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Comparative study of histopathological lesions of the placenta induced by malaria infection in HIV seropositive and seronegative women in Kinshasa

Summary

Objectives: this study aims to determine the prevalence rate of malaria infection and inventory histological placental lesions due to Plasmodium falciparum in Kinshasa.

Material and Methods: 147 HIVpositive parturients and 149 HIV negative asymptomatic women were recruited, after informed consent, in 7 reference maternity hospitals in Kinshasa.

Placental biopsies were taken and examined at the Pathology Department of the University Clinics of Kinshasa. Placental malaria histological lesions were classified according to Bulmer *et al* (1993).

Results: The prevalence rate of placental malaria infection was 72.00% (95% CI: 66.70%-77.20%) for the entire study population. It was 91.00% (95% CI: 85.30%-95.20%) for HIV positive mothers vs 53.70% (95% CI: 45.30%-61.90%) for HIV negative mothers ($p<0.0001$). The most frequently encountered histological lesions consisted of acute lesions and chronic active lesions. They predominated among HIV positive multiparous women. Whereas in the placentas of HIV negative mothers, sequelae lesions predominated.

Conclusion: The prevalence of placental malaria infection in Kinshasa was 72.00% (95% CI: 66.70%-77.20%). Co-infected multiparas were more exposed to acute and chronic active malaria placental histological lesions. Additional studies are desirable to assess the extent of this problem across the entire Democratic Republic of Congo (DRC), which happens to be a mini-continent.

Keywords: Plasmodium falciparum, placental lesions, HIV, Kinshasa, DRC

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Introduction

Placental malaria infection is one of the most dramatic consequences of malaria during pregnancy because it leads to increased fetal and neonatal morbidity and mortality.[1] This neonatal morbidity results in a high number of children who are born with low birth weight. Intrauterine growth retardation (IUGR) would be the main mechanism for the reduction in birth weight (BW), through the alteration of trophic exchanges between the mother and the fetus.[2] The prematurity frequently occurring during these high-risk pregnancies would also be an aggravating factor in the reduction in birth weight.[3] But the severity and occurrence of these complications are more marked in regions with unstable malaria endemicity, where they occur in all pregnant women regardless of parity.[4] On the other hand, in areas of stable malaria endemicity, the consequences of placental malaria infestation are less worrying, most often resulting in moderate maternal anemia and reduced birth weight.[5]

Unfortunately, these intertropical regions where transmission is perennial are also regions where HIV/AIDS infection is most prevalent.[6] The resulting co-infection complicates an already precarious situation.[7] Although HIV itself does not have a specific lesion on the placenta, placental malaria is more frequent and severe in co-infected pregnant women,[1] all parities combined, multiparous women having the same risks of infestation than the pauciparous ones. In this work, we sought to estimate the prevalence rate of placental infection due to P.falciparum and to define the distribution of types of histological placental malaria lesions in a population of HIV+ and HIV- parturients, in Kinshasa.

Material and methods

This study took place in 7 maternity wards in Kinshasa integrated into the Program for the Prevention of Mother-to-Child Transmission of HIV (PMTCT). These maternity wards were chosen because of the importance of their obstetric activity and their geographical location. During prenatal consultations in these structures, participants included in the study were tested and informed of their HIV status. They systematically received chemoprophylaxis with Sulfadoxine-Pyrimethamine (SP), in two doses. They previously gave their informed consent before their inclusion in the study. Any parturient presenting with symptomatic AIDS or having a proven malaria attack or even taking antiretrovirals (ARVs) was excluded from the study. This is a "case-control" study. The parturients were enrolled consecutively from 01/24/2006 to 09/11/2006. One hundred and forty-seven HIV-positive parturients (Cases) and 149 HIV-negative parturients (Controls) were enrolled during this period.

