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Placentary Malaria, What Biological Diagnosis?

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Abstract: ***The consequences of malaria associated with pregnancy result from the placental inflammation responsible for the disruption of fetal maternal exchanges causing suffering, weight loss and miscarriages. Thus, the biological diagnosis of placental malaria becomes an essential tool in the prevention of the consequences of malaria during pregnancy. Direct diagnostic techniques are more reliable, but because of the unavailability of the placenta during pregnancy indirect techniques are useful. However, implementation and interpretation of the diagnosis indirect results still a controversial issue at present. Recent studies are moving towards the identification of determining cytokines at the peripheral level of a consequent placental inflammation of placental malaria.***

Keywords: malaria, placenta, cytokines, immunoglobulins, diagnosis.

1. Introduction

Although the World Health Organization (WHO) has stated that death rates from malaria have declined, malaria remains one of the leading causes of morbidity and mortality. L are children under five as well as pregnant women are still paying heavy tribute with an estimated 228 million cases in 2018 of which almost 93% of cases in 2017 were reported in the Africa Region of the WHO. Pregnant women and children represent the segment of the population most vulnerable to malaria. In fact, malaria harms the health of the mother, exposes her to an increased risk of death and impact on the health of the fetus, leading to prematurity and low birth weight. In 2018, around 11 million pregnant women in sub-Saharan Africa presented with a malaria infection, 16% of whom were born with low birth weight [1]. It is in this context that the report of the WHO malaria worldwide in 2019 includes a special section on the burden of malaria and its consequences on the s two groups. In the same order, numerous studies have been carried out on prevention, therapy and the pathophysiology of malaria, targeting these groups. This review of literature is a contribution to the prevention of the consequences of malaria by addressing the exploration of immunological mediators determinants in diagnosing biological placental malaria.

Immunology of pregnant women

Pregnancy is a complex physiological process in which the female body has to accept the fetal allograft. Progesterone, the immunosuppressive hormone produced by the yellow corps and the placenta, will be involved in the regulation of maternal immune responses against fetal allograft [2]. The woman's organism will enter the immune modulation process in three phases.

Early phase of pregnancy and the mother's immune response:

In non-pregnant women, the art effectors and mediators of immunity involved in other physiological mechanisms outside their mistress activity that is the immune response. Menstrual periods are characterized by a proliferation of neutrophils, the eosinophils and the macrophages secrete mediators and accompanied by metalloproteinases (MMPs) causing the degeneration of the lamina basa endometrial dragging menstruation. This pro inflammatory reaction also occurs when the dominant oocyte is released during ovulation.

In pregnant women after fertilization, a proinflammatory reaction occurs with a massive influx of macrophages and T cells into the uterus in response to the presence of seminal fluid and sperm cells. This phase, which corresponds to the adhesion of the embryo and to the trophoblastic invasion, is conditioned by significant inflammation via cytokines (I L-1, IL-6, TNF-α), growth factors (GM-CSF, CSF-1) and enzymes, which attenuates to allow the inflow of another cell type, the NK cells. NK cells are essential for feto-placental growth and for decidualization which corresponds to the invasion of the maternal endometrium by fetal trophoblastic cells to lead to the vascularization of the deciduous [3-4]. The accumulation of NK in the uterine space is maximum at the beginning of pregnancy with 70% of the cells of the decidue then decreases from the twentieth week to disappear at the end.

The second phase or phase of fetal growth and development:

The mother, the placenta and fetus are symbiotic with sector responses anti-inflammatory TH2 predominant under the action of Treg. The Treg produce IL-10 and TGF-b to inhibit the activated T cells. The chorionic gonadotropic hormone

(hCG) produced by trophoblasts is thought to be involved in the migration of Tregs.

The third phase or preparation for childbirth:
The answers proinflammatory are needed to contract uterus and expulsion of newborn and placenta [5]. Independently of malaria infection, the frequencies of CD4 + T cells, T effectors and monocytes expressing CD86 decreased between inclusion and delivery while those of T CD8 +, the DC expressing CD86 are increased [6].

Biological diagnosis of placental malaria
The direct or indirect evidence of the presence of P. Plasmodium in the man is an issue resolved at present. However, despite numerous funding from the United Nations and private partners, the biological border between symptomatic and asymptomatic malaria remains a headache. The complexity of the symptomatology of malaria is not only linked to the pathophysiology but also to the complexity of the immunological response, especially in pregnant women.

