Association of malaria and HIV infection in pregnancy with reduced transfer of antimalarial antibodies to the newborn

Laura Moro[1], Azucena Bardají[1,2], Carlota Dobaño[1,2], Elisa Serra-Casas[1], Betuel Sigaúque[2,3], Pau Cisteró[1], Virander S. Chauhan[4], Inácio Mandomando[2], Chetan E. Chitnis[4], Jaume Ordi[1,5], Pedro L. Alonso[1,2], Clara Menéndez[1,2], and Alfredo Mayor[1,2]

[1] Barcelona Center for International Health Research, Hospital Clínic-Universitat de Barcelona, Spain; [2] Centro de Investigação em Saúde da Manhiça, Manhiça, Mozambique; [3] Instituto Nacional de Saúde, Ministry of Health, Maputo, Mozambique; [4] International Centre for Genetic Engineering and Biotechnology, New Delhi, India; and [5] Department of Pathology, Hospital Clínic-Universitat de Barcelona, Spain.

INTRODUCTION

During pregnancy, maternal antibodies are transferred to the fetus by an active process mediated by Fc receptors in the placental syncytiotrophoblast [1]. This **maternal-fetal antibody transfer** minimizes deficiencies in antibody production in the fetus and provides a short-term passive immunity [1], conditioning the degree and length of the protection [2] and vaccination success in the newborn [3,4]. Previous studies suggest that **malaria** and **HIV** infections during pregnancy affect this placental transfer [2,5,6], although their effect over specific antimalarial antibodies remains unclear [7]. We hypothesized that HIV and *Plasmodium falciparum* infection in pregnancy might decrease placental transfer of antimalarial antibodies by altering the architecture of the placenta, and therefore contribute to an increased risk of malaria infection in the newborn. To address this, levels of maternal and cord *P. falciparum*–specific IgG, IgM and IgG subclasses were measured and the effect of HIV and malaria infections and other maternal factors (antibody levels, age, gravidity, treatment, anemia) on antibody placental transfer was assessed.

MATERIALS & METHODS

Retrospective study conducted in **187 Mozambican pregnant women** participating in an Intermittent Preventive Treatment in Pregnancy clinical trial (2003-2006). Peripheral, placental and cord plasma samples and placental sections were taken at delivery. Malaria was diagnosed by optical microscopy in peripheral and cord blood, by histology in placental sections and by qPCR in peripheral, placental and cord blood. HIV diagnosis was performed with two rapid diagnostic tests.

Total IgG, IgM and IgG subtype levels against *P. falciparum* antigens merozoite surface protein 1-19 (**MSP1$_{19}$**), erythrocyte binding antigen 175 (**EBA175**), apical membrane antigen 1 (**AMA1**) and **parasite lysate** were measured by ELISA in mother-cord plasma pairs. Malaria infection in the mother was considered if parasites were detected by placental histology, peripheral microscopy or qPCR. Placental antibody transfer was defined as the cord-to-mother ratio (**CMR**) of the antibody levels.

