0	66.7	
mefloquine	13.0	15.4	
quinine sulphate	9.9	15.4	
other antimalarial	7.2	2.6	0.527
Prescription of two or more antimalarials	18.8	5.1	0.022
Proportion of prescriptions containing first-choice antimalarials according to the official protocol	78.4	74.4	0.578
Proportion of prescriptions with therapeutic regimens not compliant with the official protocol	12.8	15.8	0.622
Proportion of prescriptions without specifications for dose/dosing interval	30.5	35.9	0.502
Proportion of prescriptions without specifications for treatment duration	29.6	7.7	0.004

* p-value from Pearson chi-square test
** Teste do qui-quadrado de Pearson*

Table 5 - Adverse event involving antimalarials, affected systems and related symptoms. Mafalda Project, 2007/2008.
Tabela 5 *- Antimaláricos envolvidos em possíveis eventos adversos, sistemas afetados e sintomas relatados. Projeto Mafalda, 2007/2008.*

Therapeutic regimen	Systems	Reported symptoms	Frequency n(%)
chloroquine	Gastro-intestinal	Nausea, vomiting, epigastric pain, abdominal pain, indigestion	6 (31.6%)
	Central and peripheral nervous system	Headache, vertigo	3 (15.8%)
	Skin and subcutaneous tissue	Allergy, itching	2 (10.5%)
	Reproductive	Increased uterine contractions, leukorrhea	2 (10.5%)
	Autonomic nervous system	Inappetence	1 (5.3%)
artemether-lumefantrine	Central and peripheral nervous system	Irritation, insomnia	2 (10.5%)
	Skin and subcutaneous tissue	Itching	1 (5.3%)
quinine sulphate and clyndamicine	Central and peripheral nervous system	Vertigo	1 (5.3%)
quinine sulphate, doxycycline and primaquine	Gastrointestinal	Vomiting	1 (5.3%)
		Total number of reported events	19

of the cases is one of the main strategies adopted by the National Program of Malaria Control. In this study, a variety of antimalarial regimens used in the treatment of pregnant women was verified, and the antimalarial chloroquine, in monotherapy, was the most frequently prescribed drug, which coincided with what was observed in another investigation[16]. The predominance of this regimen is justified by the predominance of infections by *P.vivax* in our study and, in this case, its use is indicated in the official protocol[5-7]. On the other hand, prescriptions containing regimens for pregnant women in disagreement with the official protocol were verified, such as the use, in the treatment of infections by *P. vivax*, of antimalarials such as primaquine, doxycycline, mefloquine, quinine or artemether-lumefantrine, as well as the prescription of chloroquine in the treatment of infections caused by *P. falciparum*.

The comparison of prescription indicators according to the type of plasmodium showed that those written for *P. falciparum* had worse quality. Prescriptions for this plasmodium not only presented a higher proportion of treatment regimens that were in disagreement with the official protocol, but also information on doses and/or treatment duration that was different from what is recommended[5-7]. Additionally, regarding the prescriptions for *P. falciparum*, almost double the amount of prescriptions for *P. vivax* did not contain the description of the dose/dosing interval, which does not comply with the Brazilian sanitary legislation[15]. Such results characterize a situation of risk for pregnant women, as the infections caused by *P. falciparum* are usually responsible for more severe forms of the disease and for a higher number of deaths, especially when they are not adequately treated[17]. A previous study with professionals involved in the routine of the assistance provided for malaria showed that, although the official protocol is mentioned by them as the main normative instrument for the therapeutic conducts, there are frequent errors, mainly in the treatment of *P. falciparum*[11], which

may contribute to explain the results that were found.

