Complement activation in primiparous women from a malaria endemic area is associated with reduced birthweight

A. Khattab, a,*, P.G. Kremsner, b, c, S. Meri, d

a Infection Biology Program, Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Haartmaninkatu 3, P.O. Box 21, 00014 Helsinki, Finland
b Institute for Tropical Medicine, University of Tübingen, Tübingen, Germany
c Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon
d Helsinki University Central Hospital, Helsinki, Finland

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Abstract
The hallmark of placental malaria (PM) due to Plasmodium falciparum infection is the accumulation of mature-stage parasites, monocytes and macrophages in the maternal vascular bed of the placenta. The mechanisms leading to morbidity and mortality in PM are incompletely understood. However, an inflammatory response in the placenta has been related to both severe anemia in the mother and low birthweight (<2500 g) in the newborn. In this study we analyzed whether complement activation as a mediator of inflammation could contribute to poor pregnancy outcome in PM. The concentrations of the soluble terminal complement complex (TCC) were measured as an indicator of complement activation in placental, cord and peripheral blood samples from 146 women from a malaria endemic area. Placental and cord plasma samples of primiparous women, a group vulnerable to PM, showed significantly higher levels of TCC than multiparous women. Additionally, in women with malaria history during pregnancy or placental infection by P. falciparum at delivery, the TCC levels in the corresponding placental and cord plasma samples were significantly higher than in the malaria negative group. In multiple regression analysis parity was shown to be the main determinant of TCC levels. Placental plasma samples corresponding to babies weighing less than 2700 g had significantly higher levels of TCC than babies carrying more weight. In conclusion, both primiparity and P. falciparum infection were related to a local increase of complement activation in the placentas. Association between reduced birthweight and higher levels of TCC in placental blood suggests a role for complement activation in influencing the pregnancy outcome in malaria exposed women.

1. Introduction

Adults living in malaria endemic areas have normally been exposed to repeated infections with Plasmodium falciparum and are, therefore, clinically immune to the disease [1]. However, this is not true in the case of pregnant women who can suffer from serious disease despite apparent immunity. The disease, known as placental malaria (PM), is more pronounced in primiparous women than in multiparous women [2]. The severity of placental malaria is attributed mainly to the lack of antibodies against a particular protein (var2CSA) from the multicopy variant antigens, PfEMP1s, encoded by the var gene family [3]. These variant antigens are expressed on the surface of P. falciparum-infected erythrocytes (IEs) and mediate cytoadherence to endothelial cell receptors such as CD36 and ICAM-1 [4]. Cytoadherence of IEs in the microvasculature can lead to tissue damage and organ dysfunction thereby contributing to the pathology of malaria [5]. In pregnant women, the placenta provides a new niche for the selective cytoadhesion of IEs. The IEs bind via var2CSA to chondroitin sulfate A, a glycosaminoglycan, expressed on the surface of the syncytiotrophoblast layer lining the placental chorionic villi [3,6]. Since var2CSA is an unusually conserved protein among other PfEMP1s [7], immunity to PM is acquired relatively soon and one or two pregnancies in malaria endemic areas are generally enough to confer protection [8]. Cytoadhesion properties of IEs displaying var2CSA explain the accumulation of IEs in the maternal vascular area of P. falciparum-infected placentas in primiparous women [9]. The infected erythrocytes and consequent inflammation could lead to the recruitment of monocytes and macrophages into the placenta during infection [10]. The resulting possible outcomes of PM are maternal anemia,
abortion, stillbirth, prematurity, intrauterine growth retardation and low birthweight (LBW). LBW is the greatest risk factor for death during the first month of life [11]. With up to 125 million pregnancies at risk of malaria infection every year [12] there is an urgent need for a better understanding of the pathophysiological mechanisms leading to poor outcomes associated with PM.

