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Imported malaria in pregnancy in Europe: A systematic review of the literature of the last 25 years

Federica Guida Marascia [a,b], Claudia Colomba [a,c], Michelle Abbott [a,b], Andrea Gizzi [a,b], Antonio Anastasia [a,b], Luca Pipitò [a,b], Antonio Cascio [a,b,*]

[a] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G D'Alessandro", University of Palermo, Palermo, Italy
[b] Infectious and Tropical Disease Unit, Sicilian Regional Reference Center for the Fight against AIDS, AOU Policlinico "P. Giaccone", 90127, Palermo, Italy
[c] Division of Paediatric Infectious Disease, "G. Di Cristina" Hospital, ARNAS Civico Di Cristina Benfratelli, Palermo, Italy

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ABSTRACT

Background: Malaria during pregnancy is associated with a greater risk of complications for the mother and fetus. The aim of the study is to analyze the features of imported cases of malaria in pregnant women in Europe and evaluate which factors are associated with a non-favourable outcome.

Methods: A computerized search of the literature was performed combining the terms plasmod*, malaria, pregnan*, maternal, gravid, parturient, expectant, and congenital, from January 1997 to July 2023.

Results: 28 articles reporting 57 cases of malaria in pregnant women immigrant in non-endemic areas were included. The patients mainly came from Sub-Saharan Africa. There were 10 asymptomatic cases, while the predominant clinical syndrome among the symptomatic women was fever associated with anaemia. The median latency period from permanence in endemic areas and diagnosis in European countries was 180 days (IQR 15–730). Pregnancy outcomes were favourable in 35 cases (61 %): all term pregnancies, no low-birth-weight newborns. There were 4 abortions; 1 child was delivered pre-term; 7 babies were reported to have a low birth weight; 10 cases of congenital malaria were documented. *P. falciparum* was found with a higher frequency in women with a favourable outcome, while *P. vivax* was, in all cases, associated with a worse prognosis.

Conclusions: Diagnosis of malaria in pregnant woman in non-endemic countries may be challenging and a delay in diagnosis may lead to an adverse outcome. Screening for malaria should be performed in pregnant women from endemic areas, especially if they present anaemia or fever.

1. Introduction

Malaria in pregnancy is an important cause of maternal and fetal morbidity and is a potentially life-threatening infection [1,2]. In particular, non-immune pregnant women have an increased risk of both complications and a more severe course of the infection [3].

"Imported case of malaria infection" is a case acquired in a zone where malaria is endemic and diagnosed in a non-endemic area by microbiological criteria (i.e. peripheral blood smear, thick blood smear, positive antigen, or genomic amplification) [4]. Many people from endemic countries may have parasites in their blood without symptoms of malaria because they often had previous episodes of malaria, developing immunity protection during the time [4]. The presence of erythrocytic plasmodial stages in peripheral thick blood smears in a person without fever and other symptoms compatible with malaria is defined as asymptomatic plasmodial infection (API); it has been frequently reported in hyper-endemic regions, and it seems to be more common in pregnant women than in non-pregnant women or men [4,5]. According to the World Migration Report 2022, Europe is currently the largest destination for international migrants, with 87 million migrants (30.9 % of the international migrant population): in 2020, most African-born migrants living outside the region were residing in Europe (11 million) [6]. We can distinguish immigrants born in endemic areas that had returned to their country of origin to visit friends or relatives (VFR) from first-arrival immigrants (FAI); VFR is a risk group that represents an important percentage of the imported malaria cases described in most of the studies about this matter [4]. In some cases, a temporal link with a trip back to the malarial endemic country can suggest to the physician

* Corresponding author. Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G D'Alessandro", University of Palermo, Palermo, Italy
E-mail address: antonio.cascio03@unipa.it (A. Cascio).

