Pregnancy Complications in Venezuelan Women With Malaria

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Research

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Abstract

Background

Pregnant women are particularly vulnerable to malaria infections, increasing the risk of maternal-foetal complications, mainly in areas of high endemicity. However, few studies of malaria in pregnancy (MiP) have been carried out in Latin America, a region with low endemicity and transmission of both, *Plasmodium falciparum* and *P. vivax*. Despite the high malaria burden in Venezuela in the last years, no recent studies of MiP have been conducted. Hence, epidemiological and clinical characteristics of pregnant women with malaria in Venezuela are described herein.

Methods

A retrospective study in pregnant women attending to the “Ruíz y Páez” University Hospital Complex, Bolívar state, Venezuela between February and October, 2019 was carried out. Epidemiological, clinical, and laboratory information was analysed.

Results

Thirty-seven out of 52 pregnant women analysed, were infected with *P. vivax*. Age ranged between 15 and 39 years, and adolescent pregnancies were common. Malaria infection was diagnosed mainly during the third trimester of pregnancy (63.4%). The distribution of symptoms and signs as well as clinical laboratory values was similar among *Plasmodium* spp. Although uncomplicated malaria was most frequent, 30% (13/52) had severe anaemia. A high proportion of studied women (44%) presented at least one complication during the pregnancy or delivery. Spontaneous abortion was recorded in four women, and three foetal deaths were observed. Six women had preterm delivery without any further complication.

Conclusions

A high prevalence of maternal and foetal complications was found in the studied population, highlighting the requirement for a careful medical follow up during the prenatal check-ups, aimed to reduce the negative impact of malaria in the new-born and mother.

Background

Malaria continues being the leading cause of morbidity and mortality in many developing countries. It is estimated that 229 million cases and 409,000 deaths occurred worldwide due to malaria in 2019 [1]. Pregnant women are particularly vulnerable to malaria infections, increasing the risk of maternal-foetal complications, mainly in high-endemicity areas [2]. Approximately 125 million women living in malaria-endemic areas become pregnant each year, and around three million of these are from the Region of the Americas [3].

The susceptibility to malaria in pregnancy (MiP) has long been recognized. Determining factors are the malaria endemicity in the region and gravidity. In high-transmission areas, primigravidae are at greater risk of infection, whereas the gravidity effect is less marked in low-transmission areas [4] and absent in areas with epidemic malaria [5]. Maternal age is also an independent risk factor for MiP, with higher risk at younger ages [6, 7]. Due to the acquisition of immunity in the early stages of life in hyperendemic and stable transmission areas, many of the infections during pregnancy are asymptomatic [4]. In contrast, in the areas of low endemicity and unstable transmission, clinical manifestations in pregnancy are frequent with a high probability of malaria complications [8].

In malaria-endemic regions of Latin America, a high prevalence of maternal-foetal complications has been reported in pregnant women infected with malaria including severe maternal anaemia and hepatic dysfunction [9-13], prematurity, low birth weight, and congenital malaria [14-18]. In the last decade, Venezuela has experienced a political, social, and economic crisis that has impacted the epidemiology of infectious diseases [19]. This has led to a drastic increase in the number of malaria cases, accounting for 55% of the reported cases and 70% of malaria deaths in the region in 2019 [1]. Three states, Bolívar, Amazonas, and Sucre, reported 90% of malaria cases in the country, with an increase of 55% in MiP cases [20]. Nevertheless, there is limited clinical and epidemiological information as well as the impact of MiP in the country. A retrospective study was conducted to describe the clinical and epidemiological characteristics of pregnant women with malaria attending at the “Ruíz y Páez” University Hospital Complex, in Ciudad Bolívar, Bolívar state.

Methods

Study area

The study was carried out in Ciudad Bolívar, located in the Bolívar state, southern Venezuela, at 54 masl, covering an area of 209.5 km^2, and an average temperature of 27.7 °C. Ciudad Bolívar has a population of approximately 567,000 inhabitants. In Bolívar state, 70-80% of malaria cases are caused by *P. vivax*, and 20-30% are due to *P. falciparum* [19]. Recently, it has been reported that municipalities in Bolívar State have a heterogeneous annual parasitic incidence (API), with some hotspots in the southeast part [21]. For epidemiological week N° 52 of 2016, the API was 101.7 per 1,000 inhabitants in this state [22]. The main hospital in the region is the “Ruíz y Páez” University Hospital Complex, attending patients being referred from other hospitals.

