Malaria Immunology of pregnant women

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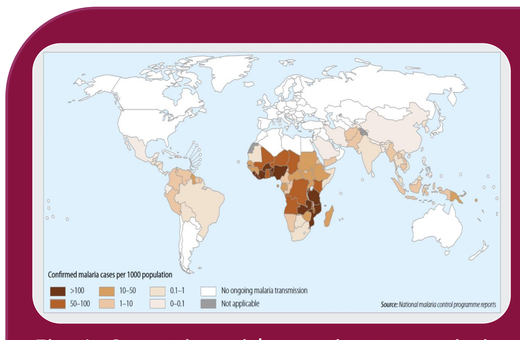


Fig. 1. Countries with ongoing transmission of malaria, 2013[2].

High risk

Introduction

Malaria prevention, control, and ultimately, elimination feature one of the most important public health challenges nowadays. Malaria-associated maternal illness and low birth weight is mostly the result of *Plasmodium falciparum* infection of pregnant woman and occurs predominantly in Africa[1].

OBJECTIVE The aim of this review is to elucidate the current situation of the immunopathology of malaria on pregnant women and which area requires further investigation.

Methods: search strategy

A systematic literature search in PubMed database was conducted between January and March 2015 using the combination of keywords including: “Malaria” AND “Pregnancy” OR “Immunity” OR “VAR2CSA” OR “Placenta”.

DIFERENCES BETWEEN INFECTED ERYTHROCYTES (IEs)[3]

	IEs from the placenta of pregnant women	IEs from non-pregnant individuals
Adhesion to CSA	Yes	No
Adhesion to CD36, ICAM-1	No	Common
Rosetting	No	Common
Agglutination	Variable	Common
Non-specific binding of IgM to IEs	Yes	No
Sex-specific IgG recognition of variant surface antigens	Yes	No
Parity-dependent IgG recognition of variant surface antigens	Yes	No