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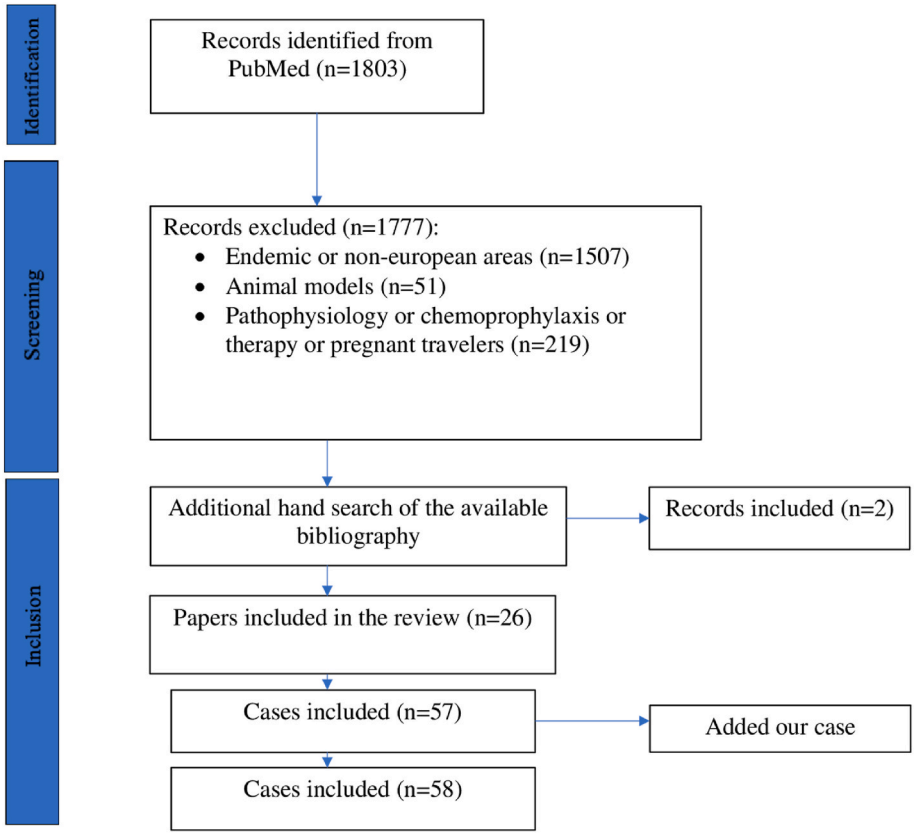

Fig. 1. Research of literature: identification of cases, screening, and inclusion.

malaria infection, especially in patients with suitable symptoms. Asymptomatic cases can represent a reservoir for malaria infection and, in pregnant women, a cause of congenital malaria. Clinical malaria episodes during pregnancy are associated with both a trend of increased infant mortality and a significantly increased incidence of malaria episodes during infancy [7]. In Europe, few studies have investigated the features of malaria infection in pregnant women [8–10]. The study aims to describe and analyze the features of malaria infection in pregnant women living in Europe and coming from endemic areas and evaluate which factors are associated with a favourable or non-favourable outcomes. We were motivated to address this topic after observing the case that is briefly described below.

2. Case report

A 22-year-old Nigerian woman in her 23rd week of pregnancy, with sickle cell trait (HbAS), blood group 0+, went to Emergency Department in September 2022 for sudden abdominal pain.

She had lived in Italy for five years during which she had never returned to Nigeria or even traveled to areas where malaria is endemic.

She never had a fever, and non-pathological findings were detected on physical examination.

Laboratory findings demonstrated severe anaemia (red blood cells 3.07×10^6/mm3, hemoglobin 5 g/dl), a white blood cell count of 5.640/mm3, platelets count of 163.000/mm3, C-reactive protein 11 mg/l and mildly elevated transaminases (AST/ALT 41/44 U/L). After excluding bleeding causes, we investigated alternative causes of anaemia, such as autoimmune causes and leishmaniasis, which turned out negative. Abdomen echography showed hepatosplenomegaly (longitudinal diameter of spleen 18.5 cm) with a homogeneous ultrasound structure. A gynecologic visit excluded fetal distress and ascertained regular growth. Although she didn't meet the temporal criteria for suspicion of malaria infection, we performed malaria diagnostic tests with thin and thick blood smears, rapid diagnostic tests (RDTs), and Polymerase chain reaction (PCR), which turned out positive for *Plasmodium falciparum*. Treatment with oral dihydroartemisinin-piperaquine (120 mg/960 mg once daily for three days) was initiated after the results. After the treatment, the microscopy turned negative. After the discharge, she underwent to gynecological follow-up, and the malarial diagnostic tests performed on the newborn were negative. The child was born healthy and did not show any problems up to a 6-month follow-up.

