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Profiles of Some Pro-Inflammatory Cytokines in Pregnant Women with Plasmodium Falciparum Malaria Infection at University of Port Harcourt Teaching Hospital and aluu Health Care Centre, Rivers State

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Abstract **Original Research Article**

Malaria in pregnancy can lead to complications for both mother and child. Pro-inflammatory cytokines like interferon gamma (IFN-ɤ), tumor necrosis factor-∝ (TNF-∝) and interleukin 18 (IL-18) are produced by macrophages that are stimulated in response to the Plasmodium falciparum infection. The study was done to estimate profiles of the above pro-inflammatory cytokine's profiles in pregnant women with Plasmodium falciparum malaria infection in University of Port Harcourt Teaching Hospital and Aluu Health Care Centre. Peripheral blood samples were collected from 115 volunteers who gave their consent- 60 infected women and 55 healthy uninfected women. The samples were analyzed using the enzyme linked immunosorbent assay for cytokines evaluation. Increased serum concentration of TNF-∝ and IL-18 were observed in infected women compared to their uninfected counterparts and the difference in the mean values between the two groups was statistically significant (P<0.05). Conversely, IFN-ɤ and PCV levels were lower in pregnant women with malaria than those without malaria. The difference however was not statistically significant (P>0.05). IL-18 and TNF-∝ concentrations differed according to trimesters and the differences in the means values for the two cytokines were statistically significant (P<0.05). PCV and IFN-ɤ levels did not differ significantly from the 1st to the 3rd trimester. Increased concentrations of TNF-∝ and IFN-ɤ were observed in the multigravids when compared to primigravids and this difference was statistically significant (P<0.05). The mean birth weight of neonates delivered by infected mothers was observed to be lower than that of uninfected mothers and the difference in the mean weights of the two groups was significant (P<0.05). There was no significant difference in the mean birth weights of neonates born by mothers in the 1st, 2nd and 3rd parity groupings. A negative correlation was observed between IFN-ɤ, birth weight and PCV in malaria positive mothers. A negative correlation existed between other cytokines studied (IL-18 and TNF-∝), PCV and birth weight in both infected and uninfected mothers. Parasite density in infected mothers showed a negative correlation with the three cytokines – IFN-ɤ, IL-18 and TNF-∝. Parasite density was higher in the primigravids than the multigravidas and the difference in the mean values between the groups was statistically significant (P<0.05). It is concluded that the elevated levels of TNF-∝ and IL-18 in these infected women indicate that these cytokines are vital mediators of immune response to systemic Plasmodium falciparum malaria in our environment.

Keywords: Pro-inflammatory, Inflammatory, Cytokines, Plasmodium Falciparum, malaria.

INTRODUCTION

Malaria is a parasitic infection caused by protozoa of the genus Plasmodium and transmitted via the bite of a female mosquito of the anopheles spp. Malaria infection in pregnant mothers has resulted in increased mortality especially in endemic areas like the sub-Saharan Africa, with thousands of infants dying because their mothers had malaria infection during pregnancy (Steketee *et al.*, 2001). This increased susceptibility can be attributed to changes in pregnancy-induced immune response, by hormonal factors (Rogerson, 2007) and the charm of pregnant women to the vector (Ansell, 2002). Additionally, Plasmodium falciparum-infected red blood cells in pregnant women bind to specific receptors, like chondrotin sulphate A (CSA) and adhere to the placenta (Serti, 2007).

Pregnant women are more vulnerable to malaria infection than their non-pregnant counterparts due to the immune changes associated with pregnancy, hormonal imbalance (Rogerson *et al.*, 2007) and by the charm of

pregnant women that lures the mosquitoes (Lindsay *et al.*, 2000). Pregnant women with P. falciparum infection have higher likelihood of being delivered of low-birth-weight infants (Kaushik *et al.*, 1992), while malaria in pregnancy contributes significantly to infant mortality (McGregor, 1984). There are reports of high infant mortality rate occurring annually in sub–Saharan Africa due to maternal infection with P. falciparum during pregnancy (Steketee *et al.*, 2001). The situation of high infant mortality rate among pregnant women with malaria disease is a common phenomenon in tropical countries, with the complications being pre-term deliveries and neonatal mortality (Goldenberg, 2002).

