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Prevalence of Placental Malaria Relative to Placental Cytokines and Birth Anthropometry Among Sub-Sahara Black African Women in their First or Second Pregnancy

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Abstract: Introduction: Pregnancy is a complex condition during which pathological complications such as iron deficiency anemia, infections, under- or over-nutrition and excessive production of cytokines may occur to jeopardize the well-being of the fetus. Objective: The objective of this study was to evaluate the interactions between placental or peripheral malaria (PlacMal or PerMal), Tumor Necrosis Factor-α (TNF-α), Interferon-γ (IFN-γ), Iron deficiency anemia (IDA), Platelets (Plt) and immature granulocytes (IG) in the placenta and neonatal birthweight, birth length and birth head circumference among study subjects in their 1st or 2nd pregnancy in Nigeria. Materials and Method: This was part of a prospective and exploratory study carried out among women in their 1st and 2nd pregnancy at Ikorodu General Hospital and its annex, Ita-Elewa Primary Health Care Center at Ikorodu, Lagos, Nigeria. Complete data from 78 women in their 1st or 2nd pregnancy who were assessed for TNF-α and IFN-γ, and whose socio-demographic characteristics, ante-natal history, birth anthropometry, placental hemogram and malaria parasitemia were recorded and analyzed. Data analysis was conducted using NCSS and STATA softwares. Results: Study participants in their 2nd pregnancy were significantly older (t-test=4.51, P-value=0.00004) and heavier (t-test=2.44, P-value=0.02) than those in their 1st pregnancy. While the means of TNF-α<20 pg/ml in subjects with (9.4±1.5) and without (20.3±24.1) PlacMal were notably different (t-test=3.74, P-value=0.0004), the means in subjects with (20.3±14.8) and without PerMal (19.8±25.4) were insignificant. At normal TNF of <20 pg/ml, mean birth length of neonates from 1st pregnancy (50.6±1.8 cm) was notable higher (t-test=2.98, P-value=0.005) than that those 2nd pregnancy (47.8±5.1 cm). Overall birthweight was significantly higher (3.2±0.5) when Hgb was ≥9.5 and TNF-α was <20 pg/ml than when Hgb was ≥9.5 and TNF-α was ≥20 pg/ml. Overall birth length (52.0±0.0) was notably longer (t-test=3.79, P-value=0.004) when IG was >0.456 and Hgb was <9.5 compared to when IG >0.456 and Hgb was ≥9.5. The mean platelets count ($x10^9$/L) of subjects with (27.7±14.2) and without (79.6±89.4) PlacMal were significantly different (t-test=3.94, P-value=0.002) but those of subjects with (69.2±50.5) and without (79.6±95.3) PerMal were not. Multivariate regression analysis indicates a positive, statistically significant relationship between birthweight and age group (coeff. = 0.22, SE=0.06, t-test = 3.78, P-value = 0.003). Conclusion: Placental TNF-α, IFN-γ, Platelet count, and IG may have a distinct or combined role to play the the development of gestation process and neonatal anthropometry. More studies are needed to support and substantiate these findings.

Keywords. Birth Anthropometry, Immature Granulocytes, Interferon-γ, Placental Malaria, Ponderal Index, Pregnancy, Tumor Necrosis Factor-α, Sub-Sahara Africa.

INTRODUCTION

In humans and in some animals, the proper development of placenta is central to a successful pregnancy. It is an essential organ with series of vital functions for the survival of the fetus. It is a temporary structure that may be regarded as an immune and endocrine organ that produces many hormones and growth factors in autocrine and paracrine modalities, such as progesterone, corticotropin-releasing hormone, the human chorionic gonadotropin, the human placental lactogen, fibroblast growth factor, and many others. [1]. An early study reported that the placenta is a highly specialized organ that modulates the exchange of metabolites between fetal blood in the chorionic villi and maternal blood within the intervillous spaces [2]. Similarly, to how the Blood-Brain-Barrier protects the brain from infections, the placenta also protects the uterus from direct invasion by viruses and parasites, though such barrier may be broken occasionally. Like a two-way traffic, the placenta integrates maternal and fetal circulatory systems as it supplies maternal oxygen and nutrients to the maturing fetus while extracting metabolic wastes and carbon dioxide from the fetus via the blood vessels in the umbilical cord [3]. In endemic regions, P. falciparum-infected elicits an increase in inflammation activation which is linked with increase in necrotic areas, fibrioid necrosis and syncytial aggregates [4]. Not only that, during infection of the placenta by malaria parasites, various morbid processes such as inflammation, tissue necrosis, and infiltration of the intervillous space with immune cells, haemozoin pigment, and fibrin deposit come into play [5]. The deleterious outcome of this altered biochemical functions are poor development, denatured structure and utility of the placenta, such as impaired exchange of nutrients, oxygen, and waste, resulting in a multitude of adverse pregnancy outcomes, such as anaemia, intrauterine growth retardation, and low birthweight [5]. Different dynamics play out in the placenta to ensure normal growth and non-rejection of the fetus. Hematologically, fetal hemoglobin (HbF), the principal carrier of oxygen, demonstrates a higher affinity for oxygen and a decreased affinity for 2,3-biphosphoglycerate (2,3-BPG) compared to adult hemoglobin (HbA) [6]. Platelets, a specific type of blood cells that aid in blood clot, are an essential constituent of the body's hemostatic process and have a vital function at every phase of pregnancy, including, placenta implantation, pregnancy maintenance, and control of bleeding after parturition. Low placental platelet count, or thrombocytopenia, is count <150,000/mcl, and is the second most common hematological condition after anemia, which complicates 10% of pregnancies [7]. Very low or pathological thrombocytopenia, which occurs in preeclampsia, HELLP syndrome, acute fatty liver of pregnancy, DIC, drugs, etc. is linked with unfavorable pregnancy results [7]. Fetal platelets count, essential for clotting, is usually expected to be normal but at a low count, constitutes fetal thrombocytopenia, a condition associated with serious bleeding risks, including bleeding in the brain, is often precipitated by incompatibility between the mother's and fetus's platelet types, leading to fetal and neonatal alloimmune thrombocytopenia (FNAIT) [8]. A previous paper reports that placental immature granulocytes may play many vital roles such as innate immune system to protect the fetus from infection by responding to pathogens, inflammation regulation by modulating inflammatory responses, tissue repair processes within the placenta, thus

contributing to the placenta's overall health and function and fetal development support, creating a conducive environment for fetal development [9]. Wang et al, in a recent study, associated maternal peripheral IGs with a high risk for gestational diabetes mellitus (GDM), preterm birth, and macrosomia [10]. Tumor Necrosis Factor (TNF)-α, initially recognized as a cytokine that is associated with inflammation, is synthesized throughout the female reproductive tract as well as in placentas and embryos [11]. It is regarded as a multifunctional Th1 cytokine and a very vital inflammatory cytokine out of many of such. Produced by macrophages during inflammation and also activated by the endotoxin lipopolysaccharide (LPS), TNF-α controls the growth of normal and neoplastic cells, has a significant effect on the expression of genes related to cell differentiation, and influences the function of different cells [12]. Some older publications reported that elevated levels of TNF-α are linked with certain adverse effects like gestational hypertension and gestational diabetes mellitus [13, 14], may impact materno-fetal relationship by altering the secretory profile of placental immunomodulatory factors, which in turn affects maternal immune cells and can induce the differentiation of peripheral blood monocytes into macrophages [15]. Deviant levels of TNF-α are associated with various reproductive diseases such as amniotic infections, repeated spontaneous abortions, pre-eclampsia, preterm labour or endometriosis. Certain factors, such as concentrations and duration of stimulation determine the beneficial or derogatory effect of TNF-α on pregnancy outcome [16]. As part of the immune responses, Interferon-gamma (IFN-γ), is regarded a regulatory cytokine, a function substantial role in the maintenance of viable pregnancy [12], [13], is one of these factors that have a substantial function in the maintenance of gestation. None of these cytokines probably functions in tandem with other cytokines, hormones and other components of the blood or the placenta. Moreover, the interactions of TNF-α, IFN-γ, platelets and immature granulocytes with respect to labor duration, gestational period, birth anthropometry and Ponderal Index (PI) have not been fully elucidated, especially in pregnant sub-Saharan Black African women with and without placental malaria. To bridge this gap this study aimed to evaluate the relationships between peripheral and placental malaria and placental concentrations of TNF-α, IFN-γ and other pregnancy associated variables relative to birth outcome in Nigeria.

MATERIALS AND METHODS

Pregnant women attending the ante-natal clinic, and eventually, the Labor Ward of Ikorodu General Hospital, Ikorodu, in Lagos State, Nigeria, were enrolled in the study between March and November 2024. This study investigated the relationship of two placental cytokines — Tumor Necrosis Factor-alpha (TNF-α) and Interferon-gamma (IFN-γ) — in relation to placental and peripheral malaria, hematological parameters and birth outcomes.

Study Location

The research was conducted at Ikorodu General Hospital, located in Lagos State, the economic epicenter of Nigeria, which lies along the picturesque Atlantic Ocean coastline in the southwestern region of the country. The state boasts an estimated population exceeding 21 million [14]. It encompasses 20 Local Government Areas (LGAs), of which 16 are classified

as urban, while the remaining four are designated as rural or semi-urban, including Ikorodu LGA [15], which has an estimated population of 1,041,000.