3. Methods

3.1. Systematic review

A computerized search was performed without language restriction using PubMed, combining the terms ((plasmod*[TITLE] OR malaria [TITLE]) AND (pregnan*[TITLE] OR maternal[TITLE] OR gravid [TITLE] OR parturient[TITLE] OR expectant[TITLE] OR congenital [TITLE])), from the January 1, 1997 to the July 31, 2023. Furthermore, all references listed were hand-searched for other relevant articles. An article was considered eligible for inclusion if it reported cases of pregnant women coming from endemic areas with malaria infection or API diagnosed in non-endemic European areas. Pregnant travelers were excluded. The following epidemiologic and clinical variables were considered: age, gestational age, being a first-arrival immigrant or visiting friends and relatives, clinical presentation, how the diagnosis was made, *Plasmodium* spp, laboratory findings, treatment, and outcome. We define non-favourable outcomes as one of the following situations: low birth weight (LBW), miscarriage, fetal death, fetal distress, congenital malaria, and premature delivery. A favourable outcome is represented by term pregnancy with a healthy fetus.

The selected articles were reviewed by two independent authors and judged on their relevant contribution to the subject of the study. The Preferred Reporting Items for Systematic Review and Meta-Analysis

Table 1
Univariate analysis according to outcomes and age, interval time from endemic area permanency to diagnosis, the status of migrants, gestational age at diagnosis, and microbiological and laboratory findings.

		All outcomes			
Variables (n = total of available cases data)	All patients (n = 58)	Favourable (n = 35)	Non-favourable (n = 23)	P value	cOR (95 % CI)
Age (average ± SD) (n = 51)	29 ± 7	30 ± 7 (n = 35)	27 ± 5 (n = 16)	0.13	
Interval time[a] (average ± SD) (n = 45)	395 ± 479	340 ± 479 (n = 25)	462 ± 482 (n = 20)	0.21	
Status of migrants (n = 35)					
FAI[b]	6	3	3	0.3	
VFR[c]	29	20	9	0.3	
Gestational age at diagnosis (n = 55)					
First trimester	5	3	2	0.93	
Second trimester	19	15	4	**0.02**	0.24 (0.07, 0.86)
Third trimester	22	13	9	0.91	
Post delivery	9	1	8	**0.001**	16.5 (1.89, 144.56)
Microbiology (n = 58)					
P. falciparum	47	33	14	**0.001**	0.09 (0.02, 0.49)
P.malariae	2	0	2	0.07	
P.ovale	4	2	2	0.66	
P.vivax	6	0	6	**0.001**	NA[4]
Fever or other symptoms (n = 45)	34	22	12	0.25	
Laboratory finding (n = 36)					
Anaemia	31	23	8	**0.02**	0.09 (0.01, 0.9)
Thrombocytopenia	4	3	1	0.7	
Treatment (n = 58)					
Yes	48	33	15	**0.004**	0.11 (0, 0.09)

[a] Interval since last stay in an endemic area and pregnancy.
[b] First arrival immigrants.
[c] Visiting relatives and friends.

(PRISMA) guidelines were followed [11]. This study is registered with PROSPERO, number CRD42022382591.

3.2. Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median and interquartile range (IQR), whereas categorical variables were presented as absolute frequencies. Differences in means were evaluated using an unpaired Student's t-test or Mann-Whitney *U* test, and the $\chi 2$ test was applied to categorical variables. Statistical significance was set at a p-value <0.05.

