



Malaria Complications in the Third Trimester of Pregnancy in Cotonou

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Abstract

Background: Malaria in pregnancy is a major public health problem that poses significant risks to mothers and their babies. The aim of this work was to study the maternal fetal and neonatal prognosis of malaria in pregnant women at the CNHU-HKM, the CHU-MEL and the SAINT LUC hospital in Cotonou (Benin).

Methods: This is an observational case-control study with a data collection period from July 1, 2018 to December 31, 2018. The study covered all pregnant women with a minimum gestational age of 28 weeks of amenorrhea recorded during the study period at the three hospitals. Data were collected on sociodemographic characteristics, obstetric history, pregnancy characteristics, and fetal and newborn characteristics.

Results: Anemia was observed in 81 (87.1%) cases and 44 controls (53%). Thrombocytopenia was observed in 37% of cases and 1.4% of controls. Intrauterine growth restriction was observed in 90.9% of cases newborns and 100% of controls. The prevalence of low birth weight was 35.2% in cases newborns compared to 7.5% in controls newborns. Thirteen out of 88 cases newborns (14.8%) were hypotrophic compared to 3.2% of controls newborns. Pallor and/or anemia were found in 12.5% of cases newborns versus 1.1% of controls newborns. The incidence of neonatal death was 4.5% in cases newborns versus 1.1% in controls newborns. A significant association was observed between malaria in the third trimester of pregnancy and parity ($p=0.001$), absence of antenatal consultation ($p=0.016$), non-regular use of insecticide-treated nets ($p=0.028$), anemia ($p<0.028$), thrombocytopenia ($p=0.001$), prematurity ($p<0.001$), low birth weight ($p<0.001$), hypotrophy ($p=0.006$), neonatal jaundice ($p<0.001$), and pallor ($p=0.002$).

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Conclusion: At the end of our study, we can say that maternal and perinatal morbidity associated with malaria in the third trimester of pregnancy is multiple. The results of this study can be used to guide maternal and child health promotion programs in Benin.

Introduction

Malaria is an erythrocyte infection caused by a hematozoan of the genus *Plasmodium* transmitted by a female mosquito of the genus *Anopheles* [1]. According to the latest World Malaria Report (2018), there were 219 million cases of malaria in 87 countries in 2017 [2]. In the same year, 435,000 malaria deaths were reported [2]. An analysis of the geographical distribution of malaria morbidity and mortality reveals that Africa bears a disproportionate share of the global malaria burden. In 2017, 92% of malaria cases and 93% of malaria deaths occurred in this region [2]. Approximately 80% of the malaria burden was concentrated in about 15 countries, all in sub-Saharan Africa. *Plasmodium falciparum* is the most prevalent malaria parasite in the African region of the World Health Organization (WHO). It was responsible for 99.7% of the estimated malaria cases in 2017 [2]. WHO estimates that nearly half of the world's population is exposed to malaria, with an increased risk for pregnant women and children under five years of age [2].

Every year, nearly 50 million pregnancies are recorded in malaria-endemic areas, putting these women at risk of contracting malaria [3]. Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, the fetus, and the newborn. Symptoms and complications of malaria during pregnancy vary according to the intensity and transmission of malaria in a given geographical area, as well as the individual level of acquired immunity [4]. In areas of high transmission such as Benin, where levels of acquired immunity tend to be high, *Plasmodium falciparum* infection is usually asymptomatic during pregnancy. However, the parasites may be present in the placenta and contribute to maternal anemia even in the absence of proven peripheral parasitemia. Maternal anemia, such as placental parasitemia, may be responsible for low birth weight, an important factor in infant mortality [5].

Because of the consequences for the mother, the fetus and then the newborn, malaria in general and gestational malaria in particular remain a public health priority in Benin. It has thus been the subject of several studies that have described the epidemiology and the clinic of this disease. The present study is part of this perspective and aims at studying the maternal and perinatal prognosis of malaria in the third trimester of pregnancy in pregnant women in Cotonou.

Methods

Setting and type of study

This was an observational case-control study with a data collection period from July 1, 2018 to December 31, 2018 (six months). It involved three health facilities namely the Centre National Hospitalier Universitaire - Hubert Koutoukou Maga (notably the University Clinic of Gynecology and Obstetrics and the Neonatology Unit of the Pediatrics and Medical Genetics Clinic), the Centre Hospitalier Universitaire de la Mère et de l'Enfant Lagune (notably the Neonatology Unit of the Pediatrics Department) and Hôpital Saint Luc (notably the Neonatology and Maternity Department) in Cotonou.