Study Subjects

The study participants comprised only women in their 1st or 2nd pregnancy who attended the ante-natal clinic at Ikorodu General Hospital and its annex at Ita-Elewa Primary Health Care Center. The study subjects resided in Ikorodu LGA, a relatively homogeneous community. The participants were engaged in a variety of occupations, predominantly in trade. Inclusion criteria encompassed singleton deliveries, the absence of any pathological conditions at the time of delivery that might adversely affect gestational outcomes, and being in the late stage of the third trimester. Exclusion criteria were refusal to provide consent for participation in the study, critically ill pregnant women, and instances of stillbirth. The Ante-Natal Clinic Attendance register served as the sampling frame to select subjects in the late stage of their pregnancy, utilizing simple random sampling. Those who affixed their signatures to the consent form were subsequently interviewed and monitored through their admission into the Labor Ward until delivery.

Study Design

This investigation was a descriptive, prospective study involving pregnant women in the late third trimester of gestation and their neonates following delivery. In this cohort of study subjects, no participant withdrew from the study. All signed the consent form and permitted intervention with their placenta after a comprehensive elucidation of the study's objectives and the potential societal benefits of its findings. Complete data encompassing socio-demographic characteristics, anthropometric indices of the mothers, pregnancy and delivery history, gravidity, and data from both neonates and placentas were available for cytokine analysis from 78 subjects (31.7%). Birth weight, birth length, and head circumference of the neonates were meticulously measured by trained midwives immediately post-delivery. Additionally, the neonates' APGAR scores were recorded at 1 and 5 minutes after birth. The study population was categorized into primigravida (1st pregnancy; n=22, 28.2%), secundigravida (2nd pregnancy; n=56, 71.8%). Placental TNF-α and IFN-β concentrations of <20 pg/ml and of <30 pg/ml were regarded as normal while values equal to or above these were regarded as abnormal; anemia was regarded as placental blood hemoglobin (Hgb) concentration of <9.5 and value equal to above or this was regarded as no anemia. Placental platelet count of <150,000 $x10^9$ was taken as thrombocytopenia; the count of 150,000-450,000 was taken as normal values while count of ≥450,000 was taken as thrombocytosis. Placental IG were taken to be of low, normal or high when their values were <0.018, 0.018-0.456 or ≥0.456 [16].

Sample Size Determination

The initial larger study had a sample size of 246 as reported in an earlier publication [17]. The sample size of 78 used in this study was based on convenience sampling due to the availability of cytokine assay kits at the time of the study. Those in their ≥3rd pregnancy were excluded.

Data Collection

The training of data collectors for the entire study was conducted from 12 to 19 February 2024 at the Nigerian Institute of Medical Research in Lagos. This training encompassed three days of orientation focused on data collection instruments and the prompt delivery of specimens to the laboratory. Additionally, a one-day training session was held at Ita-Elewa Primary Health Center specifically for 15 midwives, nurses, and health information officers, which emphasized the procedures to be adhered to, such as clamped arterial cord blood aspiration and the maintenance of timely, accurate, and thorough records. The hospital staff routinely weigh and electronically document each neonate's anthropometric parameters, including birth weight and birth length, although they were not trained on recording birth head circumference and mid-upper-arm circumference (MUAC), on which they were trained for the purpose of this study. Comprehensive data, encompassing the socio-demographic characteristics and anthropometric indices of the mothers, as well as their pregnancy history, delivery, and gravidity, were meticulously gathered from the mothers, using semi-structured questionnaires.

Retrieval of Products of Conception

Normal vaginal delivery encompasses the processes of labor or uterine contractions during which the cervix effaces and dilates, culminating in the expulsion of the neonate through the birth canal, followed by the delivery of the placenta. The emergence of the infant's head is succeeded by the delivery of the shoulders and the remainder of the body. Ultimately, the sustained contractions of the uterus facilitate the expulsion of the placenta, umbilical cord, and amniotic membrane from the uterine cavity. Upon delivery, the umbilical cord is double-clamped approximately 10 to 15 centimeters distally from the neonate and subsequently severed. The arterial cord was identified, and blood was aspirated utilizing a 5 ml syringe.

Preparation of the Placenta

This has also been reported in an earlier publication [17]. Briefly, after removing the amniotic sac and umbilical cord, each placenta was weighed. A wedge of placental tissue was excised, blood aspirated from the cut surface, and preserved in EDTA bottles for analysis. Thick and thin blood smears were prepared on slides and stained with Giemsa for malaria microscopy. Each placental biopsy was placed in a sterile container with 20 ml of 10% formalin and sent to a Specialist Laboratory for histopathological examination. A section of each placental tissue, about 8 µm thick, underwent standard hematoxylin and eosin staining and was evaluated using a light microscope (Leica Model DM 500) with a x100 lens and Rogerson criteria for histological evaluation and the detection of *Plasmodium falciparum* infection in placental tissue [18] .

Neonatal Data

At delivery, subsequent to the implementation of standard neonatal resuscitation protocols, the birth weight, length, and head circumference were meticulously measured and documented. Birth weight was recorded in kilograms, utilizing a digital weighing scale, with

values noted to the nearest 10 grams. Birth length, with legs fully extended, was measured in centimeters from the crown of the head to the heel using a cloth measuring tape. The head circumference was ascertained in centimeters, employing the same cloth measuring tape across the right and left temporal protuberances and the occiput. The APGAR score was assessed to evaluate neonatal vigor at 1 and 5 minutes post-natally.

Hematological Data

Comprehensive hematological parameters were acquired using the Sysmex XN-550 benchtop hematology analyzer (Kobe, Japan), in accordance with the manufacturer's guidelines. For this investigation, the hematological parameters evaluated from placental blood encompassed Red Blood Cell Count ($x10^9$/L), Hemoglobin (g/dL), Hematocrit (%), Mean Corpuscular Volume (fL), Mean Corpuscular Hemoglobin (pg), Mean Corpuscular Hemoglobin Concentration (g/L), Platelets (x10^9/L) and immature granulocytes (IG).

Cytokine Assay

The quantification of serum TNF-α and IFN-γ was performed using the Human Tumor Necrosis Factor Alpha and Human Interferon Gamma Sandwish-ELISA Kits manufactured by Sunlong BioTech (SL-1781Hu/ SL0980Hu, China). The reagents used were High-binding 96-well ELISA plate pre-coated with an antibody specific to TNF- α and IFN-γ, Recombinant TNF-α and IFN-γ standards (stock concentration known), HRP conjugate reagent, Standard Diluent, washing solution, sample diluent, chromogen solution A, chromogen solution B and stop solution. TNF- α and IFN-γ were thus evaluated according to manufacturer's instructions.

Data Analysis

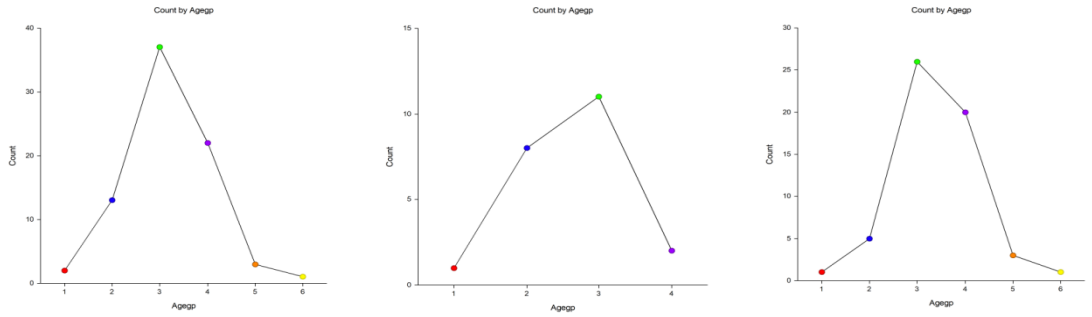
Primary field data were manually inscribed into a field logbook and subsequently transcribed, also manually, into an Excel spreadsheet, where they were cleansed and exported into Stata Statistical Software (version 16.1; StataCorp, Texas, USA) for analysis, and into NCSS version 20 to construct age frequency distributions and into Word to generate horizontal bar charts of study participants. Non-parametric tests were employed to ascertain the significance of associations among variables. There was an absence of missing data. The analyses included frequency proportions, bivariate (cross-tabulation), and multivariate regression analyses. Analysis of Variance (ANOVA) was employed to compare means of continuous variables across the three groups when the data were normally distributed. Proportions were compared using the x^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Results were expressed as mean (±standard deviation [SD]) and presented in Tables and Figures. In hypothesis testing, the level of significance was established at a P-value < 0.05. Ethical approval and informed consent. The study was conducted following the guidelines of the Declaration of Helsinki and received approval from the Health Research Ethics Committee of the Nigerian Institute of Medical Research (Institutional Review Board) with Protocol number IRB/23/096 dated 20th November 2023. Informed consent was obtained from all subjects participating in the study. The confidentiality of the study participants' data was upheld by safeguarding participants'

identities and preventing unauthorized access to their research data. Given the endemicity of malaria in the country, the threshold for placental hemoglobin concentration in the third trimester was established as 9.5-15.0 g/dL [19, 20].

RESULTS

This was part of a larger study on Placental and Peripheral malaria among women in their 1st, 2nd and ≥3rd pregnancy but cytokine data are only available for those in their 1st and 2nd pregnancy. Placental blood Tumor Necrosis Factor-Alpha (TNFα), Interferon-Gamma (INF-γ), and hematological parameters were assessed among 78 study participants after delivery. Neonatal anthropometric indices were also evaluated within 10 minutes of delivery of live babies at Ikorodu General Hospital and its annex, Ita-Elewa Primary Health Care Center, both at Ikorodu in Lagos, Nigeria.