Increased complement activation has been identified in non-infectious pathological pregnancies [13], as well as in malaria in general [14]. The complement system is a specific effector arm of the humoral immunity. It plays a key role in destroying foreign invaders and in the clean-up of endogenous waste products. The complement system can be activated by antibodies binding C1q in the classical pathway or by mannann binding lectin or ficolins to sugar residues on the target surface in the lectin pathway. The alternative pathway is spontaneously activated by binding of C3b to foreign surfaces. Activation results in the assembly of C3-cleaving enzymes (C3 convertases) on target surfaces. Amplification via the alternative pathway leads to more C3b deposition on the target. The terminal pathway is activated when C3b forms a complex with the C3-convertases and generates C5-convertases that can cleave C5, thereby yielding one anaphylatoxin C5a and one C5b molecule. Association of C5b with C6, C7, C8, and multiple C9 molecules ultimately leads to the generation of C5b-9, also known as the membrane attack complex (MAC). However, much of the C5b generated does not result in the formation of MAC, but is diverted by control proteins (e.g. clusterin and S protein) to form a soluble, lytically inert complex called soluble C5b-9. C5b-9 is referred to commonly as Terminal Complement Complex or TCC [15]. Despite the strong cytolytic activity of complement many microbes including the malaria parasite, are able to escape complement attack. Complement can attack microbes or human cells that are marked with antibodies or have an activating altered cell surface. Paternal alloantigens in the fetoplacental unit can trigger antibody production by the maternal immune system [16]. Antibodies could thus activate complement in the placental compartment through immune complex formation. However, the placental cells are usually protected by a panel of complement regulators expressed by the fetal cytotrophoblast cells and by the syncytiotrophoblast. In healthy pregnancies, these regulators such as CR1 (CD35), DAF (CD55), MCP (CD46) and protectin (CD59) down regulate complement activation and protect the placenta from complement-mediated damage [17]. In addition, the soluble complement inhibitors, factor H (FH) and C4b binding protein (C4bp) can keep complement activation under control in the fluid phase and to some extent on surfaces, as well. In certain pathological situations, pregnancy complications might occur. Particularly in preeclampsia and in antiphospholipid syndrome, complement activation is believed to contribute to the pathogenetic processes [13,18]. In PM, the IEs bind to the syncytiotrophoblasts of the placenta [6]. The bound IEs display parasite antigens on their surfaces. These could thus be targets for maternal antibodies and activate the complement system [19]. Merozoite egress from an infected erythrocyte is accompanied by the release of Plasmodium proteins (e.g. GPI-anchored proteins) and toxins (e.g. hemozoin – a Plasmodium-generated hemoglobin degradation product) into the placental intervillus space. These could either directly or via immune complex formation also lead to complement activation. Collectively, the above considerations have led us to suspect that complement activation in the placenta in connection with P. falciparum infection could lead to a poor pregnancy outcome in PM.

The complement C3a and C5a anaphylatoxins and the soluble TCC are widely used markers for complement activation. Their use singly or in combination with each other depends largely on the questions and conditions of the measurements. It is important to note that C3a and C5a, in particular, bind actively to specific cell receptors upon their generation. Therefore, the concentration of C3a rapidly decreases over time and C5a cannot be measured from clinical samples [20]. On the other hand, the soluble TCC generated from complement activation remains in its measurable free form at a steady concentration for a longer period of time [20]. Thus, in the present study the level of complement activation was estimated by measuring the concentration of the soluble TCC in placental, peripheral and cord plasma samples collected from pregnant women at delivery from a malaria endemic area. TCC levels were then analyzed with respect to PM manifestations and outcomes.

2. Materials and methods

2.1. Study participants

The study cohort has been described elsewhere in an earlier study [21]. Briefly, one hundred and fifty women, who presented at the maternity ward of the Albert Schweitzer Hospital in Lambaré, Gabon for delivery between May and October 2002, were recruited in the study. Malaria in the region is hyperendemic and perennially transmitted, and the disease is predominantly due to P. falciparum [22]. Whenever possible, demographic data (e.g. ethnic group, date of birth, weight) were collected from the study participants upon admission. At delivery, data regarding characteristics of the newborn baby (vital status at birth, birthweight, sex and the presence of twins) were collected. For those attending prenatal care, information regarding malaria infections during the course of pregnancy was obtained from the maternity record book, which documented peripheral parasitemia by thick blood smears (TBS). Written informed consents were obtained from all of the women and the study was approved by the ethics committee of the International Foundation of the hospital. A more detailed summary of the study cohort characteristics, that was not shown in the earlier study describing the cohort [21], is shown in Table 1.