Study design and participants

A retrospective study was conducted in all pregnant women with malaria, who consulted at the “Ruíz y Páez” University Hospital Complex between February and October, 2019. Malaria diagnosis was performed by microscopy using thick and thin blood smears. A clinician resident from the Gynaecology and Obstetrics Department performed the standard clinical evaluation, and a detailed physical

examination on all women included in the study. A peripheral blood sample was taken for clinical laboratory analysis according to hospital availability. Women were classified as uncomplicated or severe malaria cases according to the WHO [23] and “Ministerio del Poder Popular para la Salud” (MPPS) of Venezuela [24] criteria, regardless of the malaria parasite species. The latter criteria are more conservative in some definitions based on previous evidence: thrombocytopenia (< 100,000 platelets/μL), levels of renal and hepatic enzymes, blood pH and HCO_3 levels, hydroelectrolytic disorders, and neutrophilic leukocytosis. Pregnant women with uncomplicated and complicated malaria were treated before hospital discharge, according to the recommendation of the health authorities of the Bolivarian Republic of Venezuela [24]. Briefly, women infected with *P. falciparum* received quinine (orally, 10 mg/kg thrice a day over seven days) and clindamycin (orally, 10 mg/kg twice a day over seven days) or artemether plus lumefantrine (orally, twice a day over three days), whereas those infected with *P. vivax* were treated only with chloroquine (orally, 25 mg/kg provided in three days). Severe anaemia cases were treated at the hospital with blood transfusion. Intermittent preventive treatment (IPTp) was not provided because it is not included in the Venezuelan national policy. Adolescent pregnancy was defined as a pregnancy in a woman aged 10-19 years [25]. The gestational age was measured calculating the days since the beginning of the last menstrual period.

Statistical analysis

Data were analysed using IBM SPSS Statistics v.25.0 (IBM Corp.) and plotted with GraphPad Prism version 9.0 (GraphPad Software, San Diego, California, United States). Statistical distribution of the data was analyzed using Kolmogorov-Smirnov. Nominal variables were expressed using absolute and relative frequencies, whereas for quantitative variables measures of central tendency and dispersion were used. Fisher’s exact test was used to compare proportions. Mann-Whitney was used to compare two groups. One-way ANOVA using harmonic means followed by Tukey post-hoc analysis and Median tests were used to compare more-than-two groups. A p-value < 0.05 was considered statistically significant.

Results

Demographic and epidemiological characteristics

Data from fifty-two pregnant women with infection by *Plasmodium* spp. were analysed. Most of the women were infected with *P. vivax* (37; 71.1%) and only six (11.4%) with *P. falciparum*. Mixed infection, *P. vivax* and *P. falciparum*, was found in nine (17.3%) women (Table 1).

Most women were ≤ 25 years of age (71%; range 15-39 years) and adolescent pregnancies were common (17/52). Overall, infections were detected mainly during the third trimester of pregnancy (63.4%). From 27 women self-reporting previous lifetime malaria episodes, 22 were infected by *P. vivax*, and 24 women had the last episode in the previous year. A high proportion of the women are housewives (67.3%), and reached at least primary education, with only two having bachelor degrees (3.8%). Almost

half of the women (25/52) are single mother. An inadequate prenatal control number for the gestational age was found in 38.5% of patients. Most of the pregnant women (94.2%) came from the Bolívar state, mainly of Angostura del Orinoco (28.8%), Sifontes (23.1%), Cedeño (11.5%), and El Callao (9.6%) municipality, without significant differences in relation to *Plasmodium* species ($p = 0.23$, Fisher's exact test).

Clinical manifestations of MiP

Fever (96.1%), chills (51.9%), asthenia (48%), and headache (32.6%) were the most frequent symptoms. The distribution of symptoms and signs was similar among *Plasmodium* spp. (Fig. 1), except for headache, which was more frequent in women infected by *P. vivax* ($p = 0.02$). Diarrhoea, myalgia, and arthralgia were infrequent symptoms with less than 8% reporting those. The most frequent clinical signs at the time of physical examination were fever (86.5%) and pallor (28.8%), with no significant differences between parasite species.