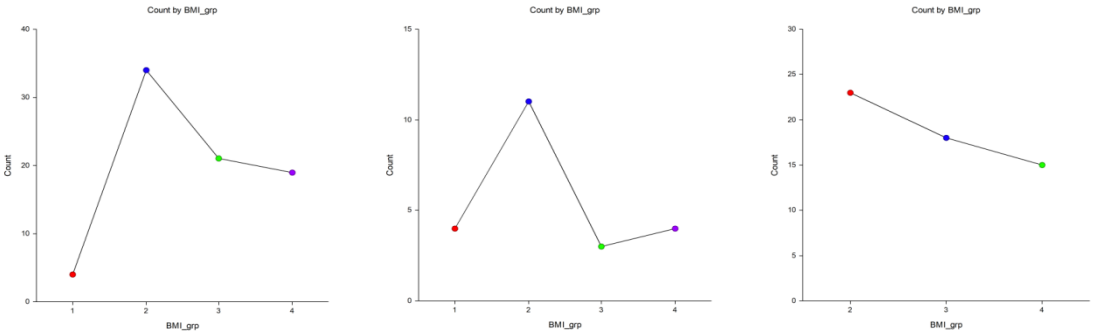
- *Socio-demographic characteristics, anthropometric indices, pregnancy-associated fever and placental malaria distribution of study subjects Table 1, Figures 1 and 2.*



(i) (ii) (iii)

Age-group 1= <20 years; 2 = 20-25 years; 3 = 26-30 years; 4 = 31 - 35 years; 5 = 36-40 years; 6 = >40 years

Figure 1: Age-group distribution of (i) all study subjects (ii) those in their 1st and (iii) 2nd pregnancy



(i) (ii) (iii)

Figure 2: Body Mass Index distribution of (i) all study subjects (ii) those in their 1st and (iii) 2nd pregnancy

Table 1: Socio-demographic characteristics, anthropometric indices, pregnancy-associated fever and placental malaria distribution of study subjects (n=78; 2024).

Variable		All (n=78)		1st Pregnancy (n=22)		2nd Pregnancy (n=56)		T-test		P-value	
		Mean (±sd)	Min./Max.	Mean (±sd)	Min./Max.	Mean (±sd)	Min./Max.				
Age (years)		28.8 (4.7)	18/42	25.7 (3.6)	19.0/32.0	30.1/(4.5)	18.0/42.0	4.51		0.00004	
Weight (kg)		67.1 (12.9)	39/122	61.2 (13.3)	39.0/85.0	69.5 (12.1)	50.0/122.0	2.54		0.02	
Height (m)		1.614 (0.08)	1.30/1.79	1.615 (0.08)	1.50/1.79	1.61 (0.08)	1.30/1.72	0.16		0.91	
BMI (Kg/m2)		25.9 (5.5)	15.2/47.7	23.6 (5.4)	15.2/35.6	26.9 (5.3)	18.6/47.7	2.44		0.02	
Variable	Sub-variable	Freq.	%	Freq.	%	Freq.	%	X_2	P-value	OR	95% CI
Age group	≤20	2	2.6	1	4.5	1	1.8	0	1	2.62	0.16, 43.81
	21-25	13	16.7	8	36.4	5	8.9	6.7	0.01	5.83	1.65, 20.63
	26-30	37	47.4	11	50	26	46.4	0.08	0.78	1.15	0.43, 3.10
	31-35	22	28.2	2	9.1	20	34.7	4.29	0.04	0.18	0.04, 0.85
	36-40	3	3.8	0	0	3	5.4	0.21	0.65	0	undefined
	>40	1	1.3	0	0	1	1.8	0	1	0	undefined
Residence	Urban	64	81.1	17	77.3	47	83.9	0.47!	0.49	1.54	0.45, 5.23
	Rural	14	18.9	5	22.7	9	16.1				
Educational status	Primary	4	5.1	2	9	2	3.6	0.19*	0.67	0.67	0.05, 2.81
	Secondary	27	34.6	10	45.5	17	30.4	1.57	0.21	0.52	0.19, 1.44
	Tertiary	46	59	10	45.5	36	64.3	2.29	0.13	2.16	0.79,5.88
	Others	1	1.3	0	0	1	1.8	0.00*	1	undefined	
Religious affiliation	Christianity	51	65.4	16	72.7	35	62.5	0.72	0.4	0.62	0.21, 1.85
	Islam	27	34.6	6	27.3	21	37.5				
Employment status	Civil servant	19	24.5	6	27.3	13	23.2	0.14	0.71	0.81	0.26, 2.48
	Artisan	10	12.8	2	9.1	8	14.3	0.06*	0.91	1.67	0.32, 8.55
	Trader	37	47.4	7	31.8	30	53.6	2.96	0.09	2.47	0.87, 6.99
	Housewife	5	6.4	1	4.5	4	7.1	0.00*	1	1.62	0.17, 15.31
	Student	1	1.3	1	4.5	0	0	0.24*	0.63	undefined	
	Unemployed	6	7.7	5	22.7	1	1.8	7.03*	0.008	0.06	0.001, 0.57
Household size	Two	12	15.4	5	22.7	7	12.5	0.61*	0.44	0.49	0.14, 1.73
	Three	29	37.2	14	63.5	15	26.8	9.07	0.003	0.21	0.07, 0.60
	Four	33	42.3	2	9.1	31	55.4	12.02*	0.0005	12.4	2.64, 58.20
	Five	4	5.1	1	4.6	3	5.4	0.00*	1	1.19	0.12, 12.08
Daily income (in Nigerian Naira)	None	2	2.6	1	4.6	1	1.8	0.00*	1	0.38	0.02, 6.39
	<3000	17	21.8	4	18.2	13	23.2	0.03*	0.86	1.36	0.39, 4.74
	3000-5000	26	33.3	7	31.8	19	33.9	0.03	0.86	1.1	0.38, 3.16
	>5000-9,999	8	10.3	3	13.6	5	8.9	0.04*	0.84	0.62	0.14, 0.85
	≥10,000	25	32	7	31.8	18	32.1	0.0008	0.98	1.01	0.35, 2.95
Fever in pregnancy	Yes	28	35.9	6	27.3	22	39.3	0.98	0.32	1.73	0.59, 5.08
	No	50	64.1	16	72.7	34	60.7				
Placental malaria	Yes	3	3.8	1	4.5	2	3.4	0.00*	1	0.78	0.07, 9.04
	GMPD	476.3		484		470.1					
	No	75	96.2	21	95.5	54	96.6				
Peripheral malaria	Yes	15	19.2	7	31.8	8	14.3	3.09	0.08	0.36	0.11, 1.15
	No	63	80.8	15	68.2	48	85.7				

*Yate's correction; ! those in their 2nd pregnancy were 1.5 times more likely to be urban than rural dwellers (X^2=0.47, P-vale=0.49, OR=1.54, 95% CI=0.45, 5.23): GMPD=Geometric Mean Parasite Density.

The means (±sd) of age (years), weight (kg) height (m) and Body Mass Index (Kg/m^2)of all the study participants were 28.8 (4.7), 67.1 (12.9), 1.614 (0.08) and 25.9 (5.5). Those in the second pregnancy were significantly older (t-test=4.51, P-value=0.00004) and heavier

(t-test=2.44, P-value=0.02) than those in their 1st pregnancy. Among all study the subjects and among those in their 1st or 2nd pregnancy, 37 (47.4%), 11 (50.0%) or 26 (46.3%) respectively were aged 26-30 years (Figure 1). Overall, 4 (5.1%), 34 (43.6%), 21 (26.9%) and 19 (24.4%) were underweight, normal weight overweight and obese; in the 1st pregnancy, 4 (18.2%), 11 (50.0%), 3 (13.6%) and 4 (18.2%) were underweight, normal weight, overweight and obese while in the 2nd pregnancy, none was underweight but 23 (41.1%), 18 (32.1%) and 15 (26.8%) were normal weight, overweight and obese (Figure 2). Further, those in the 2nd pregnancy were about 1.5 times more likely to be urban dwellers (OR=1.54, 95% CI=0.45, 5.23), 2.16 times to have tertiary educational status (OR=2.16, 95% CI=0.79, 5.88), 2.47 times to be traders (OR=2.47, 95% CI=0.87, 6.99), 12.4 times more likely to have a household size of four, (OR=12.40, 95% CI=2.64, 58.20), and 1.7 times to have fever in pregnancy (OR=1.73, 95% CI=0.59, 5.08), more than those in their 1st pregnancy.

- *Hematological profile, TNF-α and IFG-γ concentrations among pregnant women with and without peripheral or placental malaria. Table 2.*

Table 2: Hematological profile, TNF-α and IFG-γ concentrations among pregnant women with and without peripheral or placental malaria.