Study population

The study population consisted of pregnant women residing in Cotonou in 2019. Included were gestates with a minimum gestational age of 28 weeks of amenorrhea admitted during the study period in one of the three health facilities concerned and who did not have co-morbidities (hypertension, diabetes, sickle cell disease, HIV infection). Women who had multiple pregnancies and who eventually gave birth in health facilities other than those included in the study were excluded.

Definition of cases and controls

A case was considered to be any pregnant woman who met the selection criteria and contracted malaria (confirmed by examination of thick blood film or positive parasite density) in the third trimester of pregnancy. A control was any pregnant woman who met the selection criteria, did not contract malaria (confirmed by examination of thick blood film or negative parasite density) in the third trimester of pregnancy and was admitted to the same health facility as the case during the same period.

Sampling

An exhaustive recruitment of all gestates meeting the selection criteria to be cases was carried out. For one identified case, a control was selected. No matches were made.

Study variables

The dependent variable was the result of the malaria status. This variable was dichotomized into two modalities: 1 = Yes, if the examination of thick blood film or parasite density result was positive (Case) and 0 = No, otherwise (Control). The independent variables consisted of sociodemographic characteristics (age, education, marital status, occupation, ethnicity, place of residence), obstetrical history (Gravidity, parity, history of miscarriage), pregnancy history (term of 1st Antenatal Consultation (ANC), number of ANC, Intermittent Preventive Treatment (IPT), dose of IPT, regular use of mosquito net, iron and folic acid supplementation), clinical information (mode of admission, signs on physical examination, presence of fetal heart sounds), results of paraclinical examinations (biological diagnosis of malaria, presence and severity of anemia, presence of thrombocytopenia, the performance of an ultrasound in the third trimester, presence of Intrauterine Growth Restriction (IUGR), condition of the fetus when malaria was diagnosed during pregnancy), the outcome of delivery (term of pregnancy, Premature Rupture of Membranes (PROM) before or at the beginning of labor, route of delivery, Postpartum Hemorrhage (PPH), health status of the newborn (neonatal resuscitation, birth weight, presence of hypotrophy, temperature, presence of archaic reflexes, presence of neonatal jaundice, presence of pallor or anemia, neonatal death).

Data collection

The data was gathered using a questionnaire previously tested on ten pregnant women not included in the study. After adjusting the questionnaire, the women included in the study were contacted and interviewed individually. From emergency room admission records, intensive care and hospitalization records, and maternal medical records, the diagnosis of malaria in the third trimester of pregnancy was established. Additional data on delivery, fetus and newborns were collected from maternal and neonatal records.

Data processing and analysis

The collected data was entered into Epi Data 3.1 software and analyzed in STATA 11.0. After auditing the database, the variables were described as follows the relative numbers and frequencies of their modalities. The associations between the dependent variable and each of the independent variables were assessed using Pearson's Chi² or Fisher exact tests. The significance threshold was set at $p < 5\%$. The results were presented in prose, tables and graphs.

Ethical considerations

Administrative authorizations were obtained prior to data collection. Ethical standards for research were taken into account. Targets were provided with a detailed briefing note. The data collected were anonymous and confidential. They were collected individually after obtaining the free, written, and informed consent of each respondent.

Limitations of the study

We can point out some limitations to this study. Due to limited resources, our choice to take for one case only one control has limited the study's statistical power. As the data collection was carried out using a questionnaire filled in with the information declared by the pregnant women, there is a possibility of information bias. Indeed, we have noted a difficulty in some women, especially in those referred, to know the quality of their follow-up (anti-malarial prophylaxis iron and folic acid supplementation). Some women were dubious about their gestations and others were reluctant to give the number of miscarriages.

Results

Description of the study population

A total of 186 pregnant women (93 cases and 93 controls) were included in the study.

Sociodemographic characteristics

Among the cases, pregnant women aged 25 to 30 years (38.7%) were the most represented. In controls, women aged 20 to 25 years were the most numerous (32.3%). The majority of cases (38.7%) and controls (45.2%) had a higher level of education. The majority of pregnant women surveyed (90.3% in cases and 82.8% in controls) were married or in a couple. Private sector employees (29.0% of cases and controls) and salespersons (23.7% of cases and 28.0% of controls) were predominant. The majority of pregnant women resided in Cotonou (65.6% of cases and 67.7% of controls) and were of Fon ethnicity (41.9% of cases and 59.1% of controls). Table 1 presents these characteristics in detail.