Methods

The placental samples were taken in the form of triangular portions involving both sides (maternal and fetal) and going from the cord insertion zone (vertex) to the periphery (base). The triangle thus obtained was cut into central, middle and basal portions of approximately 2 x 1 x 0.5 cm. They were subsequently fixed in Bouin's aqueous solution before being sent to the Special Research Unit in AIDS Pathology (branche of the Armed Forces Institute of Pathology: AFIP) of the Department of Anatomical Pathology of University Clinics from Kinshasa, for histological and parasitological examinations.

The Bulmer histological classification[8] was used to characterize the different placental plasmodial lesions as follows:

Category N (Cat N) = absence of infection;

Category 1 (Cat 1) = acute infection: presence of parasites in maternal erythrocytes, in the intervillous spaces; presence of malarial pigment (hemozoin) in circulating erythrocytes and/or monocytes. But absence of malarial pigment and/or cells in fibrin;

Category 2 (Cat 2) = active chronic infection: presence of parasites in maternal erythrocytes, in the intervillous spaces; presence of malarial pigment (hemozoin) in circulating erythrocytes and/or monocytes. Presence of malarial pigment and/or cells in the fibrin and/or in the syncitiotrophoblasts and/or in the stroma;

Category 3 (Cat 3) = old chronic infection: absence of parasites. But presence of malarial pigment or cells confined in fibrin.

Statistical analysis

The data entered using Excel 2010 and Epi info 3.3.2 Windows software were previously validated and statistical analyzes were carried out using SPSS Windows version 13.0 software. Qualitative data were represented as proportions and quantitative variables as means±standard deviations (SD). The chi-square test, and where appropriate, Ficher's exact tests were used to evaluate the odds ratios of association between the qualitative variables. The Mantel-Haenszel test made it possible to assess the homogeneity of risk between the different strata of the study. The significance of the results was evaluated at the critical threshold of 5% probability.

Results

Obstetric parameters of HIV positive and HIV negative mothers

The average age of the study population was 28.56±6.30 (range 15 to 44 years). The average age of HIV+ mothers was higher than that of HIV- mothers (p=0.042). But the averages of parity, gestation, duration of labor and term of pregnancy did not show a significant difference between the two groups of mothers (p>0.05) (Table 1).

Incidence of placental malaria infection among HIV positive and HIV negative mothers

The incidence of placental malaria infection in the entire study population was 72.00% (95% CI=66.70%-77.20%), or 213/295. HIV+ mothers were the most exposed to placental malaria infection, i.e. 91.10% (95% CI=85.30%-95.20%) of infected placentas (133/146) compared to HIV- mothers, among whom it represented 53.70% (95% CI = 45.30%-61.90%) (80/149); (0R=8.82: 95% CI=4.58-16.97; p<0.0001); (Table 2).

Table 1 Obstetric parameters of HIV positive and HIV negative mothers

Variables	VIH+ et VIH-	VIH positive	VIH negative	
	(n) Average ± SD	(n) Average ± SD	(n) Average ± SD	p
Age	(291) 28,56±6,30	(145) 29,32±5,96	(146) 27,82±6,55	0,042
Parity	(292) 3±2	(146) 3±2	(146) 3±2	0,901
Gestity	(291) 3±2	(145) 3±2	(146) 3±2	0,786
Term	(285) 39,49±1,58	(143) 39,46±1,69	(142) 39,53±1,47	0,723
Duration of labor	(290) 11,19±10,87	(145) 11,70±1,04	(145) 10,67±0,74	0,423

SD, standard deviation.

Table 2 Incidence of placental malaria infection among HIV positive and HIV negative mothers

Variables	VIH+ and VIH- n (%)	VIH+ n (%)	VIH- n (%)	p
Infected Placentas	213 (72,00)	133 (91,10)	80 (53,70)	<0,0001
Uninfected Placentas	82 (27,20)	13 (8,90)	69 (46,30)	
Total	295 (100,00)	146 (100,00)	149 (100,00)	

Placental malaria infection according to the parity of HIV+ and HIV- mothers

The number of HIV+ primigravidae was 32/146 and that of multigravidae was 114/146. While HIV- primigravidae numbered 35/146 and HIV- multigravidae numbered 111/146. The prevalence rate of placental malaria infection did not show a significant difference, depending on parity, with regard to HIV+ mothers; p=0.309. Multigravidas were exposed in the same way as primigravidas, 92.10% (105/114) vs 87.50% (28/32) (OR=0.60; 95% CI=0.17-2.09 ; p=0.309).