2.2. Blood samples

Peripheral blood was collected from the study participants within 1 h after delivery in an EDTA-containing monovette. Blood was also extracted directly from the placenta. This was done by making several 1-cm deep incisions into the maternal side of the placenta and the flowing blood was drawn into an EDTA syringe (monovette without needle). Cord blood was collected immediately after placental expulsion following delivery. This was done by drawing venous blood into an EDTA-containing monovette via puncture of the ethanol-sterilized umbilical vein at a site distal to the placenta, to minimize the possibility of cross-contamination of maternal and cord blood. Blood samples collected from the three different compartments were used for preparing TBS to detect the presence of malaria parasites and to determine parasite densities using a previously described method [23]. EDTA-plasma samples were obtained from the withdrawn blood by centrifugation and preserved at -70 °C until further use.

2.3. Sandwich ELISA for the determination of the fluid-phase TCC in peripheral, placental and cord plasma

For the TCC ELISA, 96-well microtiter plates (Maxisorp NUNC, Thermo Scientific) were coated with the anti-C9 neoepitope Ab WU13-15 (5 

### Table 1 Characteristics of the study group.

<table>
<thead>
<tr>
<th>Age mean years, (SD)</th>
<th>All women (n = 150)</th>
<th>Primiparous women (n = 45)</th>
<th>Multiparous women (n = 105)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental TBS at delivery,</td>
<td>21 (14)</td>
<td>9 (20)</td>
<td>12 (11.4)</td>
<td>0.16d</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>55 (37)</td>
<td>23 (51)</td>
<td>32 (30.4)</td>
<td>0.016d</td>
</tr>
<tr>
<td>Mean g/dl, (SD)</td>
<td>11.03 (1.99)</td>
<td>11.23 (2.37)</td>
<td>10.94 (1.80)</td>
<td>0.46d</td>
</tr>
<tr>
<td>Anemic women, n (%)</td>
<td>71 (47)</td>
<td>19 (42.2)</td>
<td>52 (49.5)</td>
<td>0.37d</td>
</tr>
<tr>
<td>Birthweight:</td>
<td>16 (10.6)</td>
<td>8 (17.7)</td>
<td>8 (7.6)</td>
<td>0.065d</td>
</tr>
<tr>
<td>≤2700 g, n (%)</td>
<td>32</td>
<td>14 (31.1)</td>
<td>18 (17.1)</td>
<td>0.056d</td>
</tr>
</tbody>
</table>

*Indicates significant value.  
| a | Standard deviation.  
| b | Wilcoxon rank-sum test.  
| c | extracted from maternity record book.  
| d | Pearson χ² test.
the incubation, antibody coating buffer was removed, and free binding sites on the wells were blocked with 200 μl 15% BSA (Sigma–Aldrich, Steinheim, Germany) in PBS during incubation for 2 h at room temperature. Microtiter plates were then washed three times with PBS containing 0.05% Tween 20 (PBS-T). The plasma samples (100 μl diluted 1:20 in PBS-T) were added, the plates were incubated for 2 h at 4 °C, washed five times, and incubated for 1 h at room temperature with 1:1000 diluted goat anti-C7 antibody (Organon Teknika, West Chester, PA). After five washes, HRP-conjugated donkey anti-goat IgG antibody (1:3000; Jackson ImmunoResearch, West Grove, PA) in PBS-T was incubated for 1 h at room temperature, followed by five washes and the addition of HRP substrate (OPD; DAKO, Glostrup, Denmark). The reaction was stopped with 100 μl 0.5 M H2SO4, and absorbances detected at 490 nm. Arbitrary units (AU/ml) were calculated using a standard curve obtained by activating normal human serum with Zymosan A (Sigma–Aldrich; 1 mg/ml, 60 min at 37 °C). The TCC concentration in the undiluted standard was defined as 1000 AU/ml.

2.4. Statistical analysis

The data analyses were performed using the JMP (SAS) statistical software. For comparing differences between proportions, the Pearson χ² test was employed, and the Odds Ratio (OR) and the 95% confidence intervals (CI) for each comparison were also calculated. Groupwise medians were compared for significant differences between two groups by the Wilcoxon rank-sum test. SEM is used to describe the variability of means. Multiple linear regression analysis models were used to estimate the association of TCC levels, entered into the models as a continuous response variable, with parity and malaria infection, entered into the models as nominal predictor variables. p values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population

The total number of women who gave their consent to participate in the study was 150. From them 142 peripheral, 146 cord and 142 placental plasma samples were available for the measurement of TCC levels. In our study cohort the primiparous women were significantly more often infected with P. falciparum than multiparous women (OR 2.38, 95% CI 1.16–4.88, P = 0.016). Moreover, babies born to women with a history of malaria during pregnancy or with TBS positive placenta tended to be in the LBW (<2500 g) category more often than those born to non-infected women (OR 3.3, 95% CI 1.02–11.01, P = 0.023). A similar trend, albeit not a significant one, was also obtained for the effect of parity on the pregnancy outcome (LBW): in our study cohort primiparous women tended to deliver babies in the LBW category more often than multiparous women (OR 2.62, 95% CI 0.82–8.41, P = 0.065).