Obstetrical history and pregnancy characteristics

Paucigravidae (38.7% in cases and controls) and Primigravidae (35.5% in cases and 26.9% in controls) accounted for the majority of patients. The nulliparous and primiparous were also the most represented in both cases and controls. A history of miscarriage was observed in 22.6% of cases and 25.8% of controls. The great number of pregnant women (44.1 in cases and 58.1% in controls) had their first ANC in the second trimester of pregnancy. We also note that 73.1% of cases and 87.1% of controls had more than 4 ANCs before delivery. The majority of pregnant women (76.3% of cases and 97.8% of controls)

had undergone chemo-prevention against malaria. However, only 11.3% had received three doses of IPT. In contrast, in the controls, nearly half of the pregnant women who received chemotherapy received three doses of IPT. Both cases (60.2%) and controls (75.3%) regularly slept under an insecticide-treated net. Iron and folic acid supplementation was carried out in the majority of pregnant women (95.7% of cases and 96.8% of controls). Among the respondents, 59.1% of cases and 74.2% of controls had had an ultrasound scan in the third trimester. Pregnancies were most often at term (59.1% of cases and 84.9% of controls) and deliveries were most frequently performed vaginally (60.2% of cases and 77.4% of controls). Premature rupture of the membranes was recorded in 20.4% of cases and 16.1% of controls. The table 2 presents these characteristics in detail.

Table 1: Sociodemographic characteristics of pregnant women in Cotonou.

Variables	Controls (n = 93)		Cases (n = 93)	
	n	%	n	%
Age in years				
15 à 20	5	5,4	7	7,5
20 à 25	30	32,3	24	25,8
25 à 30	24	25,8	36	38,7
30 à 35	19	20,4	15	16,1
≥35	15	16,1	11	11,9
Level of education				
Not attending school	19	20,4	25	26,9
Primary	14	15,1	14	15,1
Secondary	18	19,4	18	19,4
Superior	42	45,2	36	38,7
Marital status				
Singles	16	17,2	9	9,7
Married/couple	77	82,8	84	90,3
Profession				
Civil servant / private employee	27	29,0	27	29,0
Seller/ trader	26	28,0	22	23,7
Student	14	15,1	10	10,8
Dressing table	9	9,7	9	9,7
Seamstress	7	7,5	11	11,8
Housewife	4	4,3	5	5,4
Others	6	6,5	9	9,7
Place of residence				
Cotonou	63	67,7	61	65,6
Outside Cotonou	30	32,3	32	34,4
Ethnicity				
Fon	55	59,1	39	41,9
Goun	15	16,1	16	17,2
Yoruba	9	9,7	9	9,7
Mina	7	7,5	7	7,5
Others	7	7,5	22	23,7

Table 2: Obstetric history/characteristics of pregnancy of pregnant women in Cotonou and associations with malaria in the 3rd trimester of pregnancy.

Variables	Controls (n = 93)		Cases (n = 93)		p-value
	n	%	n	%	
Gravidity					
Primigravidae	25	26,9	33	35,5	0,357
Paucigravidae	36	38,7	36	38,7	
Multigravidae	23	24,7	20	21,5	
Grand multigravidae	9	9,7	4	4,3	
Parity					
Nulliparous	36	38,7	39	41,9	0,001
Primiparous	11	11,8	32	34,4	
Pauciparous	34	36,6	15	16,1	
Multiparous	9	9,7	6	6,5	
Grand multipara	3	3,2	1	1,1	
History of miscarriage					
No	69	74,2	72	77,4	0,608
Yes	24	25,8	21	22,6	-
Date of first ANC					
1st trimester	30	32,3	36	38,7	0,016
2nd trimester	54	58,1	41	44,1	
3rd trimester	9	9,7	8	8,6	
None	0	0,0	8	8,6	
Number of ANCs					
0	0	0,0	8	8,6	0,016
1	0	0,0	1	1,1	
2	4	4,3	9	9,7	
3	8	8,6	7	7,5	
≥4	81	87,1	68	73,1	
Taking IPT					
No	2	2,2	22	23,7	<0,001
Yes	91	97,8	71	76,3	
IPT Dose					
1	12	12,9	18	19,4	<0,001
2	34	36,6	45	48,4	
3	45	48,4	8	8,6	
Regular use of mosquito net					
No	23	24,7	37	39,8	0,028
Yes	70	75,3	56	60,2	
Iron and folic acid supplementation					
No	3	3,2	4	4,3	0,700
Yes	90	96,8	89	95,7	