Variable	All		Placental Malaria				T-test (P-value)	Peripheral malaria				T-test (P-value)
			Present (n=3, 3.9%)		Absent (n=75, 96.1%)			Present (n=15, 19.2%)		Absent (n=63, 80.8%)		
	Mean (±sd)	Min./ Max.	Mean (±sd)	Min./ Max.	Mean (±sd)	Min./Max.		Mean (±sd)	Min./ Max.	Mean (±sd)	Min./ Max.	
RBC (x109L)	3.63 (1.34)	1.12/ 7.92	3.9 (0.2)	3.7/ 4.1	3.6 (1.4)	1.1/ 7.9	1.51 (0.15)	4.1 (1.2)	1.8/ 6.0	3.5 (1.3)	1.1/ 7.9	1.71 (0.10)
Hgb (g/L)	11.07 (4.33)	3.30/ 23.30	11.5 (1.5)	10.1/ 13.1	11.1 (4.4)	3.3/ 23.3	0.40 (0.71)	13.1 (5.0)	6.8/ 21.4	10.6 (4.0)	3.3/ 23.3	1.80 (0.09)
Hct (%)	0.35 (0.14)	0.09/ 0.75	0.4 (0.1)	0.3/ 0.3	0.3 (0.1)	0.1/ 0.8	1.70 (0.22)	0.4 (0.2)	0.2/ 0.6	0.3 (0.1)	0.1/ 0.8	1.88 (0.08)
MCV (fl)	92.54 (18.00)	16.60/ 126.00	92.8 (13.0)	84.5/ 107.8	92.5 (18.2)	16.6/ 126.0	0.04 (0.97)	95.9 (16.1)	65.6/ 120.5	91.7 (18.5)	16.6/126.0	0.88 (0.39)
MCH (pg)	30.47 (4.75)	21.10/ 57.60	29.2 (3.3)	26.9/ 33.0	30.5 (4.8)	21.1/ 57.6	0.66 (0.57)	30.6 (4.9)	21.2/ 37.6	30.4 (4.8)	21.1/57.6	0.14 (0.89)
MCHC (g/L)	310.10 (41.00)	75.00/ 401.00	320.7 (14.5)	306.0/335.0	309.7 (41.7)	75.0/ 401.0	1.14 (0.33)	313.5 (27.1)	261.0/ 391.0	309.3 (43.8)	75.0/401.0	0.47 (0.64)
Platelets (x109)	77.59 (88.28)	9.00/ 460.00	27.7 (14.2)	19.0/ 44.0	79.6 (89.4)	9.0/ 460.0	3.94 (0.002)	69.2 (50.5)	11.0/ 193.0	79.6 (95.3)	9.0/ 460.0	0.59 (0.56)
WBCC	3.20 (2.19)	0.29/ 10.43	5.0 (2.9)	2.3/ 8.0	3.1 (2.2)	0.3/ 10.4	1.12 (0.37)	3.3 (1.8)	0.7/ 6.2	3.2 (2.3)	0.3/10.4	0.18 (0.86)
Neut.	1.74 (1.51)	0.06/ 7.98	3.4 (2.2)	1.6/ 5.9	1.7 (1.5)	0.1/ 8.0	1.33 (0.31)	1.9 (1.2)	0.3/ 3.9	1.7 (1.6)	0.1/ 8.0	0.54 (0.59)
Lymph.	0.87 (0.78)	0.08/ 4.65	1.1 (0.5)	0.6/ 1.4	0.9 (0.8)	0.1/ 4.6	0.66 (0.57)	0.8 (0.6)	01/1.8	0.9 (0.8)	0.1/ 4.7	0.54 (0.59)
Mono.	0.15 (0.15)	0.01/ 0.56	0.3 (0.0)	0.1/ 0.5	0.2 (0.1)	0.01/ 0.6	8.66 (0.00)	0.2 (0.1)	0.03/ 0.5	0.2 (0.2)	0.01/0.6	0.0 (1.00)
Eos	0.07 (0.11)	0.0/ 0.76	0.1 (0.1)	0.0/ 0.1	0.1 (0.1)	0.0/ 0.8	0.00 (1.00)	0.1 (0.1)	0.0/0.2	0.1 (0.1)	0.0/ 0.8	0.0 (1.00)
Bas	0.08 (0.08)	0.0/ 0.38	0.02 (0.0)	0.01/ 0.04	0.1 (0.1)	0.0/ 0.4	8.66 (0.00)	0.1 (0.1)	0.0/0.3	0.1 (0.1)	0.0/ 0.4	0.0 (1.00)
IG	0.35 (0.65)	0.0/ 3.20	1.3 (1.4)	0.3/ 2.9	0.3 (0.6)	0.0/ 3.2	1.23 (0.34)	0.5 (0.9)	0.0/3.2	0.3 (0.6)	0.0/ 2.9	0.82 (0.42)
TNF-α	19.90 (23.67)	5.90 148.80	9.4 (1.5)	7.7/ 10.3	20.3 (24.1)	5.9/ 148.8	3.74 (0.0004)	20.3 (14.8)	6.3 (60.7)	19.8 (25.4)	5.9/ 148.8	0.10 (0.92)
IFN-γ	12.44 (19.24)	5.00/ 119.20	6.1 (0.5)	5.6/ 6.4	12.7 (19.6)	5.0/ 119.2	2.89 (0.005)	13.6 (19.5)	5.0/68.6	12.2 (19.3)	5.0/ 119.2	0.25 (0.80)

The mean (±sd) values of all hematological parameters, TNF-α and IFG-γ of all study subjects and of those with or without PlacMal or PerMal are as shown in Table 2. Of the red blood cell series, the mean platelet count (x109) of study subjects with PlacMal (n=3, 27.7±14.2) was notably varied (t-test=3.94, P-value=0.002) from those without PlacMal (n=75, 79.6±89.4), an observation not noted among those with PerMal. Of the white blood cell series, the mean (±sd) absolute values of monocytes (n=3, 0.3±0.0) and basophils (n=3, 0.2±0.0) were of study subjects with PlacMal were also significantly higher (t-test=3.94, P-value=0.002 respectively) among those with PlacMal compared to study subjects without PlacMal. Further, the means of placental TNF-α (9.4±1.5) and of IFN-γ (6.1±0.5) concentrations among those with PlacMal, were significantly lower (t-test=3.74, P-value=0.0004; t-test=2.89, P-value=0.005) than among study subjects without PlacMal (n=75, 20.3±24.1; 12.7±19.6 respectively), which were not observed in those with PerMal. The overall prevalence of placental malaria parasitemia was relatively low at 3.9%, while that of peripheral malaria parasitemia was 19.2%. Lastly, the mean absolute count of IG among all study women was 0.35±0.65, which rose to 1.3±1.4 in the presence of PlacMal, though not significantly different from the mean value of study subjects without PlacMal which was 0.30±0.60. Among those with PerMal, the mean absolute IG count was 0.50±0.90 which was also not significantly varied from that among study subjects without PerMal of 0.3±0.6.

- *Means (±) of birth anthropometric indices, studied cytokines and hematological parameters of all study subjects and those in their 1st and 2nd pregnancy. Table 3.*

Table 3: Means (±) of birth anthropometric indices, studied cytokines and hematological parameters of all study subjects and those in their 1st and 2nd pregnancy.

Variables	All (n=78)				1st Pregnancy (n= 22)				2nd Pregnancy (n=56)			
	n	Bthwt	Bthlth	Bthhc	n	Bthwt	Bthlth	Bthhc	n	Bthwt	Bthlth	Bthhc
TNF-α <20 (pg/ml)	59 (75.6)	3.2 (0.4)	48.3 (4.9)	34.3 (2.4)	9 (40.9)	3.2 (0.5)	50.6* (1.8)	33.9 (0.6)	50 (89.3)	3.2 (0.4)	47.8* (5.1)	34.4 (2.6)
TNF-α ≥20 (pg/ml)	19 (24.4)	3.0 (0.4)	49.1 (2.2)	34.6 (1.4)	13! (59.1)	2.9 (0.3)	49.3 (2.0)	34.4 (1.3)	6! (10.7	3.2 (0.6)	48.7 (2.8)	35.0 (1.5)
IFN-γ <30 (pg/ml)	70 (89.7)	3.1 (0.4)	48.4 (4.6)	34.3 (2.2)	15 (68.2)	3.0 (0..4)	50.5^# (1.5)	33.9 (0.9)	55 (98.2)	3.2 (0.5)	47.9# (4.9)	34.4 (2.5)
IFN-γ ≥30 (pg/ml)	8 (10.3)	2.9 (0.3)	48.7 (2.4)	35.1 (1.7)	7 (31.8)	2.9 (0.2)	48.3^ (2.1)	34.7 (1.4)	1 (1.8)	3.5 (0.0)	52.0 (0.0)	38.0 (0.0)
Hgb<9.5	25 (32.1)	3.2 (0.4)	49.2 (2.9)	34.4 (1.2)	7 (31.8)	3.1 (0.3)	50.1 (2.0)	34.4 (0.5)	18 (32.1)	3.2 (0.5)	48.8 (3.1)	34.4 (1.4)
Hgb≥9.5	53 (67.9)	3.1 (0.4)	48.1 (4.9)	34.4 (2.6)	15 (68.2)	3.0 (0.4)	49.7! (2.1)	34.1 (1.3)	38 (67.9)	3.2 (0.4)	47.5! (5.6)	34.5 (2.9)
Platelets <150,000	68 (87.2)	3.1 (0.4)	48.4 (4.6)	34.4 (2.3)	20 (90.9)	3.0 (0.4)	49.9!! (2.0)	34.2 (1.2)	48 (85.7)	3.2 (0.5)	47.7!! (5.2)	34.5 (2.7)
Platelets 150,000-450,000	9 (11.5)	3.1 (0.4)	49.0 (2.4)	33.9 (0.6)	2 (9.1)	3.2 (0.3)	49.0 (2.8)	34.0 (0.0)	7 (12.5)	3.1 (0.5)	49.0 (2.5)	33.9 (0.7)