This study did not show significant differences between medications prescribed at reference centers and at primary care units regarding prescribed antimalarials, prescriptions containing first-choice antimalarials according to the official protocol, and prescriptions with treatment regimens in disagreement with the protocol and without specifications for dose/dosing interval. These results reveal that, generally speaking, there are flaws in both types of healthcare facilities concerning compliance with the official protocol and with the Brazilian sanitary legislation. We expected that the reference centers would pay more attention to the prescriptions written for pregnant women, in view of the expectation related to the training of professionals at these units and to the type of patient that is followed up there. On the other hand, at the primary care units, even if we admit that the professionals provide adequate assistance, we would expect less complex care. Despite the similarity verified among the prescriptions, what stands out is the non-compliance with the official protocol. In other countries, authors have also shown the healthcare professionals' lack of compliance with the therapeutic guidelines contained in guides for the treatment of malaria, both for pregnant women and for the population in general[18-21].

We observed that in the centers, more prescriptions were written for two or more antimalarials compared to the primary care units. It would be plausible to suppose, in this case, that pregnant women with more severe conditions – therefore, associated with *P. falciparum*[17] – would be attending the centers. However, no significant differences were found in the proportions of diagnoses for *P. vivax* and *P. falciparum* between the reference centers and the primary care units. Alternatively, it is possible to admit that the professionals who work in reference units feel more prepared to prescribe combinations of antimalarials in pregnancy.

Chloroquine, artemether-lumefantrine and quinine sulphate were identified as antimalarials that could be involved in occurrences of adverse events. Kuemmerle and collaborators[22] analyzed a database of adverse reactions of antimalarials containing more than 21,000 records from 64 countries – including Brazil – and covering a period of 40 years of observation. It was shown that events involving chloroquine and quinine sulphate were among the majority, but that there were also occurrences with artemisinin derivatives, like artemether-lumefantrine, which, although in lower number, were considered potentially severe.

Some reflections are important. Quinine sulphate and chloroquine are considered reasonably safe medications in pregnancy, concerning the embryo or fetus[5-7]. However, the prevalence of unpleasant effects, like vomiting and headaches, even though they are not necessarily severe and do not jeopardize pregnancy, can prevent adherence. Artemisinin derivatives were introduced in the protocol of the World Health Organization only in 2001, and the monitoring of their use is still recommended[9]. These findings strengthen, therefore, the importance of the continuous monitoring of the treatment in pregnant women, as data about the pharmacokinetics, safety and efficacy of the antimalarials used in pregnancy are poorly documented[8].

Information on the magnitude of malaria in pregnant women or about treatment difficulties is scarce[23] and this study is, as far as we know, the first in Brazil to approach the specific characteristics of prescriptions of antimalarials for this group. Although the source of data does not derive from a representative sample of all the services that provide care for malaria, we believe that it is possible to generalize the results for high-risk cities located in the Amazon Region. The results showed flaws in the prescription of antimalarials for pregnant women, especially concerning compliance with the official protocol. As the course of pregnancy during an episode of malaria seems not to depend on age, parity or the background of the disease[23], it is important

that the provision of care is in accordance with what is established in official therapeutic guides for all pregnant women, especially as it is a group that needs careful attention, either because of the possibilities to affect the binomial mother-conceptus, or because of the scarcity of therapeutic measures involving medication targeted at them. In this sense, efforts must be made to improve the quality of the care offered to pregnant women, and intensive measures directed at the training of professionals who assist these patients are needed.

This study has some limitations. It is a descriptive study; therefore, it is not possible to establish causality relations. For this reason, the adverse events reported in the researched medical files should be interpreted with caution, and that is why they were treated as "possible" and not as proved. Another fact related to the study design, and which should be considered in the interpretation of the results, is the possibility of information bias. It is known that research conducted through the investigation of medical files is subject to this bias, due to the possibility of poor quality of the records. On the other hand, it is important to emphasize that one of the criteria to include cities in the study was the existence of a prescription or written guidance about the treatment. In addition, the SIVEP-Malária database was consulted. Both procedures contributed to minimize the information bias in this investigation.

We expect that the results of the present study can contribute to the proposal of recommendations for the policy to combat malaria in Brazil and for prenatal care in the country. Furthermore, we expect that the evaluation methodology that was used here can be employed in the monitoring of the treatment, during pregnancy, of the other focal endemics in which the rationale to combat them is based on early diagnosis and treatment.

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