Presence of anemia					
No	39	41,9	12	12,9	<0,001
Yes	44	47,3	81	87,1	
Type of anemia					
Moderated	43	46,2	65	69,9	0,006
Severe	1	1,1	16	17,2	
Thrombocytopenia					
No	70	75,3	46	49,5	0,001
Yes	1	1,1	27	29,0	
Ultrasound of the third trimester					
No	24	25,8	38	40,9	0,029
Yes	69	74,2	55	59,1	
Childbirth					
At term	79	84,9	55	59,1	<0,001
Pre-term	12	12,9	36	38,7	
Post-term	2	2,2	2	2,2	
Route of delivery					
Bass	72	77,4	56	60,2	0,011
Caesarean section	21	22,6	37	39,8	
PROM					
No	78	83,9	74	79,6	0,448
Yes	15	16,1	19	20,4	

Maternal morbidity

Among the cases, 25 (26.9%) pregnant women had severe malaria compared to 68 (73.1%) pregnant women who had uncomplicated malaria. Anaemia was observed in 81 cases (87.1%) and 44 controls (53%). Severe anemia was more present in cases (19.8%) than in controls (2.3%). The same was true for thrombocytopenia (37% in cases and 1.4% in controls). Table 2 presents this information in detail.

Fetal and newborn health status

The majority of fetuses in both groups were alive when malaria was diagnosed in the pregnant woman (94.6% in cases and 100% in controls). Intrauterine growth restriction was observed in 90.9% of case fetuses. In contrast, Intrauterine Growth Retardation (IUGR) was recorded in all control fetuses. The frequency of neonatal resuscitation was 20.5% in the newborns of the cases compared to 9.7% in the controls. The frequency of low birth weight was 35.2% in cases newborns versus 7.5% in controls. Thirteen newborns out of 88 cases (14.8%) were hypotrophic compared to 3.2% of controls. Pallor and/or anemia were found in 12.5% of cases newborns compared to 1.1% of control newborns. The prevalence of neonatal death was 4.5% in the newborns of cases versus 1.1% in the controls. Table 3 presents these characteristics in detail.

Factors associated with malaria in third trimester

There is a significant relationship between parity and malaria in pregnancy (p=0.001). Malaria prevalences during pregnancy are highest in nulliparous (52%) and primiparous (74.4%) women. We note a significant association between positive parasitaemia and absence of ANC (p=0.016). Non-regular use

of insecticide-treated nets significantly influenced the onset of malaria in pregnant women in the third trimester of pregnancy ($p=0.028$). Malaria infection significantly increased the occurrence of severe anemia ($p=0.006$) and thrombocytopenia ($p=0.001$) in pregnant women. There was a significant association between IUGR and thick drop positivity ($p=0.015$). There was a statistically significant relationship between prematurity ($p<0.001$), birth weight ($p<0.001$), neonatal jaundice ($p<0.001$), pallor ($p=0.002$) of the newborn and malaria in the third trimester of pregnancy.

Table 3: Characteristics of the fetus and newborn in Cotonou and associations with malaria in the 3rd trimester of pregnancy.

Variables	Controls ($n = 93$)		Cases ($n = 93$)		p-value
	n	%	n	%	
PPH					
No	91	97,8	88	94,6	0,444
Yes	2	2,2	5	5,4	-
IUGR					
No	69	74,2	50	53,8	0,015
Yes	0	0,0	5	5,4	
Neonatal resuscitation					
No	84	90,3	70	75,3	0,059
Yes	9	9,7	18	19,4	
Birth weight					
$\geq 2,500$ grams	86	92,5	57	61,3	<0,001
$< 2,500$ grams	7	7,5	31	33,3	
Hypotrophy					
No	90	96,8	75	80,6	0,006
Yes	3	3,2	13	14,0	
Temperature					
Normal	91	97,8	80	86,0	0,102
Hyperthermia	2	2,2	6	6,5	
Hypothermia	0	0,0	2	2,2	
Archaic reflexes					
Normals	90	96,8	78	83,9	0,034
Abnormals	3	3,2	10	10,8	
Neonatal jaundice					
No	86	92,5	60	64,5	<0,001
Yes	7	7,5	28	30,1	
Pallor/anemia					
No	92	98,9	77	82,8	0,002
Yes	1	1,1	11	11,8	
Neonatal death					
No	92	98,9	84	90,3	0,201
Yes	1	1,1	4	4,3	

Discussion

The general objective of this study was to study the maternal and perinatal prognosis of malaria in pregnant women at the CNHU-HKM, CHU-MEL and Saint Luc Hospital in Cotonou.

