THE ASSOCIATION BETWEEN PLACENTAL MALARIA PARASITIZATION AND PRE-ECLAMPSIA/ECLAMPSIA IN PRIMIGRAVIDAE AT MUHIMBILI NATIONAL HOSPITAL DAR-ES-SALAAM/ TANZANIA

By

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A dissertation submitted in partial fulfillment of the requirement for the degree of master of medicine (Obstetrics/Gynaecology) of the University of Dar es salaam.

University of Dar es salaam

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the University of Dar es salaam a dissertation entitled ***the association between placental malaria parasitization and pre-eclampsia/ eclampsia in primigravidae at Muhimbili National Hospital Dar es salaam - Tanzania***, in partial fulfilment of the requirements for the degree of master of medicine (obstetrics and gynaecology)

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DECLARATION AND COPYRIGHT

I Dr Chrisostom Clarence Lipingu hereby declare that this dissertation is the result of my own original work and that to the best of my knowledge it has not been submitted for a degree award in any other university.

Signature 

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I am greatly indebted to register my gratitude to my supervisor Professor Kaisi for his constructive criticism and valuable suggestions throughout my study time. I also owe many thanks to Dr Mgaya (my second supervisor) and Dr Masambu both from Histopathology Department. Their tireless efforts of encouragement and histopathological knowledge and work are highly appreciated.

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DEDICATION

This dissertation is dedicated to my parents, especially the late my mother who passed away when I was busy preparing this work. Also to my wife Piensia for her patience, sacrifice and encouragement; and to our children Ditram, Ditmar and the little boy Ditrick who were deprived of their father 's presence and personal care in the course of the study.

ABSTRACT

Objective To determine the association between placental malaria parasitazation and pre-eclampsia/eclampsia in Muhimbili National Hospital – Tanzania.

Design Unmatched case control study.

Setting Muhimbili National Hospital (MNH) labor ward.

Population Primigravidae with pre-eclampsia /eclampsia as cases and those without as controls who delivered at MNH.

Methods Peripheral blood smear to detect malaria parasite was done by taking venous blood. Pieces of placental tissue were taken and histological analysis was done to detect the presence of placental malaria parasites and pigments.

Results The study did not find statistical significant difference between pre eclampsia/eclampsia and the control group when malaria parasites and/or pigments were analyzed in the blood and in the placenta. Overall there has been a clinical significantly higher prevalence of placental malaria parasites and pigments in cases than controls but it has not been proved statistically in this study.

Conclusion Therefore the study has found no association between the presence of placental malaria parasitization and occurrence of pre eclampsia/eclampsia.

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ABBREVIATIONS.

MNH. = MUHIMBILI NATIONAL HOSPITAL
IFN. = INTERFERON
IVBMC = INTERVILLOUS BLOOD MONONUCLEAR CELLS
MPS = MALARIA PARASITES
WBC = WHITE BLOOD CELLS

INTRODUCTION AND REVIEW OF LITERATURE.

Pre eclampsia and eclampsia continue to be important public health problems. The disorder is responsible for a high proportion of hospital admissions, labor inductions, and morbidity/mortality to both mothers and babies.

Eclampsia kills around 50,000 women each year world wide[16]. In UK pre eclampsia and eclampsia together were the 3rd leading causes of pregnancy related deaths between 1979 – 1992 , with maternal mortality ratio of 1.5 death per 100,000 live births, following embolism 1.9 per 100,000 and hemorrhage 1.6 per 100,000 live births. The risk of death has been found to be highest when eclampsia occurs bellow 28 weeks of gestation and among primigavidae[16].

The study done in Zimbabwe showed that eclampsia was the leading cause of maternal mortality in 1995 accounting 26% followed by haemorrhage 25%, where as puerperal and postabortal sepsis were next common causes of maternal deaths [7].

Hypertensive diseases in pregnancy account for 15.9% of antenatal attendance in Muhimbili Medical Centre (now Muhimbili National

Hospital)[33]. The condition also predisposes to high perinatal morbidity and mortality, as shown by Urassa in his study i.e. 39% of babies born from hypertensive mothers had low birth weights of two standard deviation from the expected for gestation age, the still birth rate was 8.6% in hypertensive pregnant women compared to 7% in the control group [33] .