Laboratory findings

Data for creatinine and urea evaluation were obtained only from 33 (63.5%) patients, glycaemia in 28 (53.8%), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in 12 (23.1%). Haemoglobin (Hb) levels were analysed in all women during the malaria episode; the mean Hb level was 8.7 g/dL (SD 2.3). Anaemia (Hb < 11 g/dL) was diagnosed in 85% (44/52) of women and 30% (13/52) had severe anaemia (Hb < 7.0 g/dL). Hb levels were significantly lower in mixed than in *P. vivax* infection ($p = 0.03$; Table 2). The median platelet count was 219,000/μL ± 61,000/μL, 14% (7/52) of women had moderate thrombocytopenia (50,000-150,000/μL), and severe thrombocytopenia was not recorded. No relevant alterations of liver or kidney function were found. There were no differences in the clinical laboratory levels ($p > 0.05$) according to *Plasmodium* spp. (Table 2).

Maternal and foetal complications according to the Plasmodium spp.

Fourteen out the 52 women (27%) were classified as severe malaria at the enrolment, most of them with *P. vivax* infection (11/14; $p = 0.73$; Fisher's exact test). Twelve women had severe anaemia (Hb < 7g/dL), one severe anaemia and somnolence, and one more with somnolence as a single criterion. A high proportion (23/52) of studied women presented at least one complication during the pregnancy or delivery (Fig. 2), mainly in those infected by *P. vivax* (18/23; $p = 0.37$). Seven out of those 23 women also had severe MiP.

Six women had oligohydramnios; one also presented placental insufficiency and other preterm delivery. Spontaneous abortion was recorded in four women, and three foetal deaths were observed, one also

reported uterine rupture and other preterm delivery. A case of pre-eclampsia and another of intrauterine growth restriction were also documented. Two women had urinary tract infections, and six women presented preterm delivery without any further complication. In nine women was not possible to know the pregnancy outcome, including two women with a history of oligohydramnios, one with pre-eclampsia, and another with severe anaemia at the enrolment.

The women with complications had a lower number of previous pregnancies (2 *vs*. 3; $p = 0.08$, Mann-Whitney test) and a higher number of weeks of gestation (37 *vs.* 29; $p = 0.38$, Mann-Whitney test) than those without any complication. Likewise, no significant differences were observed according to age, parity, previous malaria exposure, or time since the last malaria episode. Although 27 women reported previous malaria cases, it is important to notice that only one woman reported malaria in previous pregnancies.

Discussion

This study describes the clinical and epidemiological characteristics of pregnant women with malaria in Venezuela. Infection by *P. vivax* was the most frequent in this study in agreement with the malaria species distribution in the country [26] as well as with other studies in pregnant women in Venezuela [9, 27, 28] and Latin American [17, 29, 30]. Mixed infections were also frequent, similar to reported by Morao *et al*. [31]. As reported previously [10, 29, 31, 32], most of the women were young, with several of them being adolescents, reflecting the fertility rate reported for Venezuela, the highest in Latin America, with 85 births per 1,000 adolescents aged between 15-19 years old in 2018 [33]. Similar to reported in Bolívar state [9], most of the women are from Angostura del Orinoco and Sifontes municipality, which perhaps be related to the continuous migration of individuals from the community to gold mining areas, contributing to the malaria transmission [19, 21, 31].

The clinical manifestations were similar to those reported by other authors [29]. In contrast to findings in Colombia by Tobón *et al*. [29], in this study headache was more frequent in women with *P. vivax* compared to *P. falciparum*. This, together with the high frequency of fever, supports the practice of performing malaria diagnostic tests at prenatal check-ups, favouring timely diagnosis in highly endemic areas as has been suggested before [16, 34]. Indeed, early malaria diagnosis and treatment reduce maternal mortality [35]. Severe anaemia is responsible for around 50% of the complications of MiP in endemic areas with intense and stable transmission [31]. In this study, 84.6% of women presented Hb alterations that ranged from mild to severe, with severe anaemia as the most frequent malaria complication among all women (23%), in agreement with several studies [32, 36], but in contrast with results from Colombia, where mild-to-moderate anaemia and severe anaemia were observed in 68% and 2.9%, respectively [10].