A blend of specific and non-specific immune response controls parasitaemia and reduces the parasite load in the circulation. In normal pregnancy, immune response of Th_2-type dominates, with the release of cytokines such as IL-10 and IL- 18, which is secreted by maternal leukocytes to limit inflammatory responses that are harmful to materno-fetal placental barrier (Lin *et al.*, 1993). In the contrary, during immune response to pathogens, Th_1-type immune response, such as TNF-α inflammatory cytokines are secreted predominantly. Insufficient amount of IL-10 to counter the excessive secretion of inflammatory cytokines against pathogens can contribute to factors related with pre-term deliveries (Baggia *et al.*, 1996). Likewise, P. falciparum parasites in the intervillous spaces of the placenta elicits the release of interferon gamma (IFN-ɤ) and tumor necrosis factor -α (TNF -α) (Fried *et al.*, 1998). Increased concentrations of TNF-α level have been reported in pregnant women with malaria, yet such women had full-term deliveries (Fievet *et al.*, 2001). Most epidemiological studies in malaria-endemic countries have shown that primigravidae are more susceptible to malaria than the rnultigravidae and complications associated with pregnancy outcome are more common in the primigravidae (Shulman & Dorman, 2003). Reports by the World Health Organization indicate that the disease is usually severe in children below 5 years old and pregnant women (WHO, 2013). Similarly many women living in malaria-endemic areas are exposed to the disease during pregnancy (Dellicor *et al.*, 2010). Annually, about 50 million women living in areas of malaria transmission become pregnant (Steketee *et al.*, 2001) and many of them succumb (Anya, 2004). Delivery of low birth weight (LBW) babies by infected mothers is a prominent complication and could be due to insufficient blood supply at the placenta, leading to intrauterine growth restriction (Beeson & Brown, 2002; Menendez *et al.*, 2000). Other complications of malaria in pregnancy include spontaneous abortions, stillbirth, prematurity and severe maternal disease, severe syndromes that include cerebral malaria, severe anemia and respiratory distress; all of which are both common and life-threatening (Nosten *et al.*, 2004).

METHODOLOGY

The patients for the study were selected by systematic randomization from the population of pregnant women attending antenatal clinic at the University of Port Harcourt Teaching Hospital (UPTH) and the University of Port Harcourt Teaching Hospital Primary Health Care Centre, Aluu by employing a cross-sectional study design. 5mls of blood were collected from pregnant women with malaria in their first, second and third trimesters, while uninfected pregnant women served as controls. The blood samples were collected into plain bottles which were spun at 450g for 15 minutes to collect serum for storage at – 20^{o}C until use. Also 2mls of blood were put into EDTA bottles for estimation of Packed Cell Volume (PCV). A drop of blood was used on slides to make a thick blood film for microscopy. Another drop of blood from the 5mls was immediately used for rapid diagnostic test for malaria parasites. The levels of the cytokines (IL – 18, IFN -ɤ and TNF – α) in the sera collected were estimated using commercial standard enzyme linked immunosorbent assay (ELISA) kits (Aviva systems Biology, USA).

$$\text{The parasite density} = \frac{\text{No of Parasite Count}}{\text{200 White Blood Cells}} \times 6000 = \text{No of parasite/ml of blood}$$

To determine the packed cell volume, blood from the ethyl diamine tetra acetic acid (EDTA) bottles was used to fill plain capillary tubes, the capillary tubes sealed at one end with sealant, placed in a hematocrit centrifuge and spun for 5 mins at 4,000rpm. Hematocrit reader is then used to read the outcome. The body weight of the newborn is taken immediately after delivery.

The formula below for continuous variables and for comparing two subject means was used: $N=\delta^2 [(Z_{(1-(a/2)} + Z_{(1-\beta))})^2] \div \Delta$

Where N= the desired sample size, δ= the assumed standard deviation from previous study by Nmorsi *et al.*, (2010), $Z_{(1-(a/2)}$= the standard normal deviation usually set at 1.96 which corresponds to 95% confidence interval, $Z_{(1-\beta)}$ = chosen power of sensitivity of the test, which is always given as 80% = 0.84 and A is the minimum detectable difference between subject means (Bamgboye, 2008). δ = 20.9, Δ = 29.4

Therefore, $N = 20.9^2 (1.94+0.84)^2 \div 29.4 = 114.8$ **= 115**

Ethical approval for this study was obtained from the ethical committee of the University of Port Harcourt Teaching Hospital and the University of Port Harcourt.

RESULTS

Table 1: Mean PCV and cytokine concentrations in subjects.

