CPQ Women and Child Health (2020) 3:1
Research Article

Trimester Dependent Derangements of Fibrinolytic Markers in Maternal *P. Falciparum* Malaria in Port Harcourt, Nigeria

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Received: 06 February 2020

Published: 19 February 2020

Keywords: *Maternal; Pregnancy; Malaria; Fibrinolytic Markers*

Abstract

The attack of malaria infection in pregnancy, often result to harmful effects which may involve the mother's health, the baby's health or both. This study was set to determine the effect of malaria infection in pregnancy on some fibrinolytic markers at different trimesters in pregnant women attending the ante-natal clinics in University of Port Harcourt Teaching Hospital and Rivers State University Teaching Hospital Port Harcourt, Nigeria. A total of 160 subjects were recruited into this study- eighty (80) malaria infected pregnant women and 80 non malaria infected pregnant women. Five milliliters (5ml) of venous blood was collected from each subject into ethylene diamine tetra acetic acid bottles, 3 milliliters of the samples were centrifuged for 15-minutes at 1000rpm within 30 to 45 minutes of collection, the supernatant plasma was withdrawn and transferred into plain tubes and stored in the refrigerator at -20°C for the estimation of levels of fibrinogen, tissue plasminogen activator, D-dimer, plasminogen activator inhibitor 1, plasminogen activator inhibitor 2, plasminogen and α-2-antiplasmin. The tests were performed using enzyme linked immunosorbent assay. The remaining 2 milliliters of the samples were used for the preparation of malaria parasite films. The results obtained in the analyses of fibrinolytic markers in the malaria non infected

pregnant women in the first trimester were fibrinogen 750.58±26.62ng/ml, tPA 30.06±3.32ng/ml, D-dimer 53.88±7.79ng/ml, PAI-, 81.53±3.10ng/ml, PAI-2 453.79±15.35ng/ml, plasminogen 17.71±1.10ng/ml and α-2-antiplasmin 1189.27±50.19 ng/ml, while that of the infected pregnant women were fibrinogen 777.79±23.59ng/ml, tPA 40.71±2.90ng/ml, D-dimer 83.00±6.91ng/ml, PAI-1 92.46±2.74ng/ml, PAI-2 567.79±13.61ng/ml, plasminogen 23.66±0.97 and α-2-antiplasmin 1296.07±44.49ng/ml. In the second trimester, the values in the non infected pregnant women were fibrinogen 684.96±29.99ng/ml, tPA 25.32±3.68ng/ml, D-dimer 54.45±8.78ng/ml, PAI-1 77.67±3.49ng/ml, PAI-2 453.15±17.30ng/ml, plasminogen 15.96±1.26ng/ml and α-2-antiplasmin 1106.31±56.55ng/ml respectively while the values in the infected pregnant women were fibrinogen 702.14±32.60 ng/ml, tPA 54.95±4.00ng/ml, D-dimer 77.13±9.54ng/ml, PAI-1 85.70±3.79ng/ml, PAI 2 552.82±18.80ng/ml, Plasminogen 26.01±1.34ng/ml and α-2-antiplasmin 1283.45±61.47ng/ml respectively. Finally, in the third trimester the values in the non infected pregnant women were fibrinogen 630.38±33.36ng/ml, tPA 31.45±4.10ng/ml, D-dimer 53.22±9.77ng/ml, PAI-1 80.46±3.88ng/ml, PAI 2 464.19±19.24ng/ml, Plasminogen 15.72±1.38ng/ml and α-2-antiplasmin1068.50±62.92 respectively. Significantly increased variations ($p<0.05$) in the levels of fibrinogen and tPA was observed across the trimesters while non-significant increase ($p>0.05$) was observed in the levels of the other parameters across the trimesters. The raised fibrinogen concentration observed in all the trimesters in this study confirms the hyperfibrinogenaemia which is a normal requirement during pregnancy to maintain placental implantation. Due to the variations observed in the fibrinolytic markers at different trimesters in both malaria-infected and non-infected, this study recommends that haemostatic reference values for diagnosis and treatment of pregnant women be based on pregnant women's samples and reference values for fibrinolytic markers should be compared based on gestational age, not just on pregnancy.