In 1998 eclampsia was the second cause of maternal death at Muhimbili Medical Centre (Now Muhimbili National Hospital) accounting 22.2% following anaemia (31.5%) [20]. Kiwale showed the incidence of eclampsia to be 24.2 per 1000 deliveries and 17.5% of all maternal deaths were due to eclampsia [12].

The Muhimbili National Hospital, Reproductive health data base record, shows that eclampsia was the leading cause of maternal death contributing to 25.9% of all maternal death in the year 2000, followed by PPH(18.5%), sepsis (16.7%), anaemia (13%) and malaria (11.1%) [20].

Due to high rate of termination of pregnancy in pre eclampsia and because eclampsia occurs irrespective of whether the pregnancy is term or not, the risk of prematurity is high in pre eclampsia/eclampsia group[33] . Kiwale in his study showed that 52.5% of all eclampsia

occurred before 37 weeks and overall perinatal death rate was 34.4 %, mostly due to birth asphyxia [12]. Therefore eclampsia still contributes and is responsible for a significant proportion of maternal and perinatal deaths at Muhimbili National Hospital.

Together pre eclampsia and eclampsia embrace a wide spectrum of clinical derangements. The aberration of the interaction between placental tissue and maternal factors probably are the primary causes but the exact nature of the mechanism are elusive and surrounds a lot of theories [27].

Postulated factors in the aetiology of pre eclampsia are variable and non preventable including: hormonal changes, placental changes, genetic factors, immunological factors and vascular mediated factors. All these theories agree that pregnancy and more specifically the living placenta is a *"sine qua non "* for the appearance of the disorder [17].

Malaria on the other hand still remains a single disease in pregnancy causing serious pregnancy complications whose incidence and severity depends on gestational age, parity, and level of malaria immunity [21].

Although extensive researches make us understand the epidemiology, pathophysiology and control of malaria during pregnancy, the effect of malaria on the placenta and its consequences is worth to look at.

The average prevalence of placental malaria in primigravidae is 30 – 40% while the prevalence in multigravidae is half of this rate. This depends on the endemicity of malaria infection and the rate of prophylactic use of antimalarias [6]. The obstetrical complications including, abortion, stillbirth, and premature delivery are reported to be increased in infected women with fetal loss rates ranging from 9% - 50% [6].

The study done in Nigeria by Ibhanesebhor and Okolo showed that malaria parasitemia of the placenta stood at 45.19% . About 96.45% of the parasites in the placenta were plasmodium falciparum and plasmodium malariae made up the remaining 3.55%. The histological diagnosis of placental parasitization resulted in a higher rate of placental infection than dignosis by placental smear [10].

Jaume et al in their study which was done at Ifakara /Tanzania ; showed that among the overall 1179 placentae , 415 (35.20%) showed malaria parasites (active infection), 475 (40.29%) had malaria

pigments without parasites as evidence of past infection , and 289 (24.51%) showed no evidence of malaria infection [11].

Moshi studied histochemical and immunohistochemical effect of malaria in placenta in Muhimbili Medical Center (Now Muhimbili Nationa Hospital). She found out that among 87 pregnant mothers who were studied 47% had malaria parasites . Of these 43.9% were found in placental smears i.e about 20.7% of pregnant mothers while 22% of malaria parasites were found from peripheral blood smears and 34.1% were from cord blood [19].

Lipyoga in her study found out that 63% of patients with abruptio placenta had malaria parasite in either blood or placenta. Among primigravidae who were positive for malaria parasites 10.7% were positive in placenta , 14.3% in blood , and 32% in both peripheral smear and placenta. The presence of malaria parasites in both placenta and blood was significantly associated with abruptio placenta in both primigravidae and multigravidae compared with their respective controls. The risk of abruptio placenta in multigravidae is almost three times that of primigravidae when malaria parasites are present in both blood and placenta [14].

The placenta has been found to concentrate malaria parasites such that one can have a negative peripheral blood smear with positive placental smear [19]. This is thought to be due to the sludgish of the stickier parasitised red blood cells in the eddies of slow moving placental stream in which high glucose content is found which favors the development of the parasites [19].