Crude odds ratios (cORs) and their 95 % CI for the association between non-favourable outcomes and potential risk factors were calculated using univariate analysis.

4. Results

Our search yielded 1803 articles; only 26 papers were selected for inclusion. Two additional papers were added after a hand search of the bibliography of the above papers. A total of 28 articles reporting 57 cases of malaria in pregnant women immigrant in non-endemic areas were included. A flow chart summarizing the literature research approach is reported in Fig. 1. Most of the articles were single case reports. We analyzed the anamnestic and clinical data of 58 patients, including our case. Statistical analysis according to favourable and non-favourable outcomes is shown in Table 1.

Demographic characteristics, clinical features, diagnosis, and outcome have been analytically reported in Table 2. The average age was 29 years (±6.8). Concerning gestational age, 22 women (38 %) were in their third trimester at malaria diagnosis, 19 women (33 %) were in their second trimester, 5 women (9 %) were in their first trimester, and gestational age not known in 3 women (5 %). There were 9 cases of malaria diagnosed post-partum (15 %). The patients mainly came from Africa (97 %), especially from Sub-Saharan Africa. There were 10 asymptomatic cases, while the predominant clinical syndrome among the symptomatic women was fever (28 patients, 48 %) with or without associated symptoms. Laboratory findings were available in 60 % of cases and showed anaemia (87 %) and thrombocytopenia (9 %). The median latency period from permanence in endemic areas and diagnosis in European countries was 180 days (IQR 15–730). The most common reason for travel was visiting friends and relatives (17 %); 18 women (31 %) recently had immigrated, and 12 (21 %) women had immigrated for over one year and had no recent travel history in endemic areas. *Plasmodium falciparum* was the main reported (81 %); the other cases were associated to *Plasmodium ovale, Plasmodium vivax, Plasmodium malariae*, and one was a mixed infection by *Plasmodium falciparum* and *Plasmodium malariae*. The malaria diagnostic tests used were thick blood smear in all cases, excluding those for which the method of diagnosis was not reported (3 %); a RDT was used as complementary diagnostic support in 6 cases (10 %), and PCR testing was carried out in 10 (17 %). Pregnancy outcomes were favourable in 35 cases (59 %): all term pregnancies, no low-birth-weight newborns. There were 4 abortions (7 %); 1 child was delivered pre-term (2 %); 7 babies were reported to have a low birth weight <2500 g (12 %); 10 cases of congenital malaria were documented (17 %). No maternal deaths were reported. The most frequent therapy was the quinine-based regimen.

5. Discussion

Malaria is a condition associated with severe complications during pregnancy [12]. Congenital malaria can occur despite the absence of any evidence of active malaria infection of the mother during pregnancy [13]. As reported in the literature and our case report, the diagnosis of malaria infection could be delayed because even if the patient is from endemic countries, the latency period between infection and the symptoms could be longer than expected. Although the incubation period is usually between 2 and 4 weeks, asymptomatic *P. falciparum* infection may persist for many years. Plasmodial infection can persist for many years as submicroscopic infection and pregnancy could represent a reactivation trigger [14]. Although the median latency period between stay in endemic areas and diagnosis in European countries was 180 days, some cases reported in Table 2 showed a latency period of 3 years or more.

The Federal Drug Administration (FDA) and American Association of Blood Bank (AABB) have set some criteria for donors who have traveled to or lived in an endemic area [15]. Structured procedures for screening pregnant women coming from endemic areas are instead lacking.

Women with previously reasonable immunity to malaria lose part of that protection in pregnancy, especially in first pregnancies, in which there is appreciable mortality [16]. Then, immunologic changes during pregnancy result in increased susceptibility to and/or severity of malaria. Instead, pregnant women residing in areas of low or unstable transmission have less pre-existing antimalarial immunity and thus are typically symptomatic and progress to complications if untreated [17]. In pregnancy, the higher risk of severe malaria is due to the generation of infected RBCs with a specific PfEMP1 receptor called VAR2CSA, which can bind to chondroitin sulfate A (CSA) on placental proteoglycans and determine the RBCs sequester in the placenta [18]. Pregnant women with malaria have a 33 % increase in pregnancy loss

Table 2
Interval time: interval since last stay in an endemic area and pregnancy; VFR: visiting relatives and friends; FAI: first arrival immigrants; LBW: low birth weight; FU: follow up; CS: cesarean section.