Parameters	P+	P-	T-test (p-value)
PCV (%)	33.88±1.64	34.72±2.86	-1.988 (0.049)*
IFN-γ (pg/ml)	21.11±8.40	22.35±15.19	-0.519 (-0.519)
IL-18 (pg/ml)	246.21±39.51	87.74±83.62	2.788 (0.007)*
TNF-α (pg/ml)	88.45±60.01	70.40±27.72	1.972 (0.05)*

PCV= Packed Cell Volume, IFN-γ = Interferon gamma, IL-18 = Interleukin 18, TNF-α = Tumour Necrotic Factor alpha, P^+=Malaria positive, P^-=Malaria negative

***Difference between both groups is statistically significant (p < 0.05)**

The above reveals that patients with malaria had a mean PCV of 33.88 ± 1.64 while the uninfected group had a mean of 34.72 ± 2.86. Similarly, the mean values for IL-18 and TNF-α in the infected patients were 246.21± 39.51 and 88.45± 60.01 respectively while those of women without malaria were 87.74± 83.62 and 70.40± 27.72 respectively. The difference for all the groups was statistically significant (p<0.05). However, the mean values for IFN-ɤ were 21.11± 8.40 for infected group and 22.35 ± 15.19 for uninfected group. The difference in the mean value was not statistically significant (p>0.05)

Table 2: PCV and Cytokine concentration according to gestational age

Parameters	1st Trimester	2nd Trimester	3rd Trimester	ANOVA (p value)
PCV (%)	34.67±2.69	34.44±2.27	34.19±2.62	0.808
IFN-γ (pg/ml)	17.38±5.66	20.70±6.45	24.06±16.91	0.221
IL-18 (pg/ml)	390.11±84.13	150.49±18.50	119.66±114.36	0.02*
TNF-α (pg/ml)	114.32±108.91	75.26±40.27	75.08±26.88	0.044*

PCV= Packed Cell Volume, IFN-γ = Interferon gamma, IL-18 = Interleukin 18, TNF-α = Tumour Necrotic Factor alpha, All values are reported in mean ± SD.

***Difference between both groups is statistically significant (p < 0.05)**

Values of PCV for mothers in the different trimesters were 34.67 ± 2.69, 34.44 ± 2.27 and 34.19 ± 2.62 for 1st, 2nd and 3rd trimesters respectively, while the IFN-ɤ levels were 17.38 ± 5.66, 20.70 ± 6.45 and 24.06 ± 16.91 for the 1st, 2nd and 3rd trimesters respectively. The differences in the mean for both groups were not statistically significant (p>0.05). The mean concentrations for IFN-ɤ in the 1st, 2nd and 3rd trimesters were 17.38 ± 5.66, 20.70 ± 6.45 and 24.06 ± 16.91 respectively. The difference in the means for the groups was also not statistically significant. On the contrary the mean levels of IL-18 and TNF-α for the 1st trimester were 390.11 ± 84.13 and 114.32 ± 108.91 respectively, 2nd trimester was 150.49 ± 18.50 for IL-18 and 75.26 ± 40.27 for TNF-α, while in the 3rd trimester the values were 119.66 ± 114.36 and 75.08 ± 26.88 for IL-18 and TNF-α αrespectively. The differences in the means for these cytokines were statistically significant (p<0.05).

Table 3: Mean maternal PCV and cytokine levels by parity

Parameters	Parity			ANOVA (p-value)
	1	2	3	
PCV (%)	34.40±2.64	34.44±2.03	33.62±2.13	0.68
TNF-α (pg/ml)	77.93±39.35	69.14±20.23	119.86±115.40	0.016*
IFN-γ (pg/ml)	19.25±7.40	24.45±11.72	34.01±33.57	0.002*
IL-18 (pg/ml)	145.14±17.17	187.56±44.67	130.18±84.83	0.738

PCV= Packed Cell Volume, IFN-γ = Interferon gamma, IL-18 = Interleukin 18, TNF-α = Tumour Necrotic Factor alpha, all values are reported in mean ± SD, *Difference between both groups is statistically significant (p < 0.05)