For HIV- mothers, this placental infection predominantly affected primigravida compared to multigravida, 68.60% (24/35) vs 48.60% (54/111) (OR=2.30, 95% CI =1.03-5.15; p=0.030) (Table 3). The Mantel-Haenszel test gave an OR of 1.63 with a 95% CI of (0.81-3.14); p=0.174).

Types of histological placental lesions induced by *P. falciparum*

Overall (HIV+ and HIV-), 27.99% (82/293) of placentas showed no trace of malaria infection (Cat N). Category 1 lesions (Cat 1) were found in 19.45% (57/293) of placentas. Those of category 2 (Cat 2) were found in 29.01% (85/293) and lesions of category 3 (Cat 3) concerned 23.55% (69/293) of placentas. The lesions most frequently found in HIV+ mothers were those of Cat 2, 71/145, or 49.00% compared to 14/148, or 9.50% for HIV- mothers (OR=26.92; CI at 95%=11.10-67.60; p<0.0001). While Cat 3 lesions were more prevalent in HIV- mothers 46/148 (31.10%) vs 23/145 (15.80%), found in HIV+ mothers (OR=2.65; CI to 95%=1.15-6.21; p=0.020; (Table 4, Figures 1, 2, 3).

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Table 3 Placental plasmodial infection according to the parity of VIH positive and VIH negative mothers

Variables	Primigravida n(%)	Multigravida n(%)	0R (IC à 95%)	p
VIH positive				
Uninfected Placentas	28 (87,50)	105 (92,10)	1,7 (0,40-6,59)	0,309
Infected Placentas	4 (12,50)	9 (7,90)		
VIH negative				
Uninfected Placentas	24 (68,60)	54 (48,60)	2,30 (1,03-5,15)	0,030
Infected Placentas	11 (31,40)	57 (51,40)		

The test of Mantel-Haenszel: OR=1,63 (IC à 95%=0,81- 3,14 ; p=0,174).

Table 4 Type of placental histological lesions induced by Plasmodium falciparum

Type of lésions	VIH+ et VIH- : n (%)	VIH+ : n (%)	VIH : n (%)	OR (IC à 95%)	p
Cat N*	82 (27,99)	13 (9,00)	69 (46,60)		
Cat 1	57 (19,45)	38 (26,20)	19 (12,80)	10,60 (4,41-26,05)	<0,0001
Cat 2	85 (29,01)	71 (49,00)	14 (9,50)	26,92 (11,01-67,60)	<0,0001
Cat 3	69 (23,55)	23 (15,80)	46 (31,10)	2,65 (1,15-6,21)	0,020
Total	293 (100,00)	145 (100,00)	148 (100,00)	8,60 (6,06-16,21)	<0,0001

*Reférence group for comparison.

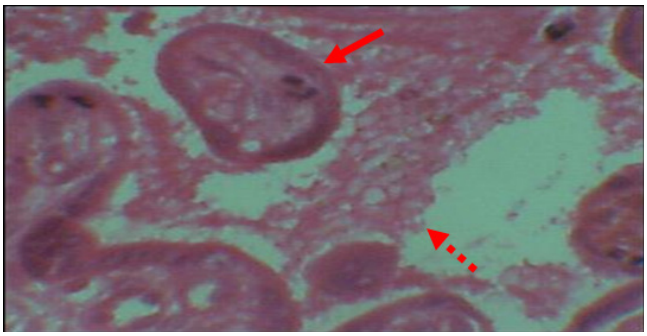

Figure 1 Microscopic picture of a category N showing villi (solid arrow) and an intervillous space containing maternal RBCs (dotted arrow). HE: x 40