Author	Age	Gestational age at diagnosis	Interval time	Diagnosis and Plasmodium spp	Symptoms	Laboratory findings	Treatment	Outcome
Develoux, M. 2017, France	18 case reports, average age 31	16.6 % Trimester 1, 33.3 % Trimester 2, 50.1 % Trimester 3	5 months, 33.3 % FAI, 66.6 % VFR	100 % blood smears, 94.4 % *P. falciparum*, 5.6 % P. ovale	22.3 % asymptomatic, 77.7 % fever or other symptoms	83.3 % anaemia, 16.7 % normal	Sixteen patients were treated with oral quinine; one patient was treated with mefloquine	39 % favourable, 22.2 % LBW, fetal death 11.1 %, 5.5 % premature delivery, 22.2 % lost to FU
Dauby, N. 2018, Belgium	27	Trimester 2	24 months	IFA, RDT, blood smear, *P. falciparum*	Fatigue, anorexia, shivering, arthralgia, diarrhea, nausea	Anaemia, elevated CRP	Atovaquone/proguanil	Favourable
Kantele, A. 2012, Finland	4 case reports, average age 26	50 % Trimester 2, 25 % Trimester 3, 25 % not known	7 months	blood smears plus 50 % RDT and 25 % PCR, 100 % *P. falciparum*	75 % asymptomatic, 25 % fever or other symptoms	100 % anaemia	Quinine	Favourable
Odolini, S. 2014, Italy	17	Trimester 3	6 months, VFR	RDT, blood smears, *P. falciparum*	Asymptomatic	Severe anaemia	Mefloquine	Favourable
Giobbia, M. 2005, Italy	29	Not known	48 months	blood smears, *P. falciparum*	Fever, headache, vomiting	Not known	Quinine iv	Favourable
Poilane, I. 2009, France	2 case reports, average age23	Trimester 2	30 months	Blood smears, *P. falciparum*	1 case of fever or other symptoms, 1 case not known	Severe anaemia in both cases plus thrombocytopenia in one of them	Quinine po	Favourable 1 case, fetal death 1 case
Rapp, C. 2006, France	23	Not known	19 months	*P. falciparum*	Not known	Not known	Not known	Favourable
Romani, L. 2018, Italy	30	Trimester 2	1 month	PCR and blood smears, *P. falciparum*	Asymptomatic	Not known	None	Congenital malaria
Zenz, W. 2000, Austria	24	Post-delivery	18 months	Blood smear, *P. falciparum* and P. *malariae*	Asymptomatic	Not known	None	Congenital malaria
Del Punta, V. 2010, Italy	Not known	Trimester 3	12 months, VFR	Blood smear, *P. vivax*	Fever	Anaemia	None	Congenital malaria
De Pontual, L. 2006, France	30	Post-delivery	24 months	Thick blood smear, *P. malariae*	Not known	Not known	None	Congenital malaria
Vottier, G. 2007, France	Not known	Post-delivery	36 months	Blood smear, *P. ovale*	Not known	Not known	None	Congenital malaria
Comellini, L. 1998, Italy	Not known	Post-delivery	8 months	Blood smear, *P. vivax*	fever, malaise, chills, and headache	Normal	None	Congenital malaria
Botelho-Nevers, E. 2015, France	Not known	Delivery	24 months, VFR	*P. falciparum*	Asymptomatic	Not known	Atovaquonee-proguanil	LBW
Gebremeskel Tekle, S. 2018, Italy	Not known	Post-delivery	2 months	Blood smear and PCR, P. *vivax*	Asymptomatic	Not known	Oral chloroquine, oral primaquine as eradication therapy	LBW, congenital malaria
Zanfini, B. 2016, Italy	27	Trimester 3	24 months	Blood smear and PCR, *P. falciparum*	Headache, vomiting, diarrhea, hyperpyrexia, pelvic and low back pain	Anaemia	Quinine, plus clindamycin	LBW
Ducarme, G. 2009, France	33	Post-delivery	3 months	Blood smear, *P. falciparum*	Fever	Anaemia thrombocytopenia	Quinine	Favourable
Mathew, D.C. 2011, UK	26	Trimester 3	8 months	Blood smear, *P. vivax*	Vomiting, dry cough, fever, lower abdominal pain, and diarrhea	Anaemia thrombocytopenia	Quinine, oral primaquine	Fetal distress
Prior, A. 2012, Portugal	22	Post-delivery	60 months, VFR	Blood smear, *P. vivax*	Asymptomatic	Not known	None	Congenital malaria
Soltanifar, D. 2014, UK	35	Trimester 3	Not known, VFR	Blood smear, *P. falciparum*	Fever, rigors, sweating,	Not known	Quinine, oral clindamycin	Favourable