The thick drop in pregnant women:
Thick peripheral blood drop is a non-determining indicator in the follow-up of pregnant women. It is in this context that WHO recommends intermittent preventive treatment (IPT) to Sulfadoxine-pyrimethanine during prenatal consultation. Indeed, the placenta by its extreme vascularization is the preferential site for the sequestration of erythrocytes infected with P. falciparum, while the blood of the peripheral circulation does not contain parasites [7, 8]. The properties of cyto-adhérence Plasmodium protect the parasite lysis by effector mechanisms of immunity or spleen [9].

In view of the above, the biological diagnosis of placental malaria cannot be made by thick gout of peripheral blood. The ideal would be to make the thick drop directly with the blood drawn from the intravenous space of the placenta.

Rapid Diagnostic Tests (RDT)
They reveal in 5 to 15 minutes the presence or absence of a Plasmodium antigen in the patient's blood. The antigens most frequently sought by this technique are: HRP-II (histidine-rich protein -II), specific for P. falciparum; pLDH (Plasmodium lactate dehydrogenase) common to the 4 Plasmodium species or specific to one of the species. WHO recommends RDTs as an intermediate test for microscopic examination of thick gout.

Placental apposition:
It is the application on an object slide of the maternal side of the placenta. After fixation and staining, the slide is examined under a microscope. The desired items are infected red blood cells, the pigments intra - macrocytic. The placental apposition do cannot be done during the follow-up of the pregnant woman because of the unavailability of the placenta.

Pathology analysis of the placenta:
It is the analysis of cellular and tissue lesions of the placenta, witnesses of the existence of active or inactive plasmodium and of fetal suffering. It is first macroscopic (appearance, coloring, etc.) and microscopic by the histological sampling of a cm3 in a para-central situation of the placenta. The placental infection criteria sought the maternal side in inter villous spaces are infected red blood cells, the pigments malarial in erythrocytes or in monocytes and excess fibrin [10]. As in the case of apposition placenta, the realization of histological analysis of the placenta cannot occur when monitoring the woman encircled because of the unavailability of the placenta.

PCR (polymerization chain reaction):
PCR allows the detection of occult infections with very weak parasitaemias, the monitoring of resistance genes and the genotyping of species. This more efficient technique requires heavier and very expensive equipment. The PCR technique is a promoter process because it is able to detect directly or indirectly the biological material involved in malaria. Thus, nowadays studies have highlighted certain effector and immunological mediators witnesses of a placental malaria [11]. However, highlighting the plasmodium genetic material or immunological mediators is not necessarily a control indicator of the placental inflammation responsible for the consequences of malaria associated with pregnancy (MAP).

Search for effectors and immunological mediators:
During the MAP, peripheral infection is generally characterized by a parasitic low density and the lack of forms trophozoites and schizont parasite except in rare cases of severe malaria. Furthermore, knowledge of the old or recent status of placental malaria in routine biological monitoring cannot be diagnosed by direct techniques at present because of the unavailability of the placenta. Thus, indirect prognosis could be one of the solutions in saving biological monitoring of placental malaria during antenatal care.

Determination of immunoglobulin IgG against Plasmodium:
Numerous studies have demonstrated the protective properties of the antibody IgG against plasmodium reducing significantly severe forms of malaria. Logie and al. have shown variability rate IgG and IgM according to the transmitting areas of malaria (Gambia, Nigeria and Switzerland) [12]. Studies on a production of IgG anti VAR 2 CSA showed a difference significant between women multi gestes compared with the first pregnancy [13, 14, 15]. The studies of the susceptibility of the isotypes IgG1, IgG2, IgG3 and IgG4 have reported that the IgG1 and IgG3 are more protective than the IgG2 and IgG4 [16; 17].

However, some authors have not shown an association between IgG and protection against malaria. The controversies observed in the different studies can explained by the nature of different candidate vaccine (MSP, AMA, VAR2CSA and GLURP) used and the areas of transmissions (stable or intermediate) of malaria.

Given the above, the dosage of immunoglobulins IgG against malaria is a biomarker not decisive in the biological monitoring of placental malaria in woman surrounded by taking into account the complexity of interpreting the results in relation to the diversity of vaccine candidates experienced.