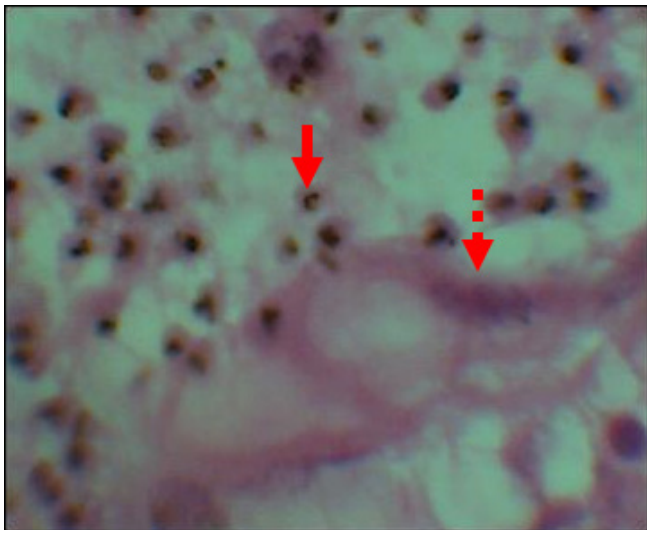

Figure 2 Histological image of category 1 showing Maternal RBCs parasitized in the EIV (solid arrow) and a Syncytiotrophoblast cell (dotted arrow). ET: x 40.

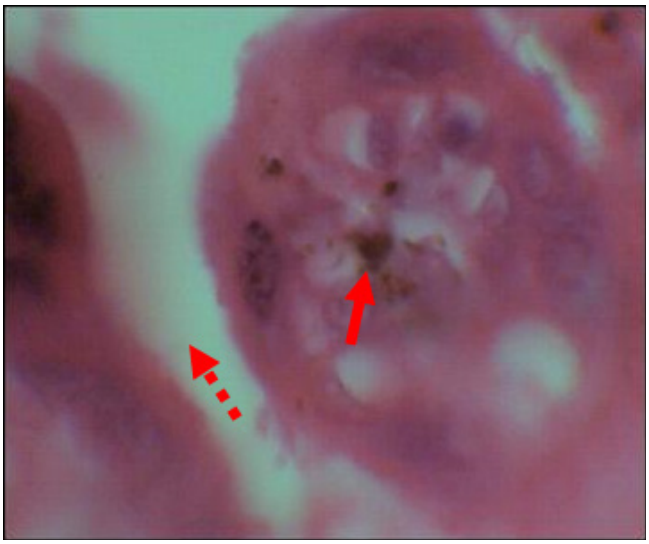

Figure 3 Microscopic picture of category 3 showing clumps of malarial pigment (hemozoin) in the villous stroma (solid arrow) and empty RBC EIVs (dotted arrow) HE : x100.

Distribution of placental malaria lesions according to developmental stage

The lesions were grouped into active lesions (acute and chronic active lesions (Cat 1 and 2) and sequelae lesions (Cat3). Acute and chronic active lesions (Cat 1 and 2) were found mainly in the placentas of HIV positive mothers, 109/132, or 82.58% compared to 33/79, or 41.77% for the placentas of HIV negative mothers (OR=6.61; 95% CI=3.50-12.46; p<0.0001). Furthermore, the sequelae lesions (Cat 3) were mainly found in the placentas of HIV negative mothers, 46/69, (58.23%) vs 23/69, (17.42%) in the placentas of HIV positive mothers (p <0.0001) (Table 5).

Distribution of placental malaria lesions according to the developmental stage and parity of HIV positive and HIV negative mothers. Acute and chronic active lesions (Cat 1 and 2) were mainly found in HIV+ multigravidas at a rate of 86.50% (90/104) compared to 67.90% (19/28) for primigravidae in the same group (OR : 0.33; 95% CI: 0.13-0.87; p=0.025). Regarding HIV- mothers, no significant difference was found in the distribution of these lesions according to parity 24/53 (45.30%) vs 8/24 (33.30%) (OR= 066; 95% CI = 0.22-1.65; p = 0.232) (Table 6).