The most important finding of this study is the high prevalence of maternal and foetal complications (44%), with preterm delivery, oligohydramnios, abortion, and foetal death as the most frequent complications. Almost all of them in women with malaria by *P. vivax,* an infection usually considered less

severe as compared to *P. falciparum* malaria. This is assumed to be related to the lack of placental sequestration in *P. vivax* infections and the parasite tropism for reticulocytes accounting for a milder form of anaemia [37]. Similar to a previous study carried out in Bolívar state [9], a higher proportion of abortions was registered in pregnant women infected with *P. vivax.* In this study, the prevalence of preterm delivery regardless other complications was higher than reported by other studies (18.6% *vs*. 7.5%- 8.5%) [38, 39]; another study in Colombia reported a higher rate of preterm delivery (70.8%), however, only included hospitalized pregnant women [29]. Anaemia has been associated with a higher proportion of preterm delivery [40], which could explain the high frequency of this complication in the studied population.

On the other hand, the number of women with oligohydramnios and intrauterine growth restriction was lower than documented by another study (40 and 80%, respectively) in Peru [41]. Herein, four spontaneous abortion and three foetal deaths were recorded in 55 studied women. This contrast with the mortality rate of 21.1 deaths per 1,000 live births reported in the country for 2016 [42]Although pregnant women have parasitaemia ten times higher than non-pregnant women, due to inadequate immune response [43], in areas of stable malaria transmission, women of childbearing age have acquired partial immunity, that protects them to some extent against acute clinical disease [44]. Whether the studied pregnant women have acquired humoral immunity or not, were beyond the scope of this study, but should be further explored.

Due mainly to logistical and financial constraints, this study has some limitations. First, the clinical and epidemiological characteristics of MiP are described only in a single diagnostic centre. Thus, additional studies are needed to investigate the impact of malaria on maternal-foetal health in different sentinel centres in the country. Second, complete paraclinical examinations were carried out only in a subset of the women. Finally, the presence of maternal-foetal complications is unknown for several women.

Conclusions

The understanding of its clinical and epidemiological characteristics together with the high prevalence of maternal and foetal complications, with an import effect in the new-born, supports the need for a careful medical follow up during the prenatal check-ups. Moreover, it constitutes important information for developing hospital care protocols in search of achieving a timely diagnosis and adequate follow-up of the patient and the new-born.

Abbreviations

Hb: haemoglobin; MiP: malaria in pregnancy; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Bioethics Committee of the “Ruíz y Páez” University Hospital Complex. The information was collected according to the Helsinki Convention and the Venezuelan regulations for this type of research.

Consent for publication

All authors have given their consent for publication.

Availability of data and materials

All data generated or analysed during this study are included within this article.

Competing interests

The authors declare no competing interests.

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Authors’ contributions

MR, EL, FSC-N, DCF-DeN, SK, and DAF-P conceived and designed the study. MR, EL, AFG, MC, LF, and NAC-Á collected clinical data. FSC-N, DCF-DeN, MVM, ML-P, and DAF-P analysed and interpreted the data. FSC-N, DCF-DeN, ML-P, and DAF-P wrote the manuscript. FSC-N, DCF-DeN, MVM, ML-P, and DAF-P critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

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Tables

Table 1. Socio-demographic characteristics according to *Plasmodium* spp.