(*continued on next page*)

Table 2 (*continued*)

Author	Age	Gestational age at diagnosis	Interval time	Diagnosis and Plasmodium spp	Symptoms	Laboratory findings	Treatment	Outcome
					headache, and vomiting			
Boissier, F. 2014. France	35	Trimester 2	12 months	Blood smear, *P. falciparum*	Fever, headache, vomiting, and diarrhea	Not known	Quinine iv	Favourable
Menasalvas Ruiz, A.I. 2016, Spain	Not known	Post-delivery	Not known	Blood smear and PCR, *P. ovale*	Sneezing and profuse night sweat without fever	Not known	None	Congenital malaria
Papaccio, M. 2021, Italy	38	Trimester 2	5 months	Blood smear, RDT and PCR, *P. ovale*	Fever, dry cough, rhinitis, malaise, myalgia, retrosternal pain, and fatigue.	Normal	Chloroquine	Favourable
Graffeo, R. 2008, Italy	34	Trimester 3	10 days	Blood smear and PCR, *P. falciparum*	Fever, vomiting, diarrhea	Severe anaemia, thrombocytopenia	Not known	Not known
Balsera, E.C. 2008, Spain	19	Trimester 3	Not known	Blood smear, *P. falciparum*	Fever, unconsciousness	Anaemia	Quinine, doxycycline	Urgent CS, normal fetal outcome
Fernandez Lopez, M. 2015, Spain	9 case reports, average age 32	22.2 % Trimester 1, 33.3 % Trimester 2, 44.4 % Trimester 3	Not known, VFR	100 % blood smears, *P. falciparum*	77.8 % fever, 22.2 % asymptomatic	88.9 % anaemia, 11.1 % not known	66.7 % quinine and clindamycin, 22.2 % artesunate and the rest received quinine and doxycycline	66.7 % favourable, 11.1 % miscarriage, 11.1 % premature delivery and 11.1 % lost to FU
Cultrera, R. 1999, Italy	23	Trimester 2	1 month	Blood smear, *P. falciparum*	Lower abdominal pain, fever, vomiting	Severe anaemia	Pyrimethamine, mefloquine at 22 nd week of pregnancy	Favourable
Rutgers, M.M. 2017, Netherlands	Not known	Trimester 3	10 months	Blood smear and PCR, *P. vivax*	Fever	Not known	Chloroquine and primaquine	Congenital malaria
Marascia Guida, F. 2023, Italy	22	Trimester 2	60 months	Blood smear, RDT and PCR, *P. falciparum*	Abdominal pain	Severe anaemia	Piperaquine/ dihydroartemisinin	Favourable

[19], and this increase can be as high as 60 % in the first trimester [20]. Parasites accumulate in the placenta, where a combination of slower blood flow and expression of CSA provides a new niche for parasites to sequester [21].

Postpartum diagnosis has been associated with a worse overall outcome because congenital malaria has a poor outcome if not promptly recognized and treated. Instead, a favourable outcome was found with a more significant frequency in women in whom the diagnosis was placed in the second trimester of pregnancy.