Platelets >450,000	1 (1.3)	3.5 (0.0)	51.0 (0.0)	35.0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	3.5 (0.0)	51.0 (0.0)	35.0 (0.0)
Absolute IG<0.018	18 (23.1)	2.9 (0.5)	46.7 (5.6)	34.4 (4.2)	3 (13.6)	2.8 (0.2)	49.7 (1.5)	34.7 (0.6)	15 (26.7)	3.0 (0.5)	46.1^^ (6.0)	34.4 (4.6)
Absolute IG 0.018-0.456	46 (59.0)	3.2 (0.4)	48.6 (4.2)	34.3 (1.1)	15 (68.2)	3.0~ (0.4)	49.7 (2.2)	33.9 (1.0)	31 (55.4)	3.3~ (0.4)	48.1^^ (4.8)	34.5 (1.2)
Absolute IG >0.456	14 (17.9)	3.1 (0.3)	50.1 (2.1)	34.7 (1.0)	4 (18.2)	2.9@ (0.2)	50.2 (2.1)	35.0 (1.4)	10 (17.9)	3.2@ (0.3)	50.1^^ (2.2)	34.6 (0.8)

*t-test=2.98, P-value=0.005; !X^2=19.80, P-value<0.0001, OR=12.04, 95% CI)3.63, 39.96): ##t-test=2.40, P-value=0.03; ^t-test=2.43, P-value=0.04: #t-test=3.39, P-value=0.001: !t-test=2.08, P-value=0.04: !!t-test=2.51, P-value=0.01: ^^F-ratio=4.48, P-value=0.01: ~ t-test=2.08, P-value=0.04: @ t-test=2.18, P-value=0.06

In TNF<20 pg/ml, the mean birth length of neonates from study participants in the 1st pregnancy (50.6±1.8 cm) was notably higher (t-test=2.98, P-value=0.005) than that from those in the 2nd pregnancy (47.8±5.1 cm). Moreover, those in the 1st pregnancy were 12 times more likely to present with TNF-α ≥20 pg/ml compared to those in their 2nd pregnancy (X^2=19.80, P-value<0.0001, OR=12.04, 95% CI)3.63, 39.96). The mean birth length of neonates from 1st pregnancy in study subjects with IFN-γ<30 pg/ml (50.5±1.5 cm) was significantly higher (t-test=2.40, P-value=0.03) than that of their counterparts with IFN-γ≥30 pg/ml (48.3±2.1 cm), and also significantly higher (t-test =3.39, P-value= 0.001) that the mean neonatal birth length in the 2nd pregnancy (47.9±4.9 cm). Moreover, study subjects in their 1st pregnancy were approximately 26 times more likely to have IFN-γ ≥30 pg/ml compared to those in their 2nd pregnancy (X^2=15.28, P-value<0.0001, OR=26.67, 95% CI =3.93, 225.18). A significant variation (t-test=2.08, P-value=0.04) was noted in the mean neonatal birth length of 1st pregnancy study subjects with Hgb≥9.5 and mean neonatal birth length of 2nd pregnancy study subjects. Study subjects in their 1st pregnancy and 2nd pregnancy were equally likely to have of Hgb≥9.5 (X^2=0.0008, P-value=0.98, OR=1.01, 95% CI =0.35, 2.92). Only one study subject in the 2nd pregnancy group, presented with a platelet count on >450,000x109. Of the remaining study subjects, the mean birth length of neonates from 1st pregnancy with platelet count <150,000 x109 (49.9±2.0 cm) was significantly higher (t-test=2.51, P-value=0.01) than the mean birth length of neonates from 2nd pregnancy with the same platelet count (47.±5.2 cm). Lastly, the majority (46, 59.0%) of study subjects had placental IG of 0.018-0.456 (absolute count). Mean birthweight of study subjects with IG <0.018 (2.9±0.5 kg) was lower than that of study subjects with IG of 150,000-450,000 (3.2±0.4) and of IG >0.456 (3.1±0.3). Also, the mean birthweight of neonates from those in their 2nd pregnancy (n=31, 3.3±0.4 kg) was significantly different (t-test=2.08, P-value=0.04) from that of their counterparts in their 1st pregnancy (n= 15, 3.0±0.4 kg), baring both had absolute IG count of 0.018-0.456. A significant variation (ANOVA F-ratio=3.73, P-value=0.03) was also observed in the mean birth lengths of neonates delivered to study participants in their 2nd pregnancy, driven by the mean birth length (50.1.±2.2 cm) of those with placental IG count (absolute) of >0.456. Finally, the difference in mean birth weights of neonates delivered to study participants in 1st (n=4, 2.9±0.2 kg) and 2nd (n=10, 3.2±0.3 kg) pregnancy and with absolute IG count of >0.456, approached a level of significance (t-test=2.18, P-value=0.06).

- *Frequency distribution of TNF-a, IFN-γ, Hgb, Platelets and Immature granulocytes in different categories of study subjects with and without Placental or Peripheral malaria. Table 4.*

Table 4: Frequency distribution of TNF-α, IFN-γ, Hgb, Platelets and Immature granulocytes in different categories of study subjects with and without Placental or Peripheral malaria.

Variables	All (n=78)		1st Pregnancy (n=22)						2nd Pregnancy (n=56)					
			All		Placental malaria				All		Placental malaria			
					+ve (n=1, 4.5%)		-ve (n=21, 95.5)				+ve (n=2)		-ve (n=54)	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
TNF-α <20	59	75.6	9	40.9	1	100	8	38.1	50	89.3	2	100	48	88.9
TNF-α ≥20	19	24.4	13	59.1	0	0	13	61.9	6	10.7	0	0	6	11.1
IFN-γ <30	70	89.7	15	68.2	1	100	14	66.7	55	98.2	2	100	53	98.1
IFN-γ ≥30	8	10.3	7	31.8	0	0	7	33.3	1	1.8	0	0	1	1.9
Hgb<9.5	25	32.1	7	31.8	0	0	7	33.3	18	32.1	0	0	18	33.3
Hgb≥9.5	53	67.9	15	68.2	1	100	14	66.7	38	67.9	2	100	36	66.7
Platelets <150,000	68	87.2	20	90.9	1	100	19	90.5	48	85.7	2	100	46	85.2
Platelets 150,000-450,000	9	11.5	2	9.1	0	0	2	9.5	7	12.5	0	0	7	13
Platelets >450,000	1	1.3	0	0	0	0	0	0	1	1.8	0	0	1	1.9
Absolute IG<0.018	18	23.1	3	13.6	0	0	3	14.3	15	26.8	0	0	15	27.8
Absolute IG 0.018-0.456	46	59	15	68.2	0	0	15	71.4	31	55.4	1	50	30	55.6
Absolute IG >0.456	14	17.9	4	18.2	1	100	3	14.3	10	17.9	1	50	9	16.7
Variables	All (n=78)		1st Pregnancy (n=22)						2nd Pregnancy (n=56)					
			All		Peripheral malaria				All		Peripheral			
					+ve (n=7, 31.8%)		-ve (n=15, 68.2%)				+ve (n=8, 14.3%)		-ve (n=48, 85.7%)	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
TNF-α <20	59	75.6	9	40.9	2	28.6	7	46.7	50	89.3	8	100	42	87.5
TNF-α ≥20	19	24.4	13	59.1	5	71.4	8	53.3	6	10.7	0	0	6	12.5
IFN-γ <30	70	89.7	15	68.2	5	71.4	10	66.7	55	98.2	8	100	47	97.1
IFN-γ ≥30	8	10.3	7	31.8	2	8.6	5	33.3	1	1.8	0	0	1	2.9
Hgb<9.5	25	32.1	7	31.8	1	14.3	6	40	18	32.1	3	37.5	15	31.2

Hgb≥9.5	53	67.9	15	68.2	6	85.7	9	60	38	67.9	5	62.5	33	68.8
Platelets <150,000	68	87.2	20	90.9	7	100	13	86.7	48	85.7	7	87.5	41	85.4
Platelets 150,000-450,000	9	11.5	2	9.1	0	0	2	13.3	7	12.5	1	12.5	7	15.6
Platelets >450,000	1	1.3	0	0	0	0	0	0	1	1.8	0	0	0	0
Absolute IG<0.018	18	23.1	3	13.6	0	0	3	20	15	26.8	3	37.5	12	25
Absolute IG 0.018-0.456	46	59	15	68.2	6	85.7	9	60	31	55.4	3	37.5	28	58.3
Absolute IG >0.456	14	17.9	4	18.2	1	14.3	3	20	10	17.9	2	25	8	16.7

Those in 2nd pregnancy were approximately 12 times more like to have placental TNF-α <20 (X_2 =19.8, P-value=0.00, OR=10.0, 95%CI=3.63, 39.96) and 25.6 times more likely to have placental IFN-γ <30 (X_2=12.4, P-value=0.0004, OR=25.7, 95%CI=2.93, 225.18) but equally like to have placental Hgb of <9.5 (X_2=0.0008, P-value=0.98, OR=1.02, 95%CI=0.35, 2.92) compared to those in 1st pregnancy. Those in 1st pregnancy were approximately 1.7 time more likely to have placental Platelet count of <150,000 (X_2=0.06, P-value=0.81, OR=1.7, 95%CI=0.32, 8.55), 0.70 times less likely to present with Platelet count of 150,000-450,000 (X_2=0.0009, P-value=0.98, OR=0.70, 95%CI=0.13, 3.66), 0.43 less likely to present with absolute IG of <0.018 (X_2=0.89, P-value=0.35, OR=0.43, 95%CI=0.11, 1.67) but were 1.73 times more likely to present with absolute IG of 0.018-0.456 (X_2=1.06, P-value=0.30, OR=1.73, 95%CI=0.61, 4.89) and equally likely to present with absolute IG of >0.456 (X_2=0.00, P-value=1.00, OR=1.02, 95%CI=0.28, 3.68).