Characteristics		Total, *n* = 52	*P. vivax*, *n* = 37	*P. falciparum*, *n* = 6	Mixed infection, *n* = 9	*p*-value[a]
		Median (IQR)				
Age (years)		22 (9)	20 (6)	29 (9)	25 (15)	0.168
Number of pregnancies		3 (2)	2 (2)	3.5 (0)	3 (1)	0.006[b]
Gestational age (weeks)		31 (18)	31 (16)	32 (19)	27 (10)	0.933
Number of controls		4 (4)	4 (5)	4 (6)	3 (4)	0.724
Previous malaria (number of episodes)[c]		2 (8)	2 (8)	3 (16)	2 (2)	0.951
		n (%)	*n* (%)	*n* (%)	*n* (%)	*p*-value[d]
Occupation	Housewife	35 (67.3)	27 (73.0)	3 (50.0)	5 (55.6)	0.400
	Merchant	6 (11.5)	3 (8.1)	1 (16.7)	2 (22.2)	0.273
	Mineworker	6 (11.5)	4 (10.8)	2 (33.3)	–	0.139

[a]*p*-value using medians test; [b]medians are significantly different only between *P. vivax* and *P. falciparum*; [c]number of previous episodes was available only for 27 women; [d]*p*-value using Fisher's exact test. IQR: interquartile range.

Table 2. Paraclinical findings in pregnant women with malaria

Laboratory parameters	*Plasmodium* spp.				*p*-value[a]
	Total, *n* = 52	*P. vivax*, *n* = 37	*P. falciparum*, *n* = 6	Mixed infection, *n* = 9	
	Mean (SD)				
Haemoglobin (g/dL) (*n* = 52)	8.7 (2.3)	9.3 (2.1)	7.3 (2.3)	7.3 (2.2)	0.013[b]
Haematocrit (%) (*n* = 52)	27.3 (7.1)	28.8 (6.7)	23.4 (7.1)	23.9 (7.5)	0.062
Platelets ($\times 10^3$/μL) (*n* = 51)	219 (61)	209 (57)	229 (67)	251 (67)	0.173
Glycemia (mg/dL) (*n* = 28)	79.2 (14.0)	81.2 (14.3)	82.2 (11.1)	70.8 (14.0)	0.263
Urea (mg/dL) (*n* = 33)	19.7 (8.5)	19.8 (9.5)	16.4 (6.2)	22.2 (5.4)	0.543
Creatinine (mg/dL) (*n* = 36)	0.7 (0.18)	0.7 (0.18)	0.64 (0.16)	0.73 (0.2)	0.668
	Median (IQR)				*p*-value[c]
Leukocytes ($\times 10^3$/μL) (*n* = 31)	9.0 (4.4)	9.4 (6.6)	6.6 (5.3)	9.00 (3.0)	0.475
AST (mg/dL) (*n* = 12)	32 (23.5)	32.0 (18.0)	–	32.5 (44.0)	1.000[c]
ALT (mg/dL) (*n* = 12)	18 (12.5)	17.0 (7.5)	–	25.5 (40.0)	0.222[c]
Total bilirubin (mg/dL) (*n* = 14)	1.13 (1.12)	1.30 (1.23)	–	0.88 (1.34)	0.592[c]

[a]*p*-value using One-way ANOVA test; [b]*Post-hoc* analysis (Tukey): significant difference only between *P. vivax* and mixed malaria ($p = 0.037$); [c]*p*-value using median test. SD: standard deviation, IQR: interquartile range, ALT: alanine aminotransferase, AST: aspartate aminotransferase.

Table 3. Paraclinical alterations in pregnant women with malaria

Laboratory parameters	*Plasmodium* spp.				*p*-value[a]
	Total, *n* = 52	*P. vivax*, *n* = 37	*P. falciparum*, *n* = 6	Mixed infection, *n* = 9	
Hb (*n* = 52)					0.044
Normal Hb (≥ 11 g/dL)	8 (15.4)	8 (21.6)	–	–	
Mild anaemia (9.1-10.9 g/dL)	17 (32.7)	13 (35.2)	2 (33.3)	2 (22.2)	
Moderate anaemia (7-9 g/dL)	14 (26.9)	11 (29.7)	0 (0)	3 (33.3)	
Severe anaemia (< 7 g/dL)	13 (25)	5 (13.5)	4 (66.7)	4 (44.5)	
Haematocrit (*n* = 52)					0.550
Not decreased (≥ 20%)	45 (86.5)	33 (89.2)	5 (83.3)	7 (77.8)	
Decreased (< 20%)	7 (13.5)	4 (10.8)	1 (16.7)	2 (22.2)	
Platelets (*n* = 51)					0.446
Normal (> 150,000/µL)	44 (86.3)	30 (83.3)	5 (83.3)	9 (100.0)	
Thrombocytopenia (50-150,000/µL)	7 (13.7)	6 (16.7)	1 (16.7)	–	
Creatinine (*n* = 36)					0.562
Normal (0.5-1.0 mg/dL)	34 (94.4)	23 (95.8)	6 (100.0)	5 (83.3)	
Mild (1.1-1.5 mg/dL)	2 (5.6)	1 (4.2)	–	1 (16.7)	