Recent researchers have found that elevated level of production of interferon (IFN) gamma by intervillous blood mononuclear cells (IVBMC)have protective effect against placental malaria [32]. The study hypothesizes that the impairment of T- cell derived cytokine production especially that of protective IFN gamma is the factor contributing to the susceptibility of HIV (+ ve) pregnant mother to plasmodium falciparum malaria infection in pregnancy [32].

Placenta is the preferred site of sequestration and development of malaria parasites. The intervillous spaces have been found to be filled with parasites and macrophages interfering with oxygenation and nutrient transport to the fetus. Villous hypertrophy and fibrinoid necrosis of villi (complete or partial) have been observed [3].

Malaria is known to cause placental ischaemia which is the prerequisite for the development of pre eclampsia [1,21]. Pre eclampsia / eclampsia also are more common in endemic areas for falciparum malaria. It is evident also that both pre eclampsia and falciparum malaria are common in primigravidae [1,21] .

Intact endothelium is important for the maintenance of vascular integrity, preventing platelet aggregation and for proper tone of vascular smooth muscles. Many observations point to the central role of endothelial cells in the pathogenesis of pre eclampsia [1]. Shanklin and Sibai described ultrastructural endothelial injury in the placental bed [1]. Functional and biochemical evidence of damaged endothelial cells such as high concentration of von willebrand factor, endothelin and fibronectin have been described in patients with preeclampsia [1] .

These morphologic and functional changes of endothelial cells can be held responsible for triggering the clinical syndrome of pre eclampsia, including ; arterial vasospasm, increased thrombocyte aggregation and increased capillary permeability leading to hypertension , proteinuria , oedema and sometimes thrombocytopenia and hypoperfusion of organs[1].

PLACENTA THE TARGET SITE.

Pre eclampsia being exclusive disease of pregnancy implies that it will resolve after delivery of the placenta. Placenta acts like endothelium and plays a key role in the pathogenesis of pre eclampsia [1]. It is believed that placental ischaemia causes the release of so called " *factor x* ", which is currently known to be oxygen free radical [1].

When the production of oxygen free radical exceeds the neutralization capacity of free radical scavengers a condition of imbalance is created which favors the formation of lipid peroxides from unsaturated fatty acids. Oxygen free radical as well as lipid peroxides are toxic for endothelial cells [1].

Pregnancy is a major risk factor for malaria infection and disease. Malaria parasitisation of maternal placental blood is a frequent occurrence at parturition [14,21]. The cellular infiltration of intervillous spaces by malaria parasites impairs placental function leading to placental ischaemia . Placental infiltration by malaria parasites is related by most researchers to low birth weight, intrauterine growth retardation and perinatal loss through antepartum and intrapartum asphyxia [21,33].

Galbraith studied pathology and immunopathology of placentae from mothers in malarious area in Gambia. He found out that there is considerable thickening of trophoblastic basement membranes; also there are trophoblast necrosis (ischaemia) and loss of microvilli particularly associated with monocyte containing malaria pigment and large intervillous aggregations of parasitized red blood cells , monocytes, pigment, and fibrin [8].

PRIMIGRAVIDAE AS A RISK FACTOR.

Genuine pre eclampsia is a disease of first pregnancies. Majority of patients with eclampsia at Muhimbili National Hospital are below the age of 20 years. About 60% of patients with eclampsia are primigravidae but maternal mortality has been found to be higher in multigravidae (12.2%) than primigravidae (3.1%)[12]. A previous normal pregnancy is reported to be associated with a markedly lowered incidence of pre eclampsia [1].

Most observers also agree that malaria and infected placentae are most common in primigravidae and that the prevalence of malaria and infected placenta decrease with succeeding pregnancies [21,30].

PERIOD OF PRE ECLAMPSIA IN RELATION TO PEAK GESTATIONAL AGE FOR FALCIPARUM PARASITAEMIAS.

From the definition of pre eclampsia it is evident that the symptoms start to occur after 20th week of gestation . Though this is true the pathological mechanism usually occurs earlier than that, during 1st trimester [24] . In holoendemic areas the peak prevalence of falciparum parasitaemias is between 9 to 16 weeks of gestation. Mutabingwa found out that the parasitaemia prevalence rate is high at the gestation age of 15 weeks [21].