Cell phenotyping of immunological effectors

The phénotypage cell immunological effectors is through the technique cytometer to flow. The principle of flow cytometer is increasingly refined today with the precise identification of a broad spectrum of markers of cell differentiation.

The profile of effector cells of immunity during MAP has been the subject of numerous publications. In fact, the accumulation of red blood cells parasitized by adhesion to the Chondroitin Sulphate A (CSA) of the placenta triggers an inflammatory response with accumulation of B lymphocytes (LB), natural killers (NK) and neutrophils (PN) at the level of the inter villous space [12, 13]. This profile varies according to the phases of the evolution of pregnancy (early pregnancy, growth and delivery) [18]. Ibitokou and al. observed an increase in CD 86+ B lymphocytes and monocytes monocytes strongly expressing the CD86 marker during PAG [18]. Indeed, monocytes and B cells are involved in the inflammation of the placenta during placental malaria [19, 20, 21]. The low rates of dendritic cells (DC) have been also observed in the MAP [22]. Although macrophages and NK are involved in the process of eliminating pathogens from the organism, their variation was not significant during MAP [18].

The cellular profile associated with MAP, which is mainly characterized by LB and monocytes, cannot be considered as biomarkers which determine placental malaria. Indeed, these cells are involved in the mechanism inflammation, but they do have effectors and not witnesses keys from the ignition placental responsible for the suffering fetal, loss of e weight and miscarriage.

The search for immunological mediators of placental malaria

The biomarkers sought must obey to a number of criteria to determine whether the indirect diagnosis of placental malaria. They must be identified or highlight a glycoprotein or a biological material belonging to the Plasmodium, should be involved directly participating in the mechanism the pathogenicity specific placental malaria. So, we will have to deal with either a biomarker or a group of biomarkers.

The work research has shown that some peripheral markers could predict placental infection at delivery independamment the presence of parasites circulating. Thus, biomarkers routine diagnostic as CRP, leptin, ferritin and biomarker diagnostic specialist as sFlt-1, C3a, C5a and angiopoietin 1.2 have been the subject of study to identify biomarkers witnesses placental malaria [11, 23]. Although these works have shown a correlation between these biomarkers and placental malaria, these biomarkers are not specific to placental malaria. They are also involved in other pathologies associated with pregnancy as the eclampsia, the anemia.

The exploration of cytokines as biomarkers of peripheral blood, the signature of placental malaria, is one of the lines of research to explore. Indeed, the soluble immunological mediators of local inflammation of the placenta can be identified in the peripheral circulation. Plasmodium by expression of the protein erythrocyte adheres to CSA resulting infiltration into space interveilleux immunological effectors. This inflammation causes an imbalance of the space interveilleux in disrupting trade foetomaternels causing and suffering, loss of weight and miscarriage. It is in this context that the proinflammatory cytokines IL-1, IL-6, IL-8, IL-12, TNF- α, IFN- γ and IL-10 have been the subject of several publications as key biomarkers of placental malaria [24, 25]. However, not all of these cytokines correlate with the presence of plasmodium in the placenta [26]. High concentrations of IFN-γ and low concentrations of IL-12, IL6 have been associated with the consequences of placental malaria [24, 27, 26, 28]. IL-10 was significantly associated with placental malaria by comparing positive and negative placental malaria subjects in a study carried out during childbirth in Tanzania [1 1, 27, 29]. Pamela and al. have demonstrated the effect cytotoxique of TNF-α in the process of inflammation in mice, raising the effects beneficial to the placenta when it is blocked by specific antibodies [30].

In view of the above, and in order to refine the range of key biomarkers which are the signature of placental malaria, IL-10, IFN- γ and TNF-α can be considered as determining biomarkers. However, studies specific additional be conducted to document this assertion.

2. Conclusion

The biological diagnosis of placental malaria is a question that remains relevant today. It will improve the prevention (followed by TPI), therapeutic evaluation (resistance parasite) and the rates of births manageds. PCR and the ELISA remains diagnostic tools of choice, but it is essential to refine the number of biomarkers key placental malaria at the peripheral level through research.

Conflict of interest: authors declare there is no conflict of interest.

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