Table 5 Distribution of placental malaria lesions according to developmental stage

Evolutive stage	VIH+and VIH-n(%)	VIH+ n (%)	VIH- n (%)	OR (IC à 95%)	p
Active lesions	142 (67,30)	109 (82,58)	33 (41,77)	6,61 (3,50-2,46)	
Sequelae lesions	69 (32,70)	23 (17,42)	46 (58,23)		<0,0001
Total	211 (100,00)	132 (100)	79 (100)		

Table 6 Distribution of placental malaria lesions according to the developmental stage and parity of HIV positive and HIV negative mothers

Status	Evolutive stage of lesions	Primigravidae : n (%)	Multigravidae n (%)	0R (IC à 95%)	p
VIH positive					
Sequelae lesions (Cat3)		9 (32,10)	14 (13,50)	0,60 (0,22-1,65)	0,025
Active lesions (Cat1-2)		8 (33,30)	24 (45,30)		
VIH negative					
Sequelae lesions (Cat3)		16 (66,70)	29 (54,70)		0,232
Active lesions (Cat1-2)		19 (67,90)	90 (86,50)	0,33 (0,13-0,87)	

The test of Mantel-Haenszel had found OR =0,45 ; IC à 95% =0,22-0,917 ; p=0,028).

Discussion

Co-infection is truly a factor in worsening placental malaria. While the overall prevalence rate of placental malaria infestation for the entire study population was 72%, co-infected parturients had a prevalence rate of 91%. On the other hand, that of seronegative parturients was 41.57% in a study carried out in Tanzania,[9] in a comparative study carried out in Rwanda and published in 1998, found a prevalence rate of malaria infection of the order of 75 % in HIV+ placentas and 73% in HIV- placentas. They found no significant difference in placental malaria infestation between the two types of placentas. As for Izuka et al (2017), who conducted their research in Nigeria, noted a prevalence of placental malaria of 68.6% among HIV-positive women.[10] This lower rate compared to that given by our results could be linked to the instability of the endemic in the region concerned.

Grouped according to their acuity, the most active lesions (Cat1 and 2) were found in the placentas of HIV+ parturients and more particularly in those of HIV+ multiparous women. Therefore, multiparous are visibly more infected compared to pauciparous. They no longer benefit from the protection enjoyed by HIV-negative multiparous women. These results are consistent with those published by Kwenti (2018).[11] The prevalence rate of placental malaria infestation found among HIV-negative parturients in our study was slightly higher than those collected by COT et al.[12] These authors summarized data from studies carried out on placental malaria infection between 1915 and 2002. They gave a range of prevalence rates ranging from 10 to 34%.

But it should be noted that most of these studies were carried out in regions where malaria transmission is seasonal rather than perennial. The increased susceptibility to placental infection due to P.falciparum, described in co-infected pregnant women, could be explained, at least in part, by a dysfunction of the local and systemic immune defense, affecting both the cellular side. and humoral. This dysfunction would be characterized by the reduction in the production of pro-inflammatory cytokines (IFN-γ and TNF-α, IL-2), production normally ensured by placental macrophages (IVBMCs: Intervilous Blood Monoclear Cells) and a partial alteration of the humoral reaction towards antigens expressed by certain evolutionary stages of P.falciparum and towards specific syncitiotrophoblastic receptors, responsible for cytoadherence and sequestration of parasitized red blood cells in the placenta, notably chondroitin sulfate A.[13]

The weakening of the placental barrier that these histological malaria lesions could cause, even if it is not yet sufficiently documented, may explain the facilitating role that these lesions could play in the vertical transmission of HIV. This role is also mentioned by Hoo et al.[14] These results, which are the first obtained in our environments, in Kinshasa, in the Democratic Republic of Congo (DRC), open new perspectives for undertaking similar studies in other regions of this country with continental dimensions where the endemicity of malaria and the prevalence of HIV infection is highly variable.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

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