The pathway culminating in placental ischaemia holds the key to our understanding of the pathophysiology of pre eclampsia. Researchers focus on both the so called "defective placentation" and the missing link between placental ischaemia and generalized endothelial dysfunction[1]. The origin of this placentation defect is multifactorial consisting of three major components: Immune maladaptation , Genetic predisposition and Vascular mediated factors e.g Chronic hypertension , Diabetes mellitus , Autoimmune disorders[1]. And probably placental malaria parasitisation may be one of the predisposing factors.

FETAL EFFECT

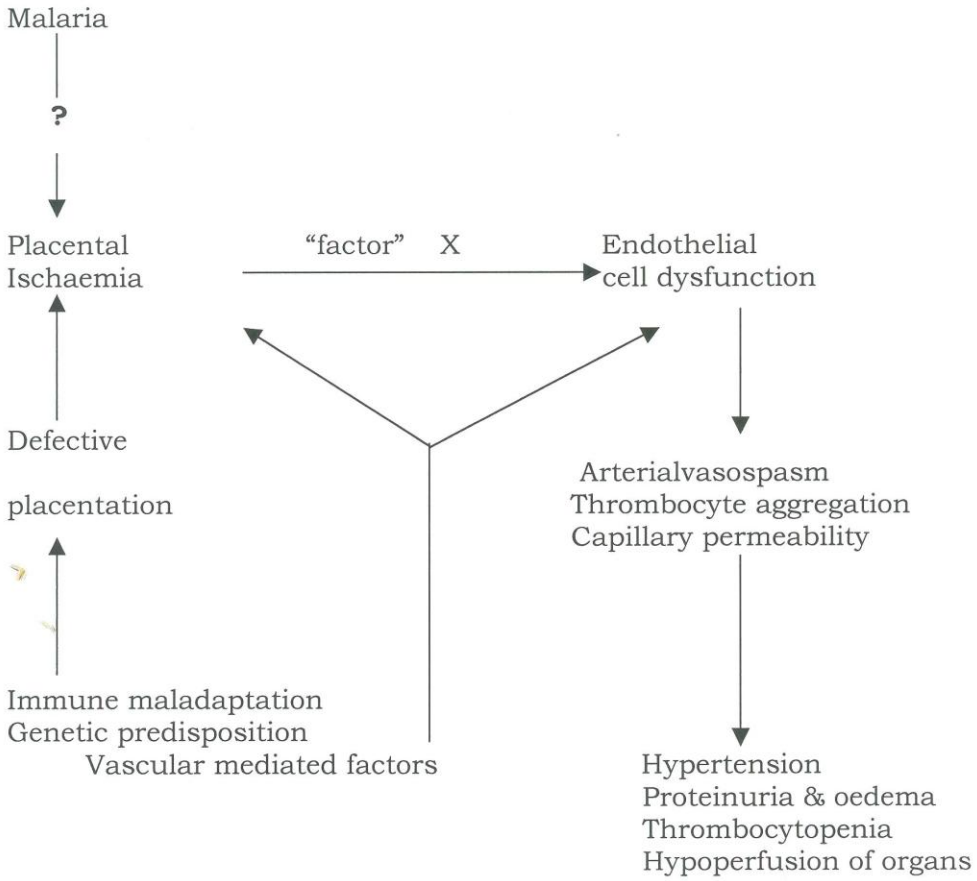
Both placental malaria infection and pre-eclampsia are associated with intrauterine growth retardation, intrauterine fetal death and premature deliveries. Perinatal deaths occur as a result of adverse condition during pregnancy, labor and delivery or in the first days of life. Placental malaria infection is known to increase the risk of delivery of low birth weight infant, thus potentially increasing the risk of perinatal and infant mortality [18].

Considering these facts there may be an association between the two conditions which is yet to be established (placental malaria infection and the development of pre eclampsia / eclampsia).