Hummoral immunity

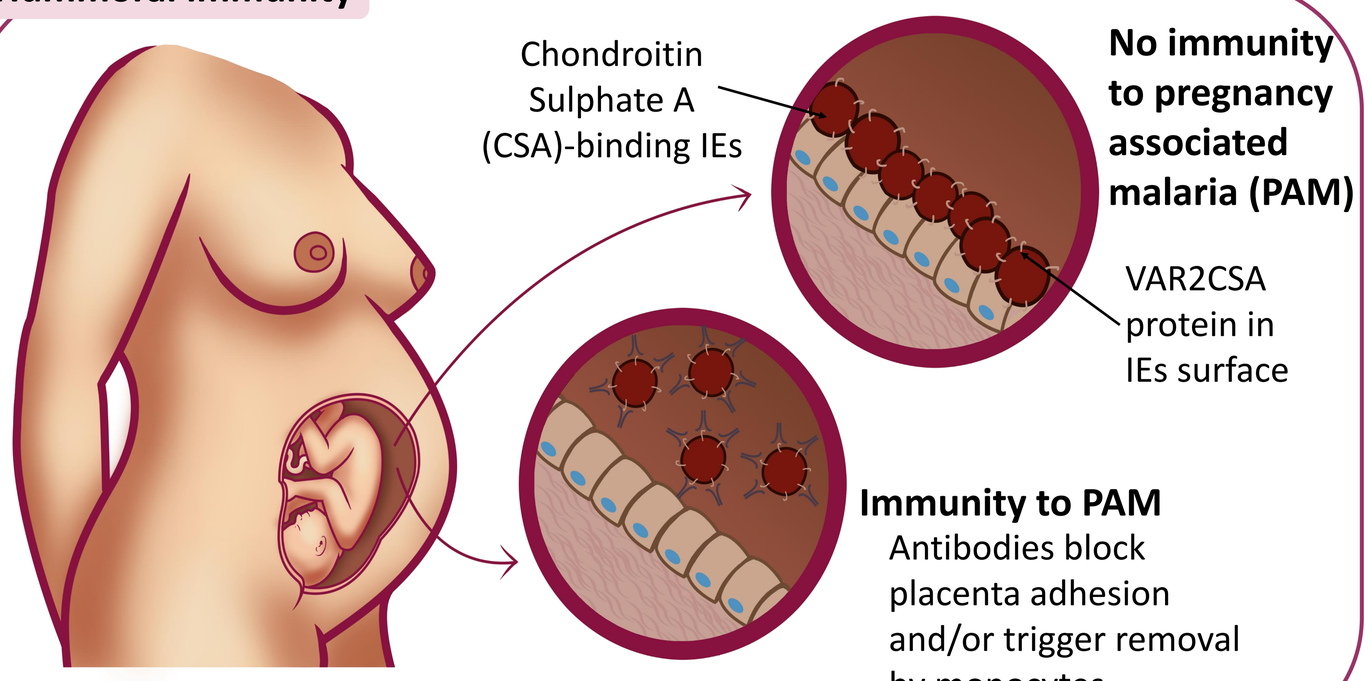


Fig. 2. Binding of infected erythrocytes to the placenta[4].

Cytokine balance

Pregnant healthy women

$\uparrow T_H2$: IL-10, IL-4, IL-6, IL-13

$\downarrow T_H1$: IL-1β, IL-12, IFN-γ, IL-2

A pregnant female’s immune system has to defend both mother and foetus from pathogens, while at the same time has to tolerate the foetus[5].

Malaria pregnant women

Strong T_H1 response Up-regulation of inflammatory cytokines → TNF-α, IFN-γ, IL-1β, IL-2 → $\uparrow T_H1$ → Maternal anaemia, spontaneous abortions, low birth weight and pre-term delivery[6]

Cytoadherence and multigravidae protection

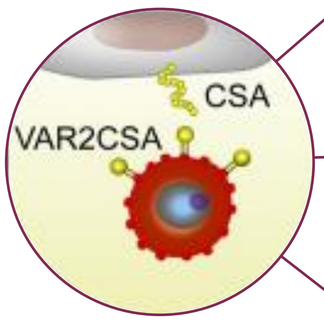
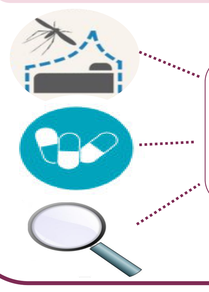


Fig. 3. VAR2CSA mediates IE binding to placental CSA[9].

- Adhesion to the CSA of the placenta
  - IEs placental sequestration
  - Limits maternal-fetal exchanges, leading to clinical complications for both mother and child[7]
- Several expositions along successive pregnancies
  - Multigravidae women acquire antibodies against VAR2CSA
- Highly variable and complex structure
  - Cross-reactive epitopes have been recently identified[7,8], which represent a key element to develop a VAR2CSA-based vaccine

Malaria control implications in natural acquired immunity



Exposure to malaria may fall

Antibody to placental-binding IEs may be less developed

Susceptibility to malaria may spread into later gravidities, and among the infants who are infected[10]

Conclusion

- The greatest difficulty of the malaria immune response is the complex, multistage, multiantigen life cycle of *Plasmodium*, that adheres to the placenta mediating the VAR2CSA protein. There is a reduction of IgG transference from mother to foetus and the cytokine balance is directed towards a strong T_H1 response.
- **RESEARCH NEEDS:**
  - A novel VAR2CSA-based vaccine
  - The role of protective maternal antibodies in the newborn
  - Evaluation of intermittent preventive treatment regimes, the emerging resistance outcomes and new rapid diagnosis techniques
  - Studies with *Plasmodium vivax* and *Plasmodium knowlesi*
  - Co-infection with other pathogens such as HIV and Dengue

GAPS IN KNOWLEDGE
How does exposure in utero to *P. falciparum* influence malaria in infants?
Does *P. falciparum* exposure in utero influence infant susceptibility to other infections?
What is the role of the antibody mother-to-foetus transmission?
How do malaria control interventions affect the pregnant women natural acquired immunity?
How can emerging resistance to malaria treatment be handled?
How long does immunity in pregnant women last?

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