[a] *p*-value using Fisher's exact test. Creatinine reference range: 0.4 to 0.8 mg/dL; Urea reference range = 5.0 to 12.0 mg/dL. SD: standard deviation; IQR: interquartile range; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Figures

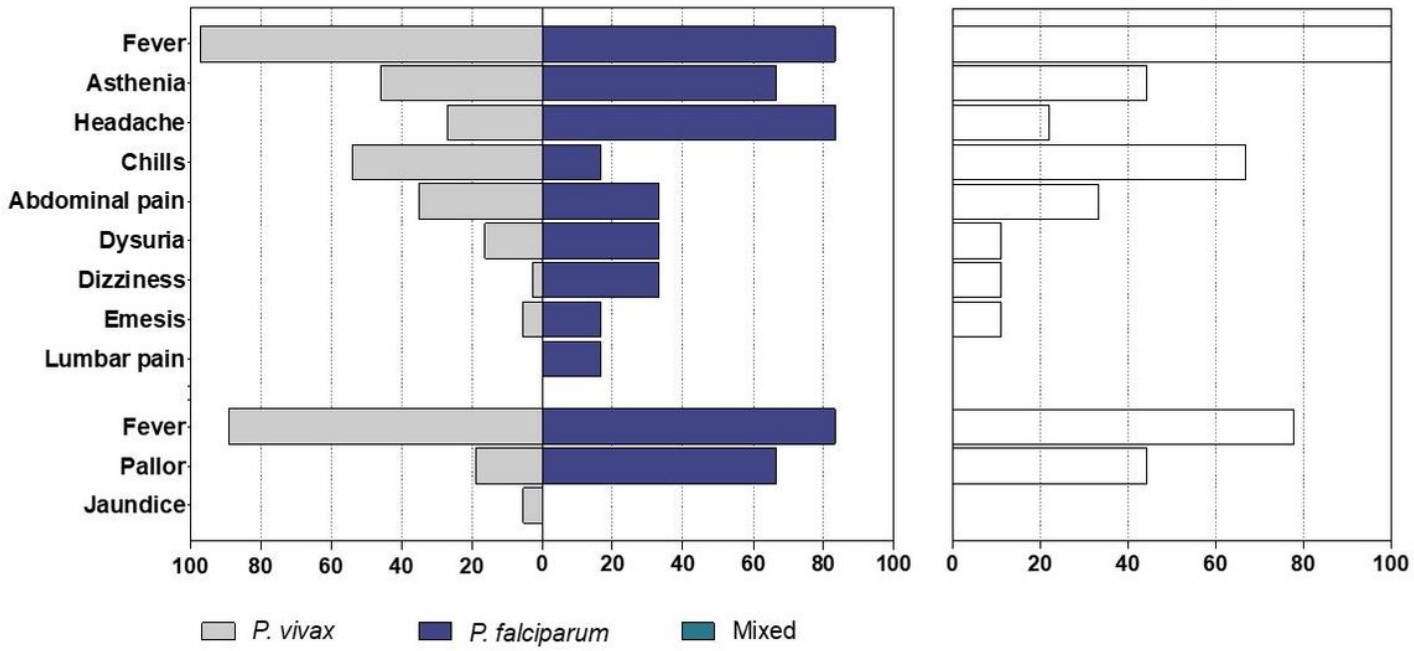

Figure 1

Symptoms and signs in pregnant women with malaria according to the Plasmodium spp. Most frequently reported symptoms and found signs are presented as percentages over the total of each parasite species. Proportions were compared with Fisher's exact test; $p > 0.05$, except for headache in P. vivax infections ($p = 0.02$).