3.2. TCC levels in peripheral, placental and cord plasma

Since, PM is presented by poor pregnancy outcomes we wanted to examine whether excessive complement activation in the placenta could contribute to PM complications. Here, the TCC levels were measured in plasma samples from three different compartments, the placental, cord and the peripheral blood from women attending the maternity ward at Albert Schweitzer hospital for delivery. The mean value of the measured TCC levels was highest in the peripheral blood plasma samples (10.1 ± 0.44 AU/ml) followed by placental samples (6.9 ± 0.44 AU/ml) and the cord samples (1.5 ± 0.23 AU/ml). These levels were significantly different between all possible pairs of compartments data (Wilcoxon, p < 0.0001). TCC levels in peripheral, placental and cord plasma samples showed no correlation between each other (data not shown).

3.3. Influence of parity on TCC levels

PM in stable malaria transmission areas affects mainly women in their first pregnancies. In the following pregnancies, PM incidence declines [2]. This is reflected as a lower morbidity and mortality in the mothers and their babies and as a smaller placental infection rate [2]. Therefore, parity is an important parameter to consider when evaluating the levels of complement activation in PM. In the current study cohort, parity had a significant influence on the levels of TCC in the placental and cord plasma samples. TCC levels were significantly higher in the placental (Fig. 1A, Wilcoxon, p = 0.02) and cord (Fig. 1B, Wilcoxon, p = 0.03) plasma samples of primiparous women than in those of the multiparous women. However, peripheral plasma samples did not show any significant difference between the two groups.

3.4. Influence of malaria infection on TCC levels

Parasite sequestration in the placenta of P. falciparum infected pregnant women could lead to complement activation and increase in the TCC level. Therefore, the whole data set from each compartment was stratified into malaria parasite-positive and malaria parasite-negative groups and analyzed statistically. The malaria parasite-positive group is created by adding the malaria infection at delivery to the recorded past infection cases to exclude any possible contribution of submicroscopic chronic infection from the latter group to the measured TCC levels in the malaria parasite-negative group. To warrant validity of this grouping TCC levels of the two groups were compared statistically and found to be similar i.e. no significant difference between TCC levels in the two groups in placental (Wilcoxon, p = 0.9), cord (Wilcoxon, 0.8) and peripheral (Wilcoxon, p = 0.5) plasma samples. As expected, placental plasma samples of women with placental infection or malaria history had significantly higher levels of TCC (Fig. 2A, Wilcoxon,
p = 0.03) than women with no records of malaria at delivery or during pregnancy. Additionally, cord plasma samples matched with women with infected placenta or history of malaria during pregnancy had significantly higher TCC levels than those matched with the counter group (Fig. 2B, Wilcoxon, p = 0.01). However, once again peripheral plasma TCC levels failed to show any significant difference between the two groups. So far high TCC levels were found to be significantly associated with both primiparous women and malaria infection. However, these two variables were also shown to be associated with each other (OR 2.38, 95% CI 1.16–4.88, P = 0.016). Therefore, multiple linear regression models have been used to estimate which of these two variables could significantly predict TCC levels. The multiple regression fitting models suggested that only parity can significantly predict TCC levels after adjusting for parity and malaria for both placental (F = 4.35, p = 0.039) and cord (F = 5.71, p = 0.018) plasma.