Abbreviations

LMP- last menstrual period
WHO- World Health Organization
tPA- Tissue plasminogen activator
uPA- urokinase type plasminogen activator
PAI-1- Plasminogen activator inhibitor 1
PAI-2- Plasminogen activator inhibitor 2
UPTH- University of Port Harcourt Teaching Hospital
RSUTH-Rivers State University Teaching Hospital
HIV- Human immunodeficiency virus
HCV- Hepatitis C virus
HBsAg- Hepatitis B surface antigen
EDTA- Ethylene diamine tetra acetic acid

Background

Derangement in fibrinolytic markers occasioned by the presence of malaria or pregnancy, could lead to clinical conditions, such as haemorrhage, thromboembolism, foetal growth restriction, miscarriage, maternal

mortality and morbidity. The existence of malaria in pregnancy is, therefore, a major challenge. During the period of normal pregnancy, profound changes in coagulation and fibrinolytic activities occur as a consequence of hormonal stimuli and placental growth. Following these changes also, is the predisposition of pregnant women to thromboembolic condition as the pregnancy progresses and even until delivery [1]. It is believed that childbirth usually occurs between 38-40 weeks after conception covering between the last dates of normal menstrual period (LMP) in human [2,3]. The World Health Organization (WHO) defines the normal term for delivery as between 37-42 weeks [4].

The period of pregnancy to delivery is typically divided into three trimesters, each about three months [2]. These divisions are distinctions that are very useful in describing the changes that take place over time). The attack of malaria parasite in pregnancy, often result to harmful effects which may involve the mother's health, the baby's health or both (Agomo and Oyibo [5] and Hasan *et al.* [6] reported that malaria during pregnancy especially the severe form of *Plasmodium falciparum* could lead to impairment of the coagulation system which will result to fibrin deposition usually seen in malaria infection.

During coagulation process, fibrinogen is one of the factors that are involved in the formation of blood clots to prevent loss of blood and fibrinolysis is a normal body mechanism which keeps the blood in a fluid state by breaking down the product of coagulation using plasmin at various sites [7]. According to Trehen & Fergusson [8], fibrinogen is very important in the maintenance of normal pregnancy. Failure to complete a normal pregnancy was associated to fibrinogen deficiency or hypofibrinoginaemia because hyperfibrinoginaemia in normal pregnancy maintains the integrity of placenta implantation. Tissue plasminogen activator as the primary initiator of fibrinolysis is reported to be reduced during pregnancy due to the gradual increase in plasminogen activator inhibitor-1 (O'Riordan & Higgin [9] and (Prisco *et al*, [1] but increase in tPA occur due to increase level of plasminogen activator inhibitor-2 (PAI-2). Studies done by Kruithof [10] and Nakashima [11] indicate that gradual and linear increase in tPA and uPA levels occur during pregnancy with levels higher than normal in third trimester in pre-eclampsia. Van Wersch & Ubachs by Kruithof [10] and Nakashima [11] indicate that gradual and linear increase in tPA and uPA levels occur during pregnancy with levels higher than normal in third trimester in pre-eclampsia. Van Wersch & Ubachs [12], reported that tPA is the only fibrinolytic marker found to be diminishing with gestational age leading to reduced fibrinolytic activity during pregnancy. D-dimer as the primary degradation product of cross-linked fibrin serves as direct marker of ongoing coagulation and fibrinolysis. Adam & Greenberg [13] and Prisco *et al.* [1] reported that during pregnancy, despite the high levels of PAI-1 and PAI-2, there is a highly significant positive correlation between gestational age and D-dimer concentration which continues with steady increase until delivery. Studies on the derangement in fibrinolytic markers at different trimesters caused by malaria in pregnancy has not been adequately reported among Nigerian women and this could be a major challenge to maternal health during pregnancy, this study therefore, was designed to determine the changes in some fibrinolytic markers in the malaria infected-pregnant women and non-infected pregnant women at their different trimesters during pregnancy.

Materials and Methods

Study Site

The study was conducted at the University of Port Harcourt Teaching Hospital, Port Harcourt (UPTH) and Rivers State University Teaching Hospital, (RSUTH) both in Port Harcourt metropolis. UPTH is on the East-West road Choba, Port Harcourt while Rivers State University Teaching Hospital, (RSUTH) is located in Old GRA in the heart of Port Harcourt capital city of Rivers State, Nigeria. The two hospitals have the several units usually found in tertiary hospitals, which include well managed ante-natal care clinics.