Table 3 above of the maternal PCV and cytokine levels in primigravidae (1st) and multigravidae (2nd and 3rd) reveals that the PCV levels for the primigravidae group was 34.40 ± 2.64, para- I (2nd timers) was 34.44 ± 2.03 and para- II (3rd timers) was 33.62 ± 21.3. The difference in the means between the groups was not statistically significant (p>0.05). The difference in the mean values of IL-18 in the different groups was not statistically significant (p>0.05). In the primi group the level was 145.14 ± 17.76 while the levels were 187.56 ± 44.67 and 130.18 ± 84.83for the para1 and II groups respectively. The levels of IFN-ɤ and TNF-α for the primigravid group were 19.25 ± 7.40 and 77.93 ± 39.35, while for the second time mothers the cytokine levels were 24.45 ± 11.72 and 69.14 ± 20.23 respectively and the 3rd time mothers had levels of 34.0 ± 33.57((IFN-ɤ) and 119.86 ± 115.40 (TNF-α). However, the differences in the mean values of IFN-ɤ

and TNF-α for the three groups were statistically significant.

Table 4: Mean child birth weight according to malaria status

Parameters	Descriptive characteristics		
	Maternal malaria status	Mean ± S. D	T-test (p-value)
CHILD WEIGHT (kg)	P+	3.29±0.20	-4.715 (<0.0001) *
	P-	3.57±0.42	

P^+=Malaria positive, P^-=Malaria negative * Difference between both groups is statistically significant ($p<0.05$)

Table 4 is a comparison of the birth weights of neonates of the infected and uninfected mothers, with the mean child weight from infected mothers as 3.29 ± 0.20 and for uninfected mothers as 3.57 ± 0.42. The difference in the mean values was statistically significant.

Table 5: Birth weight of child and Parity of mother

Parameter	Parity	Mean ± S. D	P-Value
Child Weight (kg)	1st	3.49±0.36	0.258
	2nd	3.36±0.36	
	3rd	3.45±0.45	

The mean birth weight recorded for neonates of 1st parity mothers was 3.49± 0.36kg, that for 2nd parity mothers was 3.36±0.36kg and the neonates of 3rd parity mothers had mean weight of 3.45±0. 45kg.There was no significant difference ($p>0.05$) in the birth weights across the groups.

Table 6: Correlation of maternal cytokine levels, PCV and child weight

Cytokines	Malaria negative mothers		Malaria positive mothers	
	Child weight (kg)	Maternal PCV (%)	Child weight (kg)	Maternal PCV (%)
IFN-γ (r)	-0.1417	-0.0393	-0.3924*	-0.2790*
1L-18 (r)	0.1387	-0.0194	0.1511	0.1214
TNF-α (r)	0.016	0.0182	0.0602	-0.0185

IFN-γ = Interferon gamma, IL-18 = Interleukin 18, TNF-α = Tumour Necrotic Factor alpha, *Correlation (r) is statistically significant ($p<0.05$)

Table 6 is the correlation of the child weight, maternal PCV and cytokine concentration showing a negative correlation between IFN-γ, child weight (r = -0.1417) and maternal PCV (r=-0.0393) in malaria negative mothers, while there were significant ($p < 0.05$) negative correlation between IFN-γ, child weight (r=-0.3924) and maternal PCV (r=-0.2790) in malaria positive mothers.

Table 7 Correlation of parasite density and cytokine concentration in malaria positive mothers

ρ vs	Pearson's (r)
IFN-γ	-0.0359
IL-18	-0.0359
TNF-α	-0.0359

ρ: parasite density

Table 7 indicates negative correlations between the cytokines IFN- (r = 0.0013), IL-18 (r = 0.0013), TNF- (r = 0.0013) and parasite density in malaria positive mothers.

Table 8: Correlation of parasite density, PCV level and child weight in malaria positive mothers

ρ vs	Pearson's (r)
Birth weight	-0.0952
PCV	-0.2919*

ρ– parasite density *Correlation is statistically significant ($p < 0.05$)

Table 8 above shows a negative correlation between parasite density and birth weight (r = 0.0952), with a significant negative correlation between parasite density and PCV (r = -0.2919) in malaria positive mothers.

DISCUSSION

In this study, the PCV in mothers with P. falciparum malaria was lower than in uninfected mothers, while the difference in the mean values between the infected and uninfected groups was statistically significant. This finding agrees with earlier studies by Grania *et al.,* (1998) which also reported a higher PCV in uninfected mothers and concluded that anaemia is often induced by P. falciparum infection due to hemolysis of parasitized erythrocytes. The levels of IL-18 were significantly higher in the pregnant women with P. falciparum malaria than in the uninfected pregnant women and the difference was statistically significant. Torre *et al.,* (2001) also observed a significant increase in the serum concentrations of IL-18 during acute and recovery phases of uncomplicated P. falciparum malaria in pregnant women. IL-18 has regulatory functions in immune response, including the synthesis of TNF-α and IFN-ɤ by macrophages, and the induction of cytotoxicity levels observed in infected women.