BACKGROUND AND JUSTIFICATION OF THE STUDY

- Eclampsia constitutes about 4% of admission in the labour ward and one of the leading causes of maternal mortality at Muhimbili National Referral Hospital which is the largest hospital in Tanzania.
- The theory of pathogenesis of pre-eclampsia centers on ischaemic placenta as a prerequisite for alteration of endothelial cell function and development of pre-eclampsia.
- Studies show that placental malaria parasitization causes placenta ischaemia and the placenta is an alternative site for parasite multiplication.
- The epidemiology of malaria in pregnancy coincides with that of pre-eclampsia I.e both conditions are common in primigravida. Pre-eclampsia starts to appear at 20 weeks of amenorrhoea few weeks after the peak gestational age for malaria in pregnancy (about 16 to 18 weeks).
- Experience in Tanzania shows that geographical distribution in the two conditions is also similar i.e pre-eclampsia is common in endemic areas for falciparum malaria and eclampsia is common during rainy season where malaria transmission rate is also high.

Summary of the Postulated Pathogenesis of Pre eclampsia[1]



Therefore the association between the two conditions i.e placental malaria parasitization and pre-eclampsia / eclampsia will open a new line of further research . This will probably help us in finding mode of prevention of pre-eclampsia / eclampsia and reducing maternal mortality due to eclampsia

RESEARCH QUESTION

IS THERE ANY ASSOCIATION BETWEEN PLACENTAL MALARIA PARASITIZATION AND PRE-ECLAMPSIA/ECLAMPSIA ?.

HYPOTHESIS

THERE IS NO ASSOCIATION BETWEEN PLACENTAL MALARIA PARASITIZATION AND PREECLAMPSIA/ ECLAMPSIA.

OBJECTIVES

A. BROAD OBJECTIVE

To determine the association between malaria placental parasitization and the occurrence of pre-eclampsia /eclampsia in primigravidae in Muhimbili National Hospital.

B. SPECIFIC OBJECTIVES

1. To compare the presence of peripheral blood malaria parasitaemia in pre-eclampsia / eclampsia and the control group in primigravidae.
2. To compare the presence of placental malaria parasitization in pre-eclampsia /eclampsia and the control group in primigravidae.

3. To compare the presence of placental malaria pigments in pre eclampsia / eclampsia and the control group.

METHODOLOGY

Study area:

The study was done at the labor ward of Muhimbili National Hospital which is the largest referral and National Hospital in Tanzania. The labor ward cares nearly all eclamptic patients in Dar es salaam, the largest city in Tanzania with the average population of about 3.5 million people. The hospital has special obstetric ward for eclampsia and other serious obstetrical conditions. The patients with pre-eclampsia are taken care of at room 1 of the main labor ward.

Study design :

A prospective case control study was done.

Case Definitions

Pre-eclampsia

A blood pressure of $\geq$ 140/90 mmHg after 20 weeks of pregnancy if the prior blood pressure is not known accompanied by proteinuria in two different occasions 6hours apart and / or oedema [25,26,27] .

Eclampsia

Is the occurrence of seizures in patients with pre-eclampsia after excluding other causes of seizures.

Proteinuria

Protein in urine from a " clean catch mid stream " or catheter urine sample showing at least 2+ by dipstick method OR >0.3g in a 24 hours urine collection [25,26,27]. (The former method was used.)

Study population and Control group

Cases: - Primigravidae with pre-eclampsia in labor or eclampsia

Controls:- Non-pre-eclamptic / non eclamptic primi-gravidae in labor.

Study variables-

Study factors:

Peripheral blood for malaria parasite.

Placenta for analysis of malaria parasites and pigments.

Cases under study:

Pre-eclampsia/eclampsia

Exclusion Criteria:

The patients presenting with the following were excluded from the study Epilepsy, Fever , Chronic hypertension, Chronic renal failure, Multiple pregnancy, Diabetes mellitus, and Patient's refusal .

Sample size

The sample size was calculated by considering that the proportion of placental malaria parasites in general population is 40%. The Odds ratio is 2.

The sample size was therefore calculated by using the following formula:-

$$N = \frac{p_1 (1-p_1) + p_2 (1-p_2)}{(p_1 - p_2)^2} [(Z\alpha + Z \beta)^2]$$

Where N :- is the sample size for each group

P_1 :- is the proportion of placental malaria parasites in cases.