Those in 2nd pregnancy were approximately 12 times more like to have placental TNF-α <20 (X_2 =19.8, P-value=0.00, OR=10.0, 95%CI=3.63, 39.96) and 25.6 times more likely to have placental IFN-γ <30 (X_2=12.4, P-value=0.0004, OR=25.7, 95%CI=2.93, 225.18) but equally like to have placental Hgb of <9.5 (X^2=0.0008, P-value=0.98, OR=1.02, 95%CI=0.35, 2.92) compared to those in 1st pregnancy. Those in 1st pregnancy were approximately 1.7 time more likely to have placental Platelet count of <150,000 (X^2=0.06, P-value=0.81, OR=1.7, 95%CI=0.32, 8.55), 0.70 times less likely to present with Platelet count of 150,000-450,000 (X^2=0.0009, P-value=0.98, OR=0.70, 95%CI=0.13, 3.66), 0.43 less likely to present with absolute IG of <0.018 (X^2=0.89, P-value=0.35, OR=0.43, 95%CI=0.11, 1.67) but were 1.73 times more likely to present with absolute IG of 0.018-0.456 (X^2=1.06, P-value=0.30, OR=1.73, 95%CI=0.61, 4.89) and equally likely to present with absolute IG of >0.456 (X^2=0.00, P-value=1.00, OR=1.02, 95%CI=0.28, 3.68).

- *Gestational age and birth outcomes among women with and without placental malaria and among those with and without peripheral malaria. Table 5.*

The prevalence of PlacMal malaria in this study population was very low at 3.8%, and that of peripheral malaria at 19.2%. The mean birthweight and the mean PI of neonates from study subjects with PlacMal (n=3, 2.8±0.1 kg; n=3, 2.3±0.1) were notably lower (t-test=5.08, P-value=0.002; t-test=2.80, P-value=0.007) than those from mothers without PlacMal (n=75, 3.2±0.4 kg; n=75, 3.1±2.0). The mean PI of neonates from study subjects

with (n=15, 2.5±0.2) and without (n=63, 3.2±2.2) PerMal were also notably different (t-test=2.18, P-value=0.03).

Table 5: Gestational age and birth outcomes among women with and without placental malaria and among those with and without peripheral malaria

Variable	Placental Malaria				Peripheral malaria			
	+ve (n=3, 3.8%)		-ve (n=75, 96.2%)		+ve (n=15, 19.2%)		-ve (n=63, 80.8%)	
	TNF-α		TNF-α		TNF-α		TNF-α	
	<20	≥20	<20	≥20	<20	≥20	<20	≥20
	(n=3, 3.8%)	(0, 0.0%)	(n=56, 74.7%)	(n=19, 25.3%)	(n=10, 66.7%)	(n=5, 33.3%)	(n=49, 77.8%)	(n=14, 22.2%
	Mean (±sd)		Mean (±sd)		Mean (±sd)		Mean (±sd)	
Gestational age (weeks)	37.9 (1.9)	0.0 (0.0)	39.0 (1.2)	39.0 (1.3)	38.4 (0.9)#	38.0 (1.9)	39.1# (1.3)	39.4 (1.0)
Duration of Labor (hours)	6.4 (2.9)	0.0 (0.0)	6.6 (3.4)	7.7 (3.8)	5.8 (1.3)	8.6 (6.1)	6.8 (3.6)	7.3 (2.9)
Birthweight (Kg)	2.8 (0.1)*	0.0 (0.0)	3.2 (0.4)*	3.0 (0.4)	3.1 (0.4)$	2.7 (0.2)$	3.2 (0.4)	3.1 (0.5)
Birth length (cm)	49.3 (0.6)	0.0 (0.0)	48.2 (5.0)	49.1 (2.2)	49.7 (1.9)	50.0 (1.4)	48.0 (5.2)	48.8 (2.4)
Birth Head circumference (cm)	34.3 (0.6)	0.0 (0.0)	34.3 (2.5)	34.6 (1.4)	33.8 (1.2)	33.4 (1.1)	34.4 (2.6)	35.0 (1.2)
Placental weight	0.5 (0.1)	0.0 (0.0)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
Ponderal index	2.3 (0.1)^	0.0 (0.0)	3.1 (2.0)^	2.5 (0.4)	2.5 (0.2)^^	2.2 (0.3)	3.2 (2.2)^^	2.7 (0.4)
	Freq. (%)		Freq. (%)		Freq. (%)		Freq. (%)	
APGAR score at 1 min. <7	0.0 (0.0)	0.0 (0.0)	8 (12.5)	1 (5.3)	0 (0.0)	1 (20.0)	8 (16.3)	0 (0.0)
APGAR score at 5 min. <7	0.0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Preterm gestational age (<37 wks)	1 (33.3)	0.0 (0.0)	3 (5.4)	1 (5.3)	1 (10.0)	1 (20.0)	3 (6.1)	0 (0.0)
Term gestational age (37-41 wks)	2 (66.7)	0.0 (0.0)	51 (91.0)	18 (94.7)	9 (90.0)	4 (80.0)	44 (89.8)	14 (100.0)
Post-term gestational age (>41 wks)	0.0 (0.0)	0.0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.1)	0 (0.0)

*t-test=5.08, P-value=0.002: ^t-test=2.92, P-value=0.004: #t-test=2.05, P-value=0.05: $t-test=2.58, P-value=0.0.02: ^^t-test=2.18, P-value=0.03:

The mean Gestational age (weeks) of study subjects with PerMal (38.4±0.9) was marginally significantly shorter (t-test=2.05, P-value=0.05) that the gestational age of neonates from study subjects without PerMal.

- *Multiple regression analysis between Age-group, Residence, Educational level and Absolute Immature Granulocytes as independent variable and (a) birth weight (b) birth length and (c) birth head circumference as dependent variables among all study subjects with peripheral malaria. Table 6.*

Table 6: Multiple regression analysis between Age-group, Residence, Educational level and Absolute Immature Granulocytes as independent variable and (a) birth weight (b) birth length and (c) birth head circumference as dependent variables among all study subjects with peripheral malaria.

Equation		Observed	R^2	F	P-value
Birthweight		15	0.8046	15.10	0.0003
Birth length		15	0.7846	13.36	0.0005
Birth head circumference		15	0.4053	8.86	0.0107
Variables		Coef.	Std Err.	T (P-value)	95% CI
Dependent	Independent				
Birthweight	Age group	0.22	0.06	3.78 (0.003)	0.09, 0.34
	Educational status	-0.46	0.11	-4.31(0.001)	-0.70, -0.23
	TNF-α	-0.01	0.004	-2.51 (0.03)	-0.02, -0.001
	Constant	3.69	0.36	10.17(0.00)	2.89, 4.48
Birth length	Age group	1.44	0.28	5.07 (0.000)	0.82, 2.07
	Household size	1.73	0.35	4.92 (0.000)	0.96, 2.51
	TNF-α	0.06	0.02	2.99 (0.012)	-0.02, 0.11
	Constant	38.28	1.95	19.68 (0.00)	34.00, 42.56
Birth head circumference	IG	0.84	0.28	2.98 (0.011)	0.23, 1.45
	Constant	33.27	0.28	120.32 (0.00)	32.68, 33.87

The low prevalence of placental malaria among the study participants defies multivariate regression analysis. However, the prevalence of peripheral malaria detected by RDT in all study subjects was higher, thus allowing multivariate regression analysis as shown in Table 5. Age group, educational status and TNF-α were responsible for a significant (80.5%, P-value=0.0003) variation observed in neonatal birthweight. Individually, multivariate regression analysis indicates a positive, statistically significant relationship between birthweight and age group (coeff. = 0.22, SE=0.06, t-test = 3.78, P-value = 0.003), a negative, statistically significant relationship between birthweight and educational status (coeff. = -0.46, SE=0.11, t-test = -4.31, P-value = 0.001) and between birthweight and TNF-α (coeff. = -0.01, SE=0.004, t-test = -2.51, P-value = 0.03). Age group, household size and TNF--α were responsible for a significant (78.5%, P-value=0.0005) variation observed in birth length of the neonates. Individually, positive, statistically significant associations were observed between birth length and age group (coeff. = 1.44, SE=0.28, t-test = 5.07, P-value < 0.001), household size (coeff. = 1.73, SE=0.35, t-test = 4.92, P-value < 0.001) and TNF-α

(coeff. = 0.06, SE=0.02, t-test = 2.99, P-value = 0.012). Finally, immature granulocytes alone was responsible for a significant (40.5%, P-value=0.0107) variation observed in birth head circumference of the neonates. The association between birth head circumference and immature granulocytes was positive and noteworthy (coeff. = 0.84, SE=0.28, t-test = 2.98, P-value = 0.011). All other independent variables that showed no significant association with the neonates' birthweight, birth length or birth head circumference were removed by backward elimination.