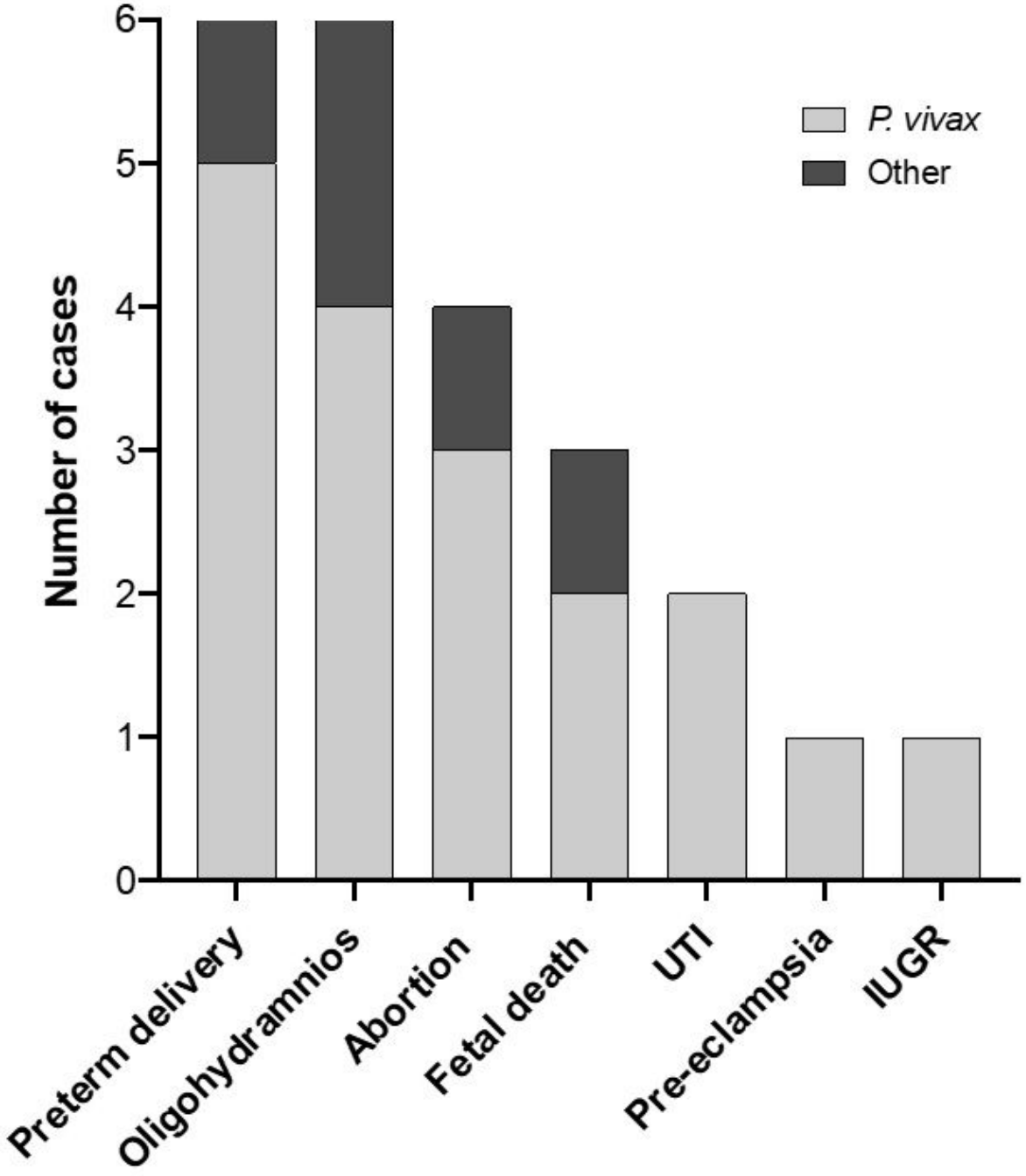

Figure 2

Maternal and foetal complications. Number of cases for each complication. For those having more than one complication, only the most important was included. Other, corresponds to cases in women with P. falciparum or mixed infection. IUGR: intrauterine growth restriction; UTI: urinary tract infections.