Subjects

Using the stratified random sampling technique, a total population of one hundred and sixty (160) subjects who were within the age of 18-50 years were enrolled into this study and investigated at the time. This comprises of 80 malaria-infected pregnant women and 80 non-malaria infected pregnant women. All the subjects in the two experimental groups were within reproductive age. The subjects were recruited after giving consent by providing the information on a well structured questionnaire which captured relevant data on their demographic and clinical information such as age, on anti- malaria or malaria vaccine, anti-inflammatory drugs, HIV drugs, cancer drugs, hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV). The subjects who did not give consent were excluded.

Ethical Consideration

Ethical approval for this study was obtained from the Research Ethics Committees of the University of Port Harcourt Teaching Hospital (UPTH) and that of Rivers State Hospitals Management Board. The Participants also gave written consent to participate in the study.

Inclusion Criteria

All subjects in the study were within the age of 18- 50 years. Pregnant subjects who tested positive for pregnancy and malaria parasitaemia (test subjects), and pregnant subjects who tested negative for malaria parasitaemia (control) were recruited for the study.

Exclusion Criteria

All non pregnant subjects were excluded from the study.

Blood Sample Collection

Blood samples were collected using standard venepuncture technique to draw five milliliters (5ml) of venous blood from the forearm vein according to the method described by [14]. 3 milliliters of the samples were dispensed into EDTA (ethylene diamine tetra acetic acid) bottles and used for the estimation of the levels of the fibrinolytic parameters while the remaining 2 milliliters were dispensed into another EDTA bottle for preparation of malaria parasite films.

Determination of Malaria Parasites

Presence of malaria parasites in the subjects were determined using both thin and thick films stained with 3% Giemsa and examined for parasitaemia using the method of [15].

Determination of Plasma Levels of Fibrinolytic Markers

The enzyme linked immunosorbent assay (ELISA) methods was used to determine the levels of plasma. The test involve the use of a sandwiched enzyme immunoassay in which the microtiter plates provided in the kit has been pre-coated with an antibody specific to the particular marker to be determined. The ELISA kits were produced by Wuhan Elabscience Biotechnology Inc. Company, China, and Pregnancy test was done using Pregnancy test strips produced by Early-Pregnancy-Test.com, 1140, 11th street, Bellingham, WA 98225.

Statistical Analysis

The results were statistically analyzed using the SAS version 9.4 developed by SAS Institute, North Carolina State University, USA. One-way analysis of variance (ANOVA) was used for comparison of means and results presented as mean ± SEM. Level of significance was set at $p<0.05$.

Results

In this study, comparison of biometric parameters of body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) of malaria infected pregnant women and non- infected pregnant women according to the trimesters of pregnancy is shown in table 1: Trimester did not exert any significant influence on the BMI and blood pressure of the study participants ($p>0.05$).

Table 1: *Comparison of Biometric Parameters among Malaria infected Pregnant Women and Malaria Negative Pregnant Women by Trimester.(Mean ± SEM)*

Trimester	Study Group$^{\beta}$	N	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)
1st	Pregnant-Negative	33	25.86±0.73	105.03±1.91	64.30±1.69
	Pregnant-Positive	42	27.76±0.64	109.48±1.70	66.64±1.50
2nd	Pregnant-Negative	26	26.90±0.82	110.92±2.16	66.08±1.91
	Pregnant-Positive	22	27.09±0.89	107.09±2.35	64.23±2.07
3rd	Pregnant-Negative	21	28.92±0.91	111.14±2.40	69.43±2.12
	Pregnant-Positive	16	27.06±1.04	113.69±2.75	69.12±2.43
	P-value		0.0842 ^{ns}	0.1255 ^{ns}	0.4941 ^{ns}

Key: SEM: Standard error of mean;βStudy groups: Pregnant-Negative (Women were pregnant but negative for Malaria parasites), Pregnant-Positive (Women were pregnant and positive for Malaria parasites).Within each parameter, means ± SEM with different superscripts are significantly different at $p<0.05$.Significance Level: *=$p<0.05$; **=$p<0.01$; ns=Not Significant ($p>0.05$).