P_2:-is the proportion of placental malaria parasites in controls.

$Z\alpha$ = Point on standard normal distribution such that an area to the right of it is Z. $Z\alpha = Z/2 = 1.96$

$Z\beta = 0.84$ for the power of 80%

The sample size is therfore144 patients for cases and 144 patients for Controls i.e total of 288 patients .

Implementation Plan

Ethical consideration

Ethical clearance was requested from the research and publication committee of MUCHS. The patients were well explained about the study and were requested to join in the study. Those patients who

accepted gave verbal consent. All patients with blood slide for malaria parasites positive were treated according to treatment protocol in Tanzania .

Material and methods

Pilot Study

A pilot study was done to test the questionnaire and methods of collecting and handling specimens.

Staff:

The main researcher was assisted by six nurse midwives who were working in the labor ward .The nurses were recruited according to their working schedule . These included three nurses in permanent night duties and three in day time duties .They were in alternative shifts to enable 24 hours data collection . The nurses were explained about the aim of the study, importance of counseling patients and methods of collecting and handling specimens and data. The main researcher was most of the time available when difficulties raised.

Research Instrument:

Data analysis was done by computer using Epi Info version 6 software program.

Notification of cases

Every primigravida admitted in the labor ward was screened for Inclusion / exclusion criteria . Proper explanations were given to

patients and non eclamptic patients and controls gave verbal consent to participate in the study.

The blood pressure was measured on admission using standard sphygnomamometer. And the primigravidae in labor with pre eclampsia or eclampsia were included in the study as cases after excluding above factors of increase blood pressure or eclampsia. The level of proteinuria was determined using albustix strips.

The necessary information was obtained from antenatal card and short interview was done to patients in non eclamptics and to the relatives in eclamptics to obtain age of the patient , occupation , marital status , and level of education.

The patients for control are the primigradae who were admitted immediately after a case but without pre clampsia / eclampsia .

Laboratory tests:-

About 0.5ml of venous blood was taken from each patient in the study. The thick blood smear was done in the labor ward by the nurses. The slides with thick smear were sent to laboratory technician who analyzed for malaria parasites. The standard protocol of Giemsa staining

method was used and counting of malaria parasites was done against 200 WBC . The subject with blood slide positive were treated according to treatment protocol.

Immediately after delivery the placenta was cleaned to remove clots by wiping with a clean dry gauze. Two sections of maternal part of placenta which are practically known to concentrate more malaria pigments were taken i.e first about 2cm from the edge of maternal surface of the placenta and secondly, a section of 2cm thick along the insertion of the cord. The sections were put in a non wettable container containing 10% phosphate buffered formalin of pH 7.4 to prevent formalin pigments formation which resemble malarial pigments.

The container was of appropriate size and with adequate volume for fixation of at least 5 times the placental volume to ensure that the pieces of placenta were not deformed and for adequate fixation. The container was covered to avoid evaporation and was labeled i.e . being given identification number and date of delivery. This was attached to the fully filled request form and sent to the histopathological laboratory.

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The placenta was left to fix for at least 24 hours in order to facilitate slicing .The placental sections were processed using automatic tissue

processing machine for paraffin wax impregnation, followed by manual paraffin wax embedding using cassettes (Tissue Tek) for making blocks, which had a the section label and were stored until the end of the study.

The section cutting was done using rotary microtomy. All sections were stained using Haematoxylin & Eosin and examined under light microscopy (Olympus type BH-2) for the presence of malaria parasites and pigments. The results were filled in the pre made questionnaire (appendix 1).

RESULTS

During the study 288 patients were recruited, these included 144 cases and 144 controls. Among the cases 35% were eclamptic patients.