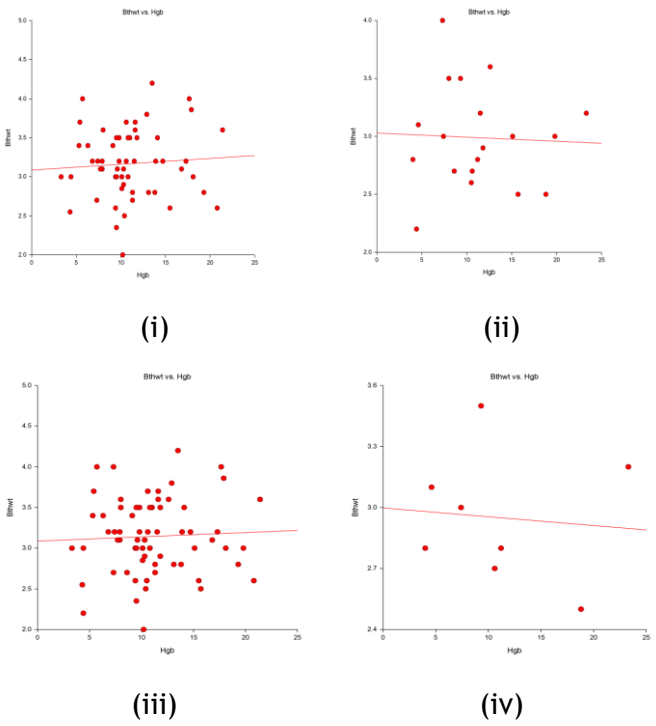
- *Interrelationships between TNF-a, IFN-γ, Platelets, Immature granulocytes and gestational age, duration of labor, birth anthropometry, placental weight and Ponderal index. Table 7, Figures 3-5.*

Table 7: Interplay of different concentrations of TNF-α, IFN-γ, Platelets and Immature granulocytes with gestational age, duration of labor, birth anthropometry, placental weight and Ponderal index.

Variable	TNF-α				IFN-γ			
	<20 (n=59, 75.6%)		≥20 (19, 24.4%)		<30 (n=70, 89.7%)		≥30 (n=8, 10.3%	
	Hemoglobin							
	<9.5 (n=17)	≥9.5 (n=42)	<9.5 (n=8)	≥9.5 (n=11)	<9.5 (n=21)	≥9.5 (n=49)	<9.5 (n=4)	≥9.5 (n=4)
Gestational age	38.8 (1.4)	39.1 (1.2)	39.0 (0.4)	39.0 (1.5)	38.7 (1.2)	39.1 (1.3)	39.3 (1.6)	38.7 (1.5)
Labor duration	7.2 (5.1)	6.3 (2.4)	8.5 (5.3)	7.0 (2.4)	7.8 (5.5)	6.5 (2.4)	7.0 (1.6)	5.8 (2.4)
Birthweight	3.2 (0.4)	3.2* (0.5)	3.1 (0.6)	2.9* (0.3)	3.2 (0.5)	3.1 (0.4)	3.1 (0.3)	2.8 (0.3)
Birth length	49.4 (3.0)	47.9 (5.4)	49.4 (2.9)	48.9 (1.8)	49.1 (3.0)	48.1 (5.1)	49.8 (2.6)	47.7 (1.9)
Birth head circumference	34.1 (1.1)	34.4 (2.8)	35.0 (1.3)	34.3 (1.4)	34.2 (1.0)	34.2 (2.6)	35.3 (1.9)	35.0 (1.8)
Placental weight	0.7 (0.2)	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.6 (0.2)	0.4 (0.1)
Ponderal index	2.7 (0.5)	3.2 (2.3)	2.6 (0.4)	2.5 (4.5)	2.7 (0.5)	3.1 (2.2)	2.5 (0.3)	2.6 (0.4)
	Platelets				Immature Granulocytes			
	<150,000		150,000-450,000		<0.018		0.018-0.456	>0.456
	Hemoglobin							
	<9.5	≥9.5	<9.5	≥9.5	<9.5	≥9.5	<9.5	≥9.5	<9.5	≥9.5

	(n=23)	(n=45)	(n=2)	(n=7)	(n=10)	(n=8)	(n=12)	(n=34)	(n=3)	(n=11)
Gestational age	38.8 (1.3)	39.0! (1.3)	38.0 (1.4)	39.9! (0.9)	38.8 (0.5)	39.3 (0.7)	38.8 (1.2)	38.9 (1.4)	39.0 (1.0)	39.5 (1.3)
Labor duration	7.6 (5.1)	6.4 (2.3)	6.0 (2.8)	7.7 (2.5)	6.2 (3.7)	5.4 (3.0)	7.9 (5.6)	6.9 (2.3)	11.7 (6.4)	6.3 (2.4)
Birthweight	3.2 (0.4)	3.1 (0.4)	3.2 (0.3)	3.1 (0.5)	3.0 (0.5)	2.9 (0.5)	3.3 (0.4)	3.2 (0.5)	3.1 (0.4)	3.1 (0.3)
Birth length	49.2 (2.9)	47.9 (5.2)	49.0 (2.8)	49.0 (2.5)	48.4 (3.7)	44.6 (7.0)	49.2 (2.0)	48.8 (4.8)	52.0** (0.0)	49.6** (2.1)
Birth head circumference	34.4 (1.2)	34.4 (2.8)	34.0 (0.0)	33.9 (0.7)	34.1 (1.1)	34.9 (6.4)	34.5 (1.3)	34.2 (1.1)	35.0 (1.0)	34.6 (1.0)
Placental weight	0.7 (0.2)	0.6 (0.2)	0.6 (0.3)	0.5 (0.2)	0.7 (0.2)	0.6 (0.3)	0.6 (0.2)	0.7 (0.2)	0.8 (0.2)	0.6 (0.2)
Ponderal index	2.7 (0.5)	3.2 (2.3)	2.7 (0.2)	2.6 (0.2)	2.7 (0.5)	3.8 (2.2)	2.8 (0.3)	3.1 (2.4)	2.2 (0.3)	2.6 (0.2)

*t-test=2.52, P-value=0.02: !t-test=2.30, P-value=0.04: **t-test=3.79, P-value=0.004:



<u>Figure 3</u>: Linear regression plots of (i) Birthweight (dependent variable) versus Hgb (independent variable) when TNF-α <20 pg/ml (ii) birthweight and Hgb when TNF-α ≥20 pg/ml in all study subjects (iii) birthweight and Hgb when IFN-γ <30 pg/ml and (iv) when IFN-γ≥30 pg/ml.

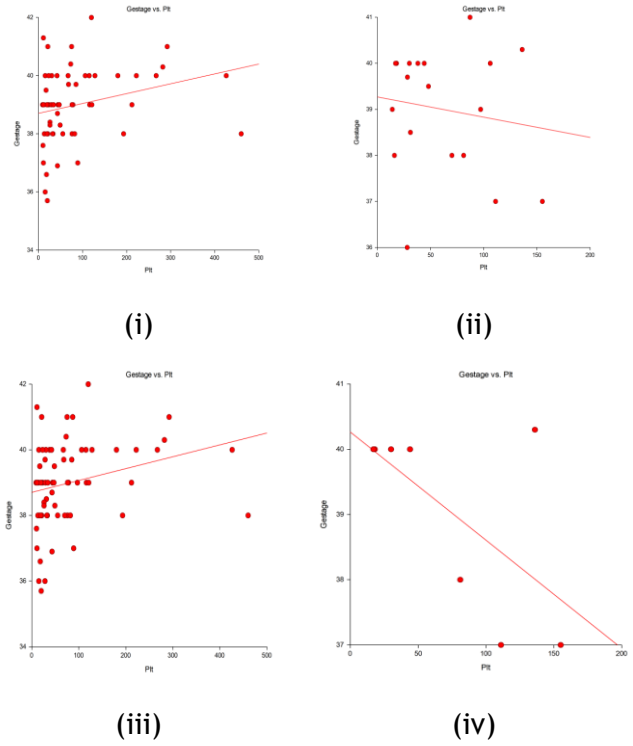


Figure 4: Linear regression plots of (i) gestational age versus Platelets count when TNF-α <20 pg/ml and (ii) of gestational age and versus platelet count when TNF-α ≥20 pg/ml in all study subjects, (iii) when IFN-γ was <30 pg/ml and (iv) when IFN-γ ≥30 pg/ml.

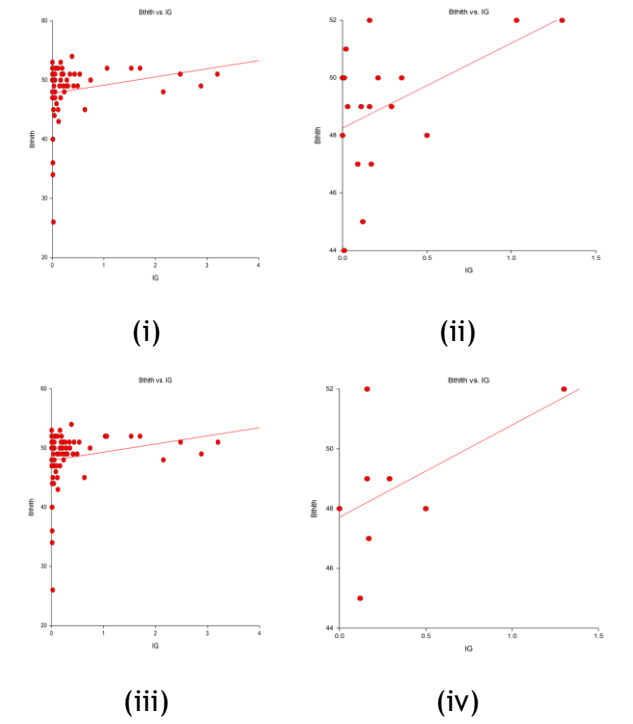


Figure 5: Linear regression plots of (i) birth length (cm) versus IG when TNF-α <20 pg/ml and (ii) when TNF-α ≥20 pg/ml (iii) when IFN-γ<30 pg/ml and (iv) when IFN≥30 pg/ml in all study subjects.