The comparison of changes in the levels of fibrinolytic markers in malaria-infected pregnant women and non-infected pregnant women at different trimesters is shown in table 2. Fibrinogen was significantly elevated (P=0.0524) in the infected pregnant women when compared with the non infected pregnant women in the three trimesters. Those in the first trimester had 777.79±23.59ng/ml and 750.58±26.62ng/ml for infected and non infected pregnant women respectively. The second trimester had mean values of 702.14±32.60ng/ml for infected pregnant women and 684.96±29.99ng/ml for non infected pregnant women while in the third trimester, the infected pregnant women had higher value of 795.06±38.22ng/ml than the non infected pregnant women value of 630.38±33.36ng/ml. It was, however, observed that the highest values were obtained in the first and third semesters. Trimester was therefore, seen to exert a significant influence on fibrinogen ($p<0.05$).

The tPA was observed to be elevated also in all the trimesters among the infected pregnant women. The values obtained were 40.71±2.90ng/ml and 30.06±3.32ng/ml for infected and non infected pregnant women respectively in the first trimester. The second trimester gave the highest value among the infected pregnant women and the lowest value among the non infected pregnant women. These values were significantly different from each other at $p<0.05$. The malaria infected women had tPA value of 54.95±4.00ng/ml while non infected women had 25.32±3.68ng/ml in the second trimester. The values in the third trimester were 49.51±4.70 ng/ml for the infected pregnant women and 31.45±4.10ng/ml for the non infected and significant variation in the concentration of tPA in the third trimester among the two groups was observed (P=0.0277).

The concentrations of D-dimer, PAI-1, PAI-2, plasminogen and α-2 antiplasmin were observed to increase in the infected pregnant women across the trimesters but these increased levels were not significant (P=0.6088 for D-dimer, P=0.8626 for PAI-1, P=0.7999 for PAI-2, P=0.1580 for plasminogen and P=0.1522 for α-2 anti plasmin) across all the trimesters. It was also observed, that trimesters did not alter the impact of malaria and pregnancy on the levels of these parameters in pregnant positive women.

Figure 1 shows box plot graph of fibrinogen among the study groups and levels in the trimester respectively. Fibrinogen concentration was elevated to a significant level only among malaria positive pregnant women. This delineates malaria as a cause of increase in fibrinogen concentration. Among the malaria negative pregnant women, trimester was not found to be a factor as the concentration of fibrinogen decreased significantly ($p>0.05$) as the trimester increases. However, there was a noticeable fluctuation of fibrinogen value in malaria positive pregnant women but not above the first trimester values. The summary of the trends in fibrinolytic parameters revealed that malaria is a major contributor of derangements in fibrinolytic parameters at different trimesters in pregnancy.

Table 2: *Comparison of the Impact of Malaria parasite and Pregnancy on Fibrinogen, tPA, D-Dimer, PAI-I, PAI-2, Plasminogen, α -2-Antiplasmin among the Pregnant Positive and the Pregnant Negative by Trimester. (Mean ± SEM)*

Trimester	Study Groupsβ	N	Fibrinogen (ng/ml)	tPA (ng/ml)	D-dimer (ng/ml)	PAI-I (ng/ml)	PAI-2 (ng/ml)	Plasminogen (ng/ml)	α-2Antiplasmin (ng/ml)
1st	Pregnant-Negative	33	750.58±26.62^{ab}	30.06±3.32^{d}	53.88±7.79	81.53±3.10	453.79±15.35	17.71±1.10	1189.27±50.19
	Pregnant-Positive	42	777.79±23.59^{a}	40.71±2.90^{bc}	83.00±6.91	92.46±2.74	567.79±13.61	23.66±0.97	1296.07±44.49
2nd	Pregnant-Negative	26	684.96±29.99^{bc}	25.32±3.68^{d}	54.45±8.78	77.67±3.49	453.15±17.30	15.96±1.26	1106.31±56.55
	Pregnant-Positive	22	702.14±32.60^{abc}	54.95±4.00^{a}	77.13±9.54	85.70±3.79	552.82±18.80	26.01±1.34	1283.45±61.47
3rd	Pregnant-Negative	21	630.38±33.36^{c}	31.45±4.10^{cd}	53.22±9.77	80.46±3.88	464.19±19.24	15.72±1.38	1068.50±62.92
	Pregnant-Positive	16	795.06±38.22^{a}	49.51±4.70^{ab}	64.24±11.19	88.09±4.45	589.44±22.05	21.24±1.58	1403.38±72.08
	P-value		0.0524*	0.0277*	0.6088 ns	0.8626 ns	0.7999 ns	0.1580 ns	0.1522 ns

Key: SEM: Standard error of mean;β Study Groups: Pregnant-Negative (Women were pregnant but negative for Malaria parasites), Pregnant-Positive (Women were pregnant and positive for Malaria parasites).Within each parameter, means ± SEM with different superscripts are significantly different at $p<0.05$. Significance Level: *=$p<0.05$; ns=Not Significant ($p>0.05$).