TABLE1: SOCIO-DEMOGRAFIC CHARACTERISTICS OF CASES AND CONTROLS

CHARACTER	CASES		CONTROLS		TOTAL	P-VALUE
	NO	%	NO	%		
AGE IN YEARS						
15 – 19	63	43.7	70	48.6	133	0.837
20 – 24	58	40.3	55	38.2	113	
25 – 29	19	13.2	16	11.1	35	
30 – 34	4	2.8	3	2.1	7	
MEAN AGE	20.799 ± 3.713		20.372 ± 2.552			0.328
MARITAL STATUS						
Single	65	45.1	64	44.4	129	0.241
Married	79	54.9	80	55.6	159	
EDUCATION						
No Education	8	5.6	18	12.5	26	0.1995
Primary	111	77	102	70.8	213	
Secondary	24	16.7	22	15.3	46	
Tertiary	1	0.7	2	1.4	3	
OCCUPATION						
House wife	69	47.9	64	44.4	133	0.6689
Self employed	15	10.4	22	15.3	37	
Employed	15	10.4	14	9.7	29	
Unemployed	45	31.3	44	30.6	89	

The mean age was 20.799 for cases and 20.375 for controls which is not statistically significant p-value = 0.328. When comparing the age groups, 84.1% of cases and 86.6% of controls were within the age group 15 - 24. However the age distribution in cases and controls is not statistically significant p-value 0.837.

Among the cases, 54.9% were married and 45.1% were single, while in controls 55.6% were married and 44.4% were single. The difference in marriage in cases and controls is not statistically significant p- value = 0.241.

Majority of the patients studied had a primary education i.e 77.0% and 70.8 in cases and controls respectively. The distribution of educational status in cases and controls has no statistical significant difference p- value = 0.1995.

As far as occupation in concerned 47.9% were housewife ,31.3% were unemployed while 20.8% were either employed or self employed. In the control group 44.4% were housewife 30.6% were unemployed and 25% were either employed or self employed. Occupation in cases and controls has no statistical difference p - value = 0.6689.

TABLE 2: GESTATIONAL AGES DISTRIBUTION IN CASES AND CONTROLS.

GESTATIONAL AGE (WKS)	CASES		CONTROLS		TOTAL	P - VALUE
	No	%	No	%		
≤ 30	2	1.4	1	0.7	3	0.172
31 – 33	5	3.5	5	3.5	10	
34 – 36	34	23.6	20	13.9	54	
37 – 39	52	36.1	66	45.8	118	
40 – 42	49	34.0	46	31.9	95	
≥ 42	2	1.4	6	4.2	8	
TOTAL	144	100	144	100	288	
MEAN GESTAGE	37.969 ± 2.643		38.576 ± 2.552			0.0472

Majority of patients studied delivered between the gestational ages 34 and 42 weeks. The distribution in cases and controls according to gestational ages at delivery is not statistically significant p- value = 0.172.

The mean gestational age at delivery was 37.696 ± 2.643 in cases and 38.576 ± 2.552 in controls. The mean gestational age at delivery in cases and controls is statistically significant p - value = 0.0472.

TABLE 3:DELIVERY BEFORE AND/OR AT TERM IN CASES AND CONTROLS:

GESTAGE	CASES		CONTROLS		TOTAL	P-VALUE
	No	%	No	%		
≤ 36 weeks	41	28.5	26	18.5	67	0.05
≥ 37 weeks	103	71.5	118	81.5	221	
TOTAL	144	100	144	100	288	

Among cases 28.5% delivered before the gestational age of 37 weeks compared with 18.5% of controls . The difference between cases and controls has marginal statistical significant OR = 1.81 95 confidence interval 1,3.28 p- value = 0.05.

TABLE 4: PERIPHERAL BLOOD SMEAR FOR MALARIA PARASITES IN CASES AND CONTROLS

MALARIA PARASITES	CASES		CONTROLS		TOTAL	P - VALUE
	No	%	No	%		
Smear positive	79	54.9	87	60.4	166	0.405
Smear Negative	65	45.1	57	39.6	122	
TOTAL	144	100	144	100	288	

When comparing the peripheral blood smear 54.9% of cases and 60% of controls had malaria parasites positive. There is no statistical significant difference between cases and controls about the presence of malaria parasites in peripheral blood OR = 0.80 95% confidence interval 0.49, 1.31 P – value = 0.405.

Overall 166 out of 288 (57.6%) of study subjects had malaria parasites positive in their blood.