The increased use of sensitive nucleic acid amplification tests (NAATs) such as PCR and loop-mediated isothermal amplification (LAMP) has shown that many malaria infections in pregnancy remain asymptomatic and below the limit of detection by microscopy. Malaria microscopy typically detects infections with at least 50–500 parasites per μL. PCR can detect fewer than five parasites per μL and has the added advantage of more accurate species identification than microscopy [22]. The use of PCR as a diagnostic method for malaria infection could raise the detection of congenital malaria, improving the management of this life-threatening disease [23].

Adverse neonatal outcomes such as birth asphyxia, low birth weight, stillbirths, and neonatal deaths are associated with maternal anaemia and, as shown in the cross-sectional study conducted by Anabire NG et al. in Ghana, this is strongly predicted by the carriage of *P. falciparum parasites* [24]. They also show that traditional preventive measures for malaria infection like supervised intake of sulphadoxine-pyrimethamine and the use of insecticide-treated bed nets are ineffective in controlling submicroscopic plasmodial infection (SPI) [24]. Our data showed that a finding of anaemia is associated with a better prognosis, probably because it is an alarm bell that pushes the clinician to investigate the presence of malaria in women from endemic areas. However, a bias related to the few cases should be considered.

It is interesting to notice that there is a pronounced effect on fetal birth weight if a pregnant woman has both malaria and a sexually transmitted infection (STI), especially in paucigravidae than multigravidae [25]. In this cohort study, conducted in Tanzania, Kenya, and Malawi, there was a high burden of malaria and STIs; almost 25 % of the women had both conditions during pregnancy. *P. falciparum* is the most imported species in southern Europe and Italy, and is responsible for 89 % of infections, *P. vivax* by 7.7 %, *P. ovale* and *P. malariae* respectively by 6 % and 1.5 % [26,27]. In our review, *P. falciparum* presence was found with a significantly higher frequency in women with a favourable outcome, while *P. vivax* was, in all cases, associated with a worse prognosis. This could be explained by the fact that the clinical picture of falciparum malaria is more striking to facilitate early diagnosis, unlike vivax malaria, which presents a more subtle picture, leading to late diagnosis and the onset of complications in the unborn child (congenital malaria). Furthermore, plasmodium vivax infection is characterized by the presence of hypnozoites in the liver, which may become active many weeks or months after the initial infection and cause a relapse. In a study conducted in the Brazilian Amazon, *P. vivax* malaria in pregnant women was associated with placental tissue damage and poor gestational outcomes, particularly in the first trimester of pregnancy [22]. Finally, treatment during pregnancy is associated overall with an improved prognosis for the unborn child.

6. Conclusion

Despite the limited number of cases reported in the literature, our review is the largest collection of imported malaria infections in pregnant women in Europe. This study highlights the significance of plasmodial infection screening tests in pregnant women from endemic areas, even if the last stay in an endemic area occurred many years before.

Malaria infection in pregnant women may be difficult to diagnose, and only prompt treatment can enhance the fetal outcome. Every clinician should regard any immigrant from an endemic region to be a possible carrier of plasmodial parasites. The number of immigrants from endemic regions is growing. Every country should conduct systematic studies for accurate estimation of the frequency of both API and SPI in migrants in order to plan appropriate intervention measures to prevent the reintroduction of malaria into non-endemic areas. Screening, in particular, should involve women of childbearing age in order to prevent risks to the developing fetus.

Limitations

The low number of cases and the incompleteness of the data reported in the cases limited our study and the statistical analysis.

CRediT authorship contribution statement

Federica Guida Marascia: Conceptualization, Data curation, Writing – original draft. **Claudia Colomba:** Conceptualization, Data curation, Supervision. **Michelle Abbott:** Visualization. **Andrea Gizzi:** Visualization. **Antonio Anastasia:** Methodology. **Luca Pipitò:** Formal analysis, Writing – review & editing. **Antonio Cascio:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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