The TNF-α levels were significantly increased in women with P. falciparum malaria when compared to uninfected women. This agrees with the study by Suigan *et al.,* (2003) who suggested that malaria parasites sequester in the intervillous spaces where they stimulate activated macrophages to secrete large amounts of TNF-α. In contrast to IL-18 and TNF-α, and Interferon gamma (IFN-ɤ) was just slightly lower in pregnant women with P. falciparum malaria. The present findings are in line with those of Nada *et al.,* (2008) where IFN-ɤ was reportedly higher in P. falciparum uninfected women and with that of Arnaud *et al.,* (2014) who reported that there were no elevated cytokines profile including TNF-α and IFN-ɤ in pregnant women with malaria, but it is contrary to the findings of Abrams *et al.,* (2003) who observed elevated levels of many cytokines including IFN- ɤ in pregnancy-associated malaria with its related outcomes. Similarly, Nmorsi *et al.,* (2010) reported increased levels of IFN-γ in pregnant women with malaria than their uninfected counterparts. The observed high levels of IL-18 and TNF-∝ in this study and perhaps other pro-inflammatory cytokines not studied in the sera of malaria infected women might suggest that these cytokines are actively involved in the control of parasiteamia in peripheral blood. The observed low levels of IFN-ɤ in infected women when compared to uninfected women might be due to the decreased number of NK cells in pregnant women which leads to decreased production of IFN-ɤ as suggested by Veenstra Van Nieuwenhoven *et al.,* (2002). Malaria further initiates a reduction IFN-ɤ levels.

The PCV levels of pregnant women in the 1st, 2nd and 3rd trimesters were not different. This is contrary to an earlier report that the prevalence of anaemia among pregnant women was estimated to be 1.8% in the 1st trimester, 8.2% in the 2nd trimester and 27.4% in the 3rd trimester (Scholl, 2005), thus indicating that anaemia increased with gestational age. In this study, comparison of the parity of the patients revealed that primigravids and secundigravids had slightly higher PCV than the multigravids, though the difference in the mean values between the three groups was not statistically significant. Earlier studies had postulated that increasing parity maybe associated with an increase in the risk of anaemia (Kumari *et al.,* 2002), while others also reported no evidence of such association (Fayed *et al.,* 1993). It is known however that in healthy pregnancy, hormonal changes lead to an increase in plasma volume which results in the reduction in heamoglobin levels (Hacker, 1992). Conversely, IFN-ɤ and TNF –α levels increased with increased parity. The difference in the mean values for the 1st, 2nd and 3rd parities was statistically significant. The present findings confirm those of Michal-Fried *et al.,* (1998) that within the gravid groups, the multigravid women had significantly elevated concentrations of IFN-ɤ during malaria infections, while the primigravid women had decreased concentrations. They had also reported that peripheral TNF-α concentration was significantly higher among multigravid women when compared to others. The increase in the levels of these two cytokines could be attributed to the fact that immunity to P. falciparum malaria during pregnancy increases with parity as had been suggested by Duffy *et al.,* (2005). The findings in this study however contradicts those of Nada *et al.,* (2008) that levels of IFN-ɤ were not different between the primiparae and multiparae when data from infected mothers were analyzed. Furthermore, this study observed that the mean weight of babies from pregnant women without P. falciparum malaria was higher than the mean recorded for babies delivered by pregnant women with the infection. The difference between the two groups was statistically significant.

Malaria in pregnancy has been proven from several studies to increase the risk of low-birth-weight infants (Ayoola, 2012) because of either preterm delivery (PTD) or intrauterine growth retardation (Fried, 1998). Newmann (2003) found out that in regions of stable malaria transmission, primigravids were more likely to have low birth weight babies than multigravids. This contradicts the finding in this study where the mean birth weight of primigravids was higher when compared to the multigravids though the difference was not statistically significant. Correlation of maternal cytokine levels with maternal PCV and child weight was negative which was statistically significant between IFN- ɤ, child weight and maternal PCV in the infected mothers indicating that increase in IFN- ɤ result in a decrease in child weight and maternal PCV. This confirms the reports by Raghupathy (1997) that Th-1 type responses like IFN- ɤ are of parasitological importance but over-production can jeopardize the pregnancy, as Th1 response is associated with maternal anaemia and premature deliveries. Malaria infection during pregnancy also increases the risk of moderate/severe maternal anaemia, a known risk factor leading to LBW (Steketee, 2001).