3.5. TCC levels and birthweight

One profound manifestation of PM is the induction of premature delivery or delivery of full term LBW babies. The pathophysiology leading to these conditions is not yet fully understood. Most newborns weigh 2700–4000 g with the average weight being about 3400 g. Newborns who weigh below 2500 g are classified as LBW babies. The study cohort included 16 babies with a birthweight of less than 2500 g at delivery. The TCC levels of the LBW group (<2500 g, n = 16) were compared with those of the rest of the cohort. Data from the three compartments (periphery, placenta and cord) showed no significant differences between the two groups (data not shown). As the number of samples in the LBW group was small we also studied babies weighing <2700 g (<25% percentile, n = 32). Placental plasma samples from births of babies with a birthweight <2700 g (n = 32) had significantly higher levels of TCC than those of the normal BW babies (Fig. 3A, Wilcoxon, p = 0.007). Yet again, the levels of TCC in the peripheral (Table 2, Wilcoxon, p = 0.11) and cord plasma samples (Fig. 3B, Wilcoxon, p = 0.11) did not show any significant differences between the low and normal baby weight groups. Additionally, when the non-stratified data was used to examine for a correlation between birthweight, as a continuous variable, and TCC levels, weak negative correlations were observed between birthweight and both placental and cord TCC levels, r = −0.2, p = 0.013 and r = −0.2, p = 0.015, respectively. Altogether, these findings suggest that complement activation could be related to the delivery of smaller babies in malaria endemic areas.

4. Discussion

Complement activation in the placenta could be one of the mechanisms that lead to poor pregnancy outcome in pregnancy associated diseases. In the current study, the levels of complement activated by infection were significantly higher in the infected women than in the non-infected women. P. falciparum-malaria infection was defined as thick blood smear positive placental blood or malaria during pregnancy documented in the maternity record book. The top, bottom and line through the middle of the box correspond to the 75th, 25th, and 50th percentile, respectively. Statistical significances of the differences between the groups were calculated by the Wilcoxon rank-sum test.
activation were measured in placental, peripheral and cord plasma samples collected from pregnant women at delivery in a malaria endemic area. Moderate levels of TCC in the placental plasma samples, relative to the slightly higher levels of TCC in the peripheral plasma samples, were detected. This could be explained by the fact that complement activation is more controlled in the placenta than in the periphery. It is worth mentioning that the higher levels of TCC in the maternal peripheral plasma samples did not show any significant differences between the investigated groups as opposed to what was seen with the placental and cord plasma samples. This suggests that TCC levels in the peripheral plasma samples do not completely reflect the actual TCC levels in the placenta produced in response to the sequestered parasites despite the fact that the placental blood space is connected with the peripheral blood circulation. This phenomenon could be explained by the continuous activation of complement in the placenta due to parasite sequestration in active infections, combined with the slower blood flow and delayed clearance from the intervillous spaces. Thus, the local variations in the levels of TCC would reflect the pathological changes in the placenta. Thereby, the contribution of the placental TCC levels that result from placental malaria infection to the peripheral blood TCC levels could be minimal when intervillous blood is mixed with peripheral blood. Significant differences between levels of certain hormones [24] and cytokines [25] in placental and peripheral blood were also previously reported. A similar scenario could also be proposed for past infection cases in which any uncleared placental infection or placental damage could remain as a source for continuing complement activation.

On the other hand, the much lower TCC levels detected in the cord samples could be explained by the immaturity of the complement system in the fetus. For example, the concentrations of C8 and C9 in full-neonates are in the range of 10–25% of the levels in adults [26]. However, despite these very low levels of TCC in cord plasma, stratification of the TCC levels according to either parity or malaria status showed significant differences between groups. Since there were no parasites detected in all cord blood samples tested by TBS in our study cohort, the most probable explanation for this finding is immune complexes transfer from the maternal to the fetal circulation that would lead to complement activation in the fetal blood. Antibody-dependent transplacental transfer of a malaria blood-stage antigen in the form of immune complexes has been reported previously in PM [27].

PM complications are more serious in primiparous than multiparous women in malaria endemic areas [8]. Our study has shown that placental plasma samples of primiparous women had significantly higher levels of TCC than those of multiparous women. This could be simply explained by the higher susceptibility of primiparous women in malaria endemic areas to malaria infection than of multiparous women. In fact, primiparous women in our study cohort were more likely to have malaria than multiparous women (OR 2.38, 95% CI 1.16–4.88, P = 0.016). In addition, we have shown that pregnant women with TBS positive placenta at delivery or TBS positive peripheral blood during pregnancy presented a significantly higher level of complement activation (TCC) in placental samples than women without evidence for malaria. However, when the above-mentioned arguments for explaining the higher levels of TCC in primiparous women were statistically evaluated by multiple regression models, parity had unexpectedly a stronger prediction power for TCC than malaria infection. This indicates that the TCC levels had stronger association with parity than malaria infection but does not preclude the role of malaria infection in increasing the levels of complement activation. It could also point out to some other unknown conditions associated with primiparous women and have contributed to complement activation.