The study subsequently evaluated the interaction between various concentrations of placental TNF-α, IFN-γ, Platelet counts and Immature granulocytes and gestational age, duration of labor, birth anthropometry, placental weight and PI in all study subjects. The mean birthweight (3.2±0.5 kg) of neonates from mothers without placental anemia (Hgb ≥9.5) and with placental TNF-α <20 pg/ml (normal level) was significantly greater (t-test=2.52, P-value=0.02) than that (2.9±0.3 kg) of neonates from mothers without placental anemia but with TNF-α ≥20 pg/ml (abnormal level).

Parametric statistical analysis showed a positive, weak and insignificant correlation (r=+0.07, t-value=0.51, P-value=0.61) between birthweight (kg) and Hgb when placental TNF-α was <20 pg/ml, but a negative weak and insignificant correlation (r=-0.04, t-value=0.17, P-value=0.87) when TNF-α≥20 pg/ml. Similarly, a positive, weak and insignificant correlation (r=+0.05, t-value=0.38, P-value=0.70) was observed between birthweight (kg) and Hgb at IFN-γ<30 pg/ml but a negative, weak and insignificant correlation (r=-0.09, t-value=0.23, P-value=0.83) was observed when IFN-γ was ≥30 pg/ml (Figure 2).

At normal levels of TNF-α (<20 pg/ml) and IFN-γ (<30 pg/ml), gestational age positively correlated with platelets count (r=+0.26, t-value=2.04, P-value=0.046 and r=+0.26, t-value=2.21, P-value=0.03 respectively). However, at higher levels of TNF-α (≥20 pg/ml) and IFN-γ (≥30 pg/ml), insignificant negative correlations (r=-0.14, t-value=0.59, P-value=0.56 and r=-0.63, t-value=1.98, P-value=0.09 respectively) were observed between gestational age and platelets count (Figure 3). Furthermore, at normal levels of both cytokines, birth length had a positive, weak, and insignificant correlation (r=+0.20, t-value=1.58, P-value=0.12 and r=+0.20, t-value=1.71, P-value=0.09 respectively) with absolute IG count. At a higher level, TNF-α, there was a positive, moderately strong, and significant correlation (r=+0.47, t-value=2.15, P-value=0.047) between birth length and with absolute IG count but at a higher level of IFN-γ, the correlation between birth length and absolute IG count was positive, moderately strong, but insignificant relationship (r=0.54, t-value=1.57, P-value=0.17). When IG count was >0.456 and was a significant difference (t-test=3.79, P-value=0.004) was observed between the mean birth length of neonates from mothers with (52.0±0.0 cm) and without (49.6±2.1 cm) placental anemia, (Figure 4).

In the presence of normal platelet count and normal hemoglobin concentration, the mean gestational age of study participants (39.9±0.9 months) was noticeably longer (t-test=2.30, P-value=0.04) than that of study participants with thrombocytopenia (<150,000 $x10^9$/L).

DISCUSSION

Whether the activities of placental cytokines such as TNF-α or IFN-γ are influenced by the degree of placental anemia in relation to pregnancy and its outcome has not been fully elucidated. This study reports the interaction of these cytokines and some hematological parameters among pregnant women in the 1st and in the 2nd pregnancy. Pregnancy itself is a complex phenomenon that involves biochemical, cellular, hormonal, and immunological activities, among others, to support and ensure a healthy fetus and safe delivery. Events operational in the placenta, the organ that serves as an interface between the mother and the fetus, mostly determine the delivery of a healthy, unhealthy, abnormal, or dead fetus.

There are key finding that need thorough discussion. First, although PlacMal was scanty, platelet count was significantly higher among pregnant women without than among those with PlacMal. Very few studies have reported this physical process. The only report relating to placental malaria and platelets counts is a study in Malawi by Mandala et al who submitted that platelet counts were significantly lower in acute phase for all investigated malaria types— uncomplicated malaria (UCM), severe malarial anemia (SMA) and cerebral malaria and that parasite density (number of parasites/μL blood) were inversely correlated to platelet (PLT) count (number of cells/L blood) [21]. That thrombocytopenia is prevalent in human malaria infection is also corroborated by the findings of Gupta et al [22]. Monocytes and Basophils were also elevated among pregnant women with PlacMal in this study. In consonance with findings in this paper, a recent study in Southern Benin reported association of PlacMal with a higher frequency of classical monocytes [23] while other studies detected a significantly higher rate of monocytes and macrophage in placentae with malaria infections [24, 25]. Monocytes are the largest type of white blood cells which can differentiate into macrophages and monocyte-derived dendritic cells. These cells were possibly drafted into the malaria-positive placenta, as part of the front line innate immune system, to fight off the invading malaria parasites, probably by phagocytosis. A subset of monocytes might even secrete cytokines in response to malaria infection [26, 27]. Basophils, often called granulocytes, are the rarest type of white blood cell that contain tiny granules full of histamine. They might have also been drafted into the placenta for protection against malaria parasites and help to heal damages to the placenta structure [28]. Ordinarily, TNF-α and IFN-ß were supposed to be higher among women with placental malaria as their production is increased during infection. Contrary to expectation, these cytokines were suppressed among pregnant women with PlacMal in this study. This may be due to the relatively few study subjects with PlacMal, very few malaria parasite in the placenta, and maternal recovery from placental malaria due to administration of Sulphadoxine-Pyrimethamine intermittent preventive therapy in pregnancy (IPTp), a policy vigorously implemented by the Lagos State Government. Another major observation is that, in the 1st pregnancy, the mean birthweight of neonates from mothers with elevated placental TNF-α concentration was lower than that of mothers with normal placental TNF-α level, though the difference did not reach a level of significance. This finding in study is in consonance with the report of Dong et al [29] who reported that P.falciparum infection of the placenta is closely related with high concentrations TNF-α. Some old studies reported that high placental TNF-α concentration is associated with low birthweight (LBW), especially for malaria-infected primigravidae [30, 31] and excessive level of IFN-ß may be detrimental for fetal growth [32]. Further analysis shows that mean birthweight was significantly low when malaria parasite was present and TNF-α was low and when Hgb was normal and TNF-α was high. This may suggest that high TNF-α may be modulating the effect of Hgb on fetal development. Further studies are needed to ascertain this finding. Probably for the first time, this study reports a major finding that birth length of neonates from study participants in the 1st pregnancy, who also had high concentrations of placental IFN-γ, was significantly shorter than the birth length of neonates from those with normal placental IFN-γ. The study also reports that, at high IG count, birth length of neonates from mothers with PlacMal was longer than that of neonates from mothers without anemia. Birth length is not often reported in scientific literature, at least not in sub-Saharan Africa, including Nigeria. In the presence of anemia, either TNF-α or IFN-γ may act independently or in synergy to elicit a longer bone formation as a compensatory mechanism for increased erythropoiesis to counter

fetal anemia. This may be one of the functions of the cytokines, in tandem with other factors, as part of the immuno-expression activities for acceptable birth outcomes. Again, this finding needs further clarification through multi-center and inter-disciplinary studies. Trans et al's opinion was that high levels of IFN-γ possibly impacts the placenta adversely, resulting in a poor gestational outcome [33]. The mean absolute count of IG in the placenta of study subjects was higher among women with PlacMal. While the presence of IG in healthy pregnant women is considered a normal physiological response to the increased drive for erythropoiesis, their presence in the placenta is not prominent except when they are drafted there during stressful conditions, infection or placentitis. Presence of IG in the malaria-positive or malaria-negative placenta is not often reported in sub-Saharan Black African women and this may be the first paper to report such phenomenon. Malaria-endemic regions, such as Nigeria, have pregnancies with the highest risk of death for the newborn but the lowest availability of data on adverse birth outcomes. This study may further provide more knowledge on malaria in pregnancy, especially placental malaria and the effect of cytokines such as TNFα and IFN-γ and other factors acting independently or in synergy on birth outcomes. This critical research topic requires deep consideration from the Federal Government of Nigeria, the African Union, International Agencies such as the World Health Organization, UNICEF and World Bank, to fund multi-center and multi-disciplinary studies in Africa, so as to contribute significantly to maternal and child health in the continent.

STUDY STRENGTH AND LIMITATIONS

The study was supported by different arms of Lagos State Government. Staff from Ikorodu General Hospital and Ita-Elewa PHC included Medical Doctors, Mid-wives, Health Management Information Service Officers, and Medical Record Keepers. Patients were cooperative. Nigerian Institute of Medical Research provided modern equipment for analysis. Various variables were collected to strengthen the study. Regarding limitation, there were delays in fund release causing inflation to affect study costs. Placental malaria was studied without assessing other changes. Some areas with malaria parasites may have been missed. Fecal samples for anemia causes were not tested. Cord blood was collected but neonatal parameters were not assessed due to funding shortage. Blood samples were collected for future malaria detection. Data in this study may not reflect current situation across Nigeria. Larger studies are needed to address issues. Sampling bias and sample size could have also affected the results of this study. Maternal hematological parameters were not evaluated.

CONCLUSION

Placental platelet count, TNF-α, IFN-γ and IG may have distinct or combined roles to play in the development of fetal anthropometry. At normal plasma or placental concentrations, and in the absence of anemia or any abnormality, both TNF-α and IFN-γ exert beneficial influences on the defenceless fetus, protecting it from infection, rejection or any other deleterious influences to ensure growth and survival. But at higher concentrations, either or both may trigger various placental or fetal pathologies as shown in this study, especially shorter gestational period, longer duration of labor, low birthweight, and low birth length,

as shown in this study. More intense multi-center and multi-disciplinary studies are needed to clarify and elucidate these finding.

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Conflict of Interest: The authors hereby declare that they, individually or collectively, have no competing interest.

Data Availability: All data supporting the findings of this publication may be made available upon request.

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