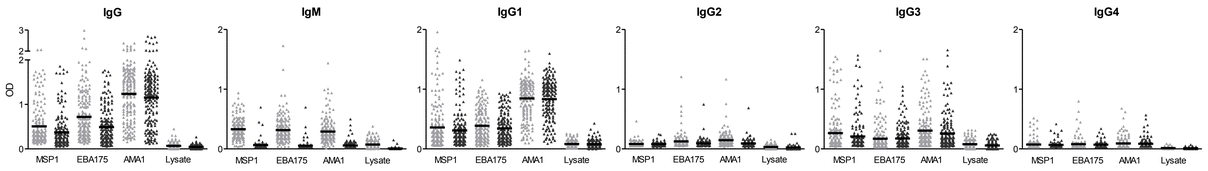
RESULTS & DISCUSSION

i. Characteristics of the study population

	Maternal HIV status: Uninfected (n=130), Nº (%)	HIV-infected (n=57), Nº (%)	P[a]
Age (years)			
<20	51 (39.2)	19 (33.3)	
20- <25	40 (30.8)	16 (28.1)	
>=25	39 (30.0)	22 (38.6)	0.506
Parity			
Primigravidae	36 (27.7)	15 (26.3)	
Secundigravidae	25 (19.2)	12 (21.1)	
Multigravidae	69 (53.1)	30 (52.6)	0.953
Anemia			
No	87 (66.9)	23 (40.3)	
Yes	43 (33.1)	34 (59.7)	**<0.001**
Malaria infection			
Negative	76 (58.5)	35 (61.4)	
Positive	54 (41.5)	22 (38.6)	0.706
IPTp group			
Placebo	65 (50.0)	23 (40.3)	
Sulfadoxine-pyrimethamine	65 (50.0)	34 (59.7)	0.224

[a] Chi-Square Test

ii. Levels of antimalarial antibodies in maternal (grey) and cord (black) plasma samples represented as ELISA optical densities.

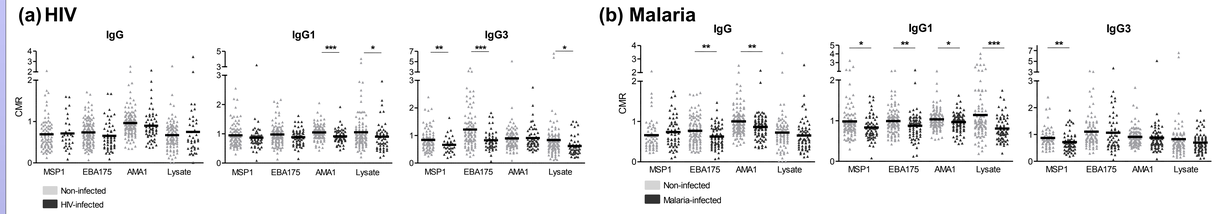


Funding: Carlos III Institute of Health, Spain, and Banco Bilbao, Vizcaya, Argentaria Foundation. **Acknowledgments:** Women and children participating in the study; staff at Manhiça District Hospital, CRESIB and CISM laboratories; MR4 for providing malaria parasites contributed by D. J. Carucci (3D7), S. J. Rogerson (CS2), and T. E. Wellems (HB3).

Contact info: Laura Moro, laura.moro@cresib.cat

RESULTS & DISCUSSION

iii. CMR of antimalarial antibodies by maternal infection status in a univariate analysis. P-values are represented as * (P<0.05), ** (P<0.01) or * (P<0.001).**



iv. Association of CMR of antimalarial antibodies with maternal HIV and malaria infection in the multivariate model. Only seropositive women for a given antibody were included.

CMR	Maternal Ab levels: Effect[a] (per 2x) (95% CI)	P	HIV infection: Effect[b] (95% CI)	P	Malaria infection: Effect[b] (95% CI)	P
IgG MSP1 (n=110)	0.91 (0.75; 1.1)	0.326	1.01 (0.79; 1.30)	0.946	1.09 (0.86; 1.37)	0.479
IgG EBA175 (n= 176)	0.92 (0.83; 1.03)	0.165	0.87 (0.73; 1.02)	0.094	0.82 (0.70; 0.96)	**0.014**
IgG AMA1 (n=184)	1.05 (0.96; 1.14)	0.285	0.91 (0.81; 1.02)	0.108	0.84 (0.75; 0.93)	**0.002**
IgG lysate (n=142)	0.87 (0.64; 1.17)	0.358	0.97 (0.67; 1.40)	0.868	0.97 (0.69; 1.36)	0.856
IgG1 MSP1 (n=151)	0.83 (0.76; 0.90)	**<0.001**	0.85 (0.74; 0.98)	**0.022**	0.89 (0.78; 1.01)	0.08
IgG1 EBA175 (n=183)	0.85 (0.79; 0.91)	**<0.001**	0.89 (0.80; 1.00)	0.059	0.88 (0.79; 0.99)	**0.029**
IgG1 AMA1 (n=187)	0.94 (0.88; 1.00)	**0.041**	0.88 (0.81; 0.94)	**0.001**	0.94 (0.87; 1.01)	0.073
IgG1 lysate (n=159)	0.94 (0.80; 1.09)	0.408	0.83 (0.70; 0.98)	**0.027**	0.77 (0.65; 0.90)	**0.001**
IgG3 MSP1 (n=121)	0.89 (0.82; 0.98)	**0.015**	0.82 (0.69; 0.97)	**0.023**	0.80 (0.68; 0.95)	**0.01**
IgG3 EBA175 (n=139)	0.76 (0.68; 0.84)	**<0.001**	0.73 (0.61; 0.88)	**0.001**	0.90 (0.75; 1.09)	0.288
IgG3 AMA1 (n=170)	0.90 (0.83; 0.97)	**0.009**	1.02 (0.89; 1.17)	0.735	0.93 (0.82; 1.06)	0.255
IgG3 lysate (n=163)	0.91 (0.80; 1.03)	0.14	0.79 (0.65; 0.97)	**0.025**	0.92 (0.76; 1.11)	0.402