The most interesting finding in our study was that placental plasma samples from deliveries of babies with smaller birthweight (<2700 g) had significantly higher levels of TCC than those corresponding to normal weight babies. This finding suggests that complement activation in the placenta could play a role in the pathogenesis of PM. It is worth pointing out that malaria might not entirely account for this finding as there was no significant difference between TCC levels in malaria negative and malaria positive groups in the <2700 g birthweight category (Wilcoxon, p = 0.63, data not shown). This is in addition to the results from the multiple regression models pointing to a stronger role of parity than malaria infection in increasing TCC levels. However, increasing the number of cases in a future study cohort and the detection of the malaria infection status by PCR and histological section of the placenta at delivery should address the role of other factors in this association and overcome the limitations of our study.

A similar role of the involvement of complement activation in inducing fetal growth restriction was previously suggested in preeclampsia, another pregnancy-related disease that is more profound in primiparous women. It has been shown that preeclamptic patients with intrauterine growth retardation (IUGR) had significantly higher plasma TCC levels than those without IUGR [28]. Since preeclampsia was not an exclusion criterion in our study it is possible that preeclampsia could have contributed to the increased levels of TCC in placental plasmas of primiparous women. This argument could also explain why primiparity rather than malaria infection was the main determinant of the TCC levels when both were entered in the logistic regression analysis models as predictor variables.

In PM, there is a massive sequestration and cytodestruction of parasitized red blood cells to the placental syncytiotrophoblast [2] and this was shown earlier to be accompanied by C3b deposition in the placenta as consequence of complement activation [29]. Parasite sequestration is usually accompanied by massive monocyte and macrophage infiltrations into the placental intervillous spaces [10]. An association between monocytes, macrophages and their secreted products with LBW was previously reported in PM [30–34]. In line with the current study, the latter observation could be explained by the possibility that sequestered parasites in the placenta could activate complement and the resulting anaphylatoxins C3a and C5a (complement activation split products) would then activate and recruit more monocytes and macrophages to a newly formed inflammation site. The consequences of these events are the secretion of abnormal levels of proinflammatory cytokines that can lead to impairment of vascular angiogenesis and inhibition of trophoblast invasion of the decidua resulting in IUGR. In fact, overproduction of TNF-α [25,33,34], IFN-γ [34] and IL-8 [33] has been previously related to LBW in PM. Also, C5a release caused by the activation of complement by P. falciparum parasite material was shown to induce an amplified inflammatory (ex. IL-6 and TNF-α) and anti-angiogenic response (sFlt-1) by primary human monocytes, in-vitro [35]. In the same study [35], C5a concentration was shown to be significantly higher in placental plasma samples of primiparous women with PM than in those without PM confirming.
our finding on PM cases showing higher levels of complement activation. Interestingly, a recent study performed in a malaria mouse model has shown that C5a could be generated independent of the known pathways of complement activation that converge at the C3 step [36]. The latter finding suggests that generation of C5a can proceed via two different mechanisms in malaria infected individuals and this possibly can result in a much higher levels of C5a causing more inflammatory responses to the disease. Furthermore, in an experimental malaria infection, blocking of C5a or the C5a receptor (C5AR) by antibodies protected mice form cerebral malaria [37] suggesting that blocking complement activation at the terminal pathway level could protect from disease severity. Additionally, a mutation in MASP2, a component of the lectin pathway of complement activation, that could eventually lead to a reduced level of C5a showed a trend towards protection from LBW in PM [38].

In conclusion, the current study shows an association between complement activation and poor fetal outcome in PM. This finding suggests a role for complement activation as one of the underlying mechanisms. Parasite-mediated complement activation could release the anaphylotoxins C3a and C5a that would recruit and activate monocytes and other inflammatory cells in the placenta. The consequences of these events are the secretion of abnormal levels of proinflammatory cytokines that can lead to impairment in vascular angiogenesis and inhibition of trophoblast invasion of the decidua resulting in intrauterine retardation [39].

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