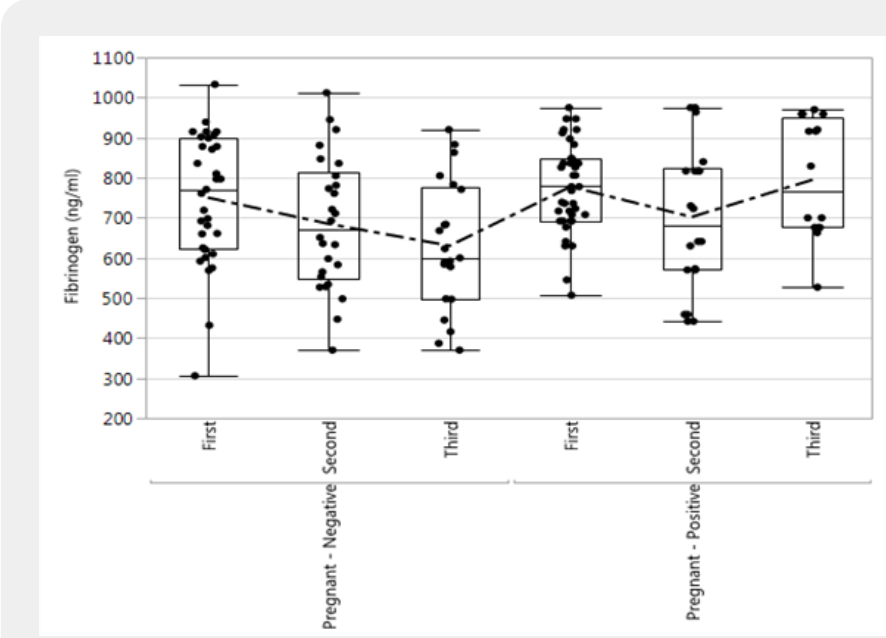

Figure 1: *Boxplot of Fibrinogen (ng/ml) for Pregnant Malaria Positive and Negative Women by Trimester. (Fibrinogen concentration was highest in first trimester)(Mean ± SEM)*

Discussion

This study revealed elevated fibrinogen concentration in all the trimesters with the highest value in third trimester among the pregnant women especially in the malaria infected pregnant women. This finding is at variance with the previous work done by Trehan & Fergusson [8] who reported increased fibrinogen only in the first trimester. Our finding in this study is also at variance with the report of Imoru & Emeribe [7] who in their study reported increase in fibrinogen concentration in first and third trimesters only. However our finding is in complete agreement with the report from studies done by Oke *et al* [16] and Choi [17]. The two different researchers reported significant increase in the concentration of fibrinogen in all the trimesters with the highest concentration being observed in the third trimesters. Our finding, therefore, could suggest hyperfibrinogenaemia which was stated by Trehan & Fergusson [8] as a requirement in normal pregnancy to maintain the integrity of placental implantation as a normal process in pregnancy. It could be said that pregnant women who had hypofibrinoginemia lacked this protection and may be prone to placental separation, haemorrhage and even miscarriage. Our finding about increase in fibrinogen concentration might also be due to increased protein synthesis by the liver hepatocytes to cope with increased protein needed for both the mother and child development during pregnancy which could have made the liver to produce more fibrinogen. The finding in this study also support the suggestion by Imoru & Emeribe [7] that haemostatic reference values being used which are based on samples from non pregnant women may not be correct because it is not relevant to pregnant women and can potentially act as limitation to accurate diagnosis and treatment of haemostatic disorders during pregnancy.

From the finding in this study, a significant elevation of tPA exerted by the trimesters was further revealed. It was observed that tPA level was higher in the infected pregnant women than the non infected in all the trimesters with the highest level being recorded in the second and third trimesters. This finding is similar to the earlier reports of Kruithof [10] and Nakashima [11]. They reported gradual and linear increase in tPA level during the period of pregnancy with higher levels than normal during the third trimester. Our findings is also similar with the report of Choi [17] where it was reported that tPA level increased during the period of pregnancy and was higher in the last trimester than the first. But the elevated tPA level seen in this study is at variance with the report of Van Wersch & Ubachs [12] which recorded that tPA is the only fibrinolytic marker which is found to be diminishing with gestational age to reduce fibrinolytic activity during pregnancy. The doubling of tPA levels in the different trimesters as recorded in this study could probably be due to the presence of the malaria parasites which could have influenced the release of tPA from the vessel walls induced by the stress of pregnancy towards child birth and this could also be responsible for the non significance variation observed in PAI-1 and PAI-2 in the different trimesters.