Parasite density in P. falciparum malaria infected mothers showed a negative correlation with IFN-ɤ, IL-18 and TNF- α, but this correlation was not statistically significant. This finding is not in agreement with a study where IFN-ɤ response to P. falciparum-infected RBCs was significantly negatively correlated with parasitemia in the study group (McCail, 2010). There was a negative correlation between parasite density and PCV and this was statistically significant. This shows an inverse relationship between PCV and parasite density; as the parasite density increases, the PCV decreases. This confirms other studies that malaria infection in pregnancy increases the risk of moderate/severe maternal anaemia (Steketee, 2001). However, correlation analysis for parasite density and child weight in malaria positive mothers showed a negative correlation between parasite density and body weight of the neonate. This indicates that there is a decrease in body weight as parasite density increases. This observation agrees with some previous findings in which accumulation of mature stage parasite in the intervillous spaces of the placenta were attributed to adverse pregnancy outcomes, such as low birth weight (Walter, 1982; Desai, 2007).

SUMMARY/CONCLUSION

The study was carried out to assess plasma levels of pro-inflammatory cytokines; TNF-∝, IFN-ɤ and IL-18 in pregnant women with P. falciparum malaria infection. There were significant differences (P<0.05) in the levels of IL-18 and TNF-∝ in pregnant women with P. falciparum malaria infection, when compared to the levels in uninfected mothers. Both cytokines were higher in the infected women. IFN-ɤ and PCV levels were however lower in pregnant women with P. falciparum malaria infection than the levels in the uninfected women. The difference was not statistically significant (P>0.05) it was observed that IL-18 and TNF-∝ concentrations differed according to trimester and the differences in the mean values for the two cytokines were statistically significant (P<0.05). Conversely, PCV and IFN-ɤ levels did not differ significantly from the 1st to the 3rd trimester. Furthermore, TNF-∝ and IFN-ɤ levels increased as parity increased and the difference was statistically significant (P<0.05) while PCV and IL-18 levels did not show significant difference in the mean levels between the primigravids and multigravids. The mean birth weight of neonates delivered by infected mothers was observed to be lower than that of uninfected mothers and the difference in the mean weights of the two groups was significant (P<0.05). Contrarily, parity had no effect on birth weight as there was no significant difference in the mean birth weights of neonates born by mothers in the 1st, 2nd and 3rd parity groupings. A significant negative correlation was observed between IFN-ɤ, birth weight and PCV in malaria positive mothers. A non-significant correlation existed between other cytokines studied (IL-18 and TNF-∝), PCV and birth weight in both infected and uninfected mothers. Parasite density in malaria positive mothers showed a negative correlation with the three cytokines – IFN-ɤ, TNF-∝ and IL-18. Primigravids had a higher prevalence of parasitaemia than the multigravids and the difference in the values that were obtained between groups were significant. In conclusion, P. falciparum malaria infection in the courses of pregnancy causes a change in the profile of pro-inflammatory cytokines such as IL-8, TNF-α and IFN-γ. The parasite induces specific immune response, stimulating the release of these Th-1 cytokines. Elevated levels of TNF-α and IL-18 in pregnant women with malaria suggest that they are up-regulated during malaria and play a role in the defense against P. falciparum. TNF-α can increase phagocytic ability of monocytes and also act on lymphocytes by increasing the elimination of P. falciparum through a non-phagocytic mechanism. IL-18 has a critical role in immune response to malaria through the induction of IFN-γ which has a central role in the cell mediated immune response against blood stage infection which induces phagocytosis and killing of the parasite-infected cells. Lower levels of IFN-γ in infected mothers than uninfected mothers are due to decreased number of peripheral NK cells in the infected mothers leading to a subsequent decrease in the production of IFN-γ. Other effects of malaria in pregnancy include anaemia and LBW. Elevated levels of IL-18 and TNF-α did not lead to significant adverse pregnancy outcomes as the levels of these cytokines are regulated by Th-2 cytokines such as IL-10.

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