[a] Defined as an increase of two times in the mean IgG levels for a woman. Adjusted for maternal factors: antibody levels, HIV and malaria infections, parity, age, anemia and IPTp group.

[b] Defined as the ratio of the mean IgG levels for the infected women with respect to the non-infected. Adjusted for maternal factors: antibody levels, HIV and malaria infections, parity, age, anemia and IPTp group.

v. Placental transfer of antimalarial antibodies and pregnancy outcomes

In a multivariate analysis, no significant associations were found with a few exceptions:
- Higher CMR of IgG3 AMA1 and lysate was associated with an increase in child hematocrit at 1 month of age (3.08 [95% CI, 1.07; 5.08]; P=0.003; and 1.90 [95% CI, 0.51; 3.29]; P=0.008, respectively). Also higher CMR of IgG lysate was associated with increased in gestational age (0.51 [95% CI, 0.01; 1.00]; P=0.047).
- A higher CMR of IgG1 MSP1 was significantly associated with increased risk of LBW at delivery (4.48 [95% CI, 1.13; 17.77]; P=0.033) and a higher CMR of IgG MSP1 associated with reduced child hematocrit at 1 month of age (-2 [95% CI, -3.70; -0.31]; P=0.023).

vi. Placental transfer of antimalarial antibodies and malaria incidence during the first year of life

- Higher CMR of IgG lysate and IgG1 AMA1 were significantly associated with an **increased risk of malaria** during the first year of life (incidence ratio, 1.48 [95% CI, 1.01; 2.18]; P=0.046; and incidence ratio, 3.11 [95% CI, 1.11; 8.71]; P=0.031, respectively).
- Antibodies as **markers of exposure** rather than protection.

CONCLUSIONS & PERSPECTIVES

- **Malaria and HIV in pregnancy are associated with a decrease in the placental transfer of antibodies against several *P. falciparum* merozoite and asexual blood-stage antigens from mother to fetus.**
- **The role of antimalarial antibodies in infant protection should be further investigated in order to design effective immunization strategies.**

REFERENCES

1. Chucri TM, *et al.* J Reprod Immunol. 2010; 87(1-2),14–20. **2.** De Moraes-Pinto MI, *et al.* Arch Dis Child Fetal Neonatal Ed. 1998; 79(3), 202–5. **3.** Albrecht P, *et al.* J Pediatr. 1977; 91(5):715-8. **4.** Jones CE, *et al.* JAMA 2011; 305(6), 576–84. **5.** Scott S, *et al.* J Infect Dis 2005; 191(11), 1854–60. **6.** Okoko BJ, *et al.* J Infect Dis 2001; *184(5), 627–32.* **7.** Ned RM, *et al.* J Infect Dis 2008; 198(11), 1609–19.