Although from our finding, there was no significant variation in the levels of PAI-2 by the trimesters, it was observed that the level of PAI-2 was higher during the third trimester in both the infected and non infected pregnant women and this finding is strongly supporting the report by Chapina & Hajjara [18] that PAI-2 increases as the pregnancy increases. The increase in the concentration of PAI-1 and PAI-2 in this study could be associated to natural protection of the pregnant women from experiencing bleeding during pregnancy period and also towards child birth because it has been documented that PAI-1 have been incriminated in abnormal, clinically significant bleeding while total absence of PAI-1 either due to congenital or acquired reason is seen in bleeding cases such as hematomas, menorrhagia, easy bruising and

postoperative haemorrhage and this is the reason for increase in plasminogen activities in second and third trimesters with a rapid decrease in their values after delivery [19]. However, no obvious explain could readily be given to explain the observation of increased level of PAI-1 and PAI-2 in the pregnant positive women than in the non pregnant subjects.

This study revealed a non significant high level of D-dimer in all the trimesters in malaria infected pregnant compared to their uninfected counterpart. The observed increase was higher in the first trimester followed by the second and third trimester. This finding is at variance with that of Mosesson [20] where D-dimer increased with gestational age but it agrees with the report of Hellgren [21] that increase fibrin deposition is suggested by increasing D-dimer levels throughout pregnancy

The higher level of D-dimer which occurred in the malaria infected pregnant women did not reveal any significance, but it also revealed that actually elevated D-dimer could be caused by the presence of widespread thrombin deposition in small arteries and arterioles (disseminated intravascular coagulation and fibrinolysis) which may have been induced by the presence of malaria parasite in these group. This condition was named by (perinatology.com) as one of the conditions that have the capacity to cause elevated D-dimer in affected persons. This suggestion correlates with the reports of Chen *et al,* [22] and Dasgupta *et al*. [23]. They stated in their different reports that malaria infection are complicated syndrome involving many inflammatory responses. And it is this mechanism of inflammation, coagulation and fibrinolysis in malaria infection that causes a direct attack of the parasites on the endothelium of the microcirculation which results to endothelial cell injury and hence leads to the release of different kinds of cytokines as well as inflammatory mediators by endothelium and other cells which are involved in harboring these inflammatory markers. When this process is initiated, it in turn activates the coagulation pathway leading to the widespread thrombin formation which is then deposited in small arteries and arterioles.

As some other markers increased with gestational age in pregnancy, α -2 antiplasmin was not seen to be significantly increased during the different trimesters. However, there was increase in the levels in third trimester more than the other trimesters. The elevated non significant level could be associated to natural preventive process of the pregnant women from bleeding. Because Binder *et al* [24] even reported that deficiency of α -2 antiplasmin lead to thrombotic tendencies and bleeding disorder. This is obviously a reality hence α -2 antiplasmin functions to prevent plasmin from cleaving to fibrin which may lead to increased fibrinolysis in the affected subjects. To avoid hyper coagulation in pregnancy complicated with malaria, raised α-2 antiplasmin is usually counter balanced by an increase in plasminogen level. This could also be the reason for the significantly elevated plasminogen concentration in the malaria infected pregnant women more than the other study groups in this study.

Conclusion

The analysis of the fibrinolytic markers in this study showed that there is significant derangement in fibrinolytic markers in the malaria positive pregnant women in the different trimesters. The raised fibrinogen concentration observed in all the trimesters, confirms the hyperfibrinogenaemia which is a normal requirement during pregnancy to maintain placental implantation. It was recommended due to the variations observed in the fibrinolytic markers at different trimesters in both malaria-infected and non-infected, this study

recommends that haemostatic reference values for diagnosis and treatment of pregnant women be based on pregnant women's samples and reference values for fibrinolytic markers should be compared based on gestational age, not just on pregnancy.

Conflicts of Interest

The authors declare no conflicts of interest.

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