Sociodemographic characteristics

Among cases and controls, the age range of 20-30 years was the most represented. In other studies with the same target, the mean age was 23.2 ± 5.2 years [6] and the median age was 26 years with an interquartile range of 25 and 30 years [7]; indicating a young age among pregnant women in developing countries. Pregnant women were mainly civil servants or private sector employees, shop assistants and artisans (hairdressers and seamstresses). These findings reflect a varied socioeconomic level among the patients. In the present study, as in the literature, paucigravidae and primigravidae were the predominant patients [6]. These figures are justified by the relatively young age of the patients.

Prenatal consultations and IPT

The number of prenatal visits made by pregnant women was over four in both groups. Only a minority (38.7% in cases and 30% in controls) had made their first prenatal consultation in the first trimester. In the cases, 8.6% waited until the third trimester to start prenatal consultations and as many did not do so at all. Our figures seem to indicate that there is a growing awareness among women to monitor their pregnancy but that this is not yet general.

The majority of the respondents in our sample had been introduced to malaria chemoprevention during pregnancy. Sulfadoxine-pyrimethamine was the only molecule used. We note that no woman exceeded 3 doses of IPT although some women started treatment in the second trimester. This is related to the lack of understanding of the recommendations for the administration of IPT doses. Indeed, WHO has not stipulated a specific number of doses because experience has shown that once a number of doses is indicated, it becomes a programmatic goal for many countries [8]. It is only recommended that IPT be administered at each antenatal visit at least one month apart until delivery, except in the first trimester [8]. The number of doses of IPT can safely exceed 3 if the recommendations are followed. The vast majority of patients, including those followed in antenatal visits, would therefore have inadequate malaria chemoprevention in the study centers. Huynh et al. in Benin in 2011 found that two-thirds of maternal infections with symptomatic malaria occur after the third dose of IPT [9]. This confirms the need to review the protocol of care for IPT in health facilities in Benin.

Use of insecticide-treated nets

The majority of pregnant women reported sleeping regularly under a mosquito net during pregnancy (60.2% of cases and 75.3% of controls). These results are similar to those of the 2017-2018 Demographic Health Survey, which shows that 74% of pregnant women use an insecticide-treated net [10]. Efforts remain to be made to ensure widespread use, which is a guarantee of effective mechanical malaria prevention.

Maternal morbidity

The majority of patients (73.1%) had uncomplicated malaria compared to 26.9% who had severe malaria. This proportion of severe malaria is significantly higher than that found in the

general adult population, which shows less than 15% of severe forms among people with malaria [11,12]. The incidence of anemia was significantly higher among cases (87.1%) than among controls (53%). This anemic prevalence is similar to that documented in 2017 by Corrêa et al. in India (92.4%) [7] and is a reminder of the correlation between malaria and anemia.

Thrombocytopenia is significantly more common in pregnant women who had malaria in the third trimester of pregnancy ($p < 0.05$). The same association was found in 2008 by Mbanya et al. in Cameroon [13].

Fetal and newborn health status

The majority of fetuses (94.6%) in the present study were alive at the time of malaria diagnosis in cases as opposed to controls where they were all alive. Although we did not observe a significant relationship between intrauterine fetal death and malaria during pregnancy, another study also found that there were more fetal intrauterine deaths in women who had malaria during pregnancy [14].

There was also no significant relationship between early neonatal death and malaria in pregnancy in the present study ($p > 0.05$), unlike a study conducted by Bardaji et al. in Mozambique in 2010 [15].

In the present study, IUGR, prematurity and hypotrophy were significantly associated with malaria in the third trimester gestates ($p < 0.05$). The same associations were observed for IUGR in the studies of Rijken et al. in 2012 [16], and Schmiegelow et al. in 2013 [17], for prematurity in the studies of Van den Broek et al. in 2014 [18] and Dombrowski et al. in 2018 [19] and for hypotrophy in the studies of Rijken et al. in 2014 [16] and Moore et al. in 2017 [14]. These results reflect the consequence of placental infection during malaria in pregnancy.

Conclusion

At the end of our study, it appears that maternal and perinatal morbidity related to malaria in the third trimester of pregnancy is multiple. Malaria in the pregnant woman was associated with anemia and thrombocytopenia and with prematurity, hypotrophy and IUGR. These findings may be related to the inadequate implementation of IPT in gestating women as observed in this study. The results of this study will help strengthen the monitoring of pregnant women in health facilities and strengthen maternal and child health promotion programs in Benin.

Conflict of interest

No financial benefit will be obtained from this manuscript

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