TABLE 5: CONCETRATION OF MALARIA PARASITES IN BLOOD SMEAR FOR CASES AND CONTROLS

CONCETRATION OF MALARIA	CASES		CONTROLS		P - VALUE
	No	%	No	%	
≤50MPS/200WBC	76	96.22	81	93.1	0.590
51 – 100MPS/200WBC	1	1.26	1	1.2	
101 – 200MPS/200WBC	1	1.26	2	2.3	
≥200MPS/200WBC	1	1.26	3	3.4	
TOTAL	79	100	87	100	

Majority of study population had malaria parasites concentration less than 50MPS/200WBC in their peripheral blood ie. 96.22% 0f cases and 93.1% of controls. The difference in the cases and controls is not statistically significant p - value = 0.590.

TABLE 6:THE PRESENCE OF PLACENTAL MALARIA PARASITES IN CASES AND CONTROLS

PLACENTAL MALARIA	CASES		CONTROLS		TOTAL	P - VALUE
	No	%	No	%		
MALARIA POSITIVE	18	12.5	14	9.7	32	0.364
MALARIA NEGATIVE	126	87.5	130	90.3	256	
TOTAL	144	100	144	100	288	

Among the study population 11.1% had placental malaria positive. Among the cases 12.5% had malaria parasites in the placenta compared to 9.7% of the control group. This difference in the presence of placental malaria parasites in cases and controls is not statistically significant. OR = 1.33 95% confidence interval 0.6,2.96 P – value 0.364.

TABLE 7: THE PRESENCE OF PLACENTAL MALARIA PIGMENTS IN CASES AND CONTROLS.

MALARIA PIGMENTS	CASES		CONTROLS		TOTAL	P - VALUE
	No	%	No	%		
PIGMENTS POSITIVE	16	11.1	10	6.9	26	0.303
PIGMENTS NEGATIVE	128	88.9	134	93.1	262	
TOTAL	144	100	144	100	288	

Among the study population 9% were positive for placental malaria pigments. Placental malaria pigments were present in 11.1% of cases compared to 6.9% of the control group. The difference in cases and controls about the presence of placental malaria pigments is not statistically significant. OR = 1.67, 95% confidence interval 0.69,4.17 P – value = 0.303

TABLE 8: THE PLACENTAL MALARIA PARASITE S / PIGMENTS IN CASES AND CONTROLS.

PARASITES & PIGMENTS	CASES		CONTROLS		TOTAL	P - VALUE
	No	%	No	%		
PARASITES & PIGMENTS POSITIVE	13	9.02	8	5.6	21	0.364
PARASITES& /OR PIGMENTS NEGATIVE	131	90.98	136	94.4	267	
TOTAL	144	100	144	100	288	

Placental malaria parasites and pigments together were present in 7.29% of the population studied. Among the cases 9.02% had both placental malaria parasites and pigments compared to 5.6% of controls. This difference in cases and controls is not statistically significant. OR = 1.69 95% confidence interval 0.62,4.62 P – value = 0.364.

TABLE 9: SUMMARY OF THE PRESENCE OF PERIPHERAL MALARIA PARASITE AND PLACENTAL MALARIA PARASITE AND PIGMENTS IN CASES AND CONTROLS.

CATEGORY	PERCENTAGE OF CASES	PERCENTAGE OF CONTROLS
PERIPHERAL MALARIA POSITIVE	54.9	60.4
PLACENTAL MALARIA POSITIVE	12.5	9.7
PLACENTAL PIGMENTS POSITIVE	11.1	6.9
PLACENTAL MALARIA & PIGMENTS POSITIVE	9.02	5.6

Generally there is higher proportion of cases with placental malaria parasites ,pigments and combination of parasites and pigments than controls . Although all the difference in cases and controls are not statistically significant.

DISCUSSION

Pre eclampsia and eclampsia are still obstetric conditions with a lot of theories and speculations. Most of the studies done in developed countries have not been conclusive and suggest the pathogenesis of pre eclampsia/eclampsia to be centered on the placental ischaemia. The condition still surrounds a lot of theories and researches are still done .

A study done in Nairobi - Kenya showed that only 28% of eclampsia had no evidence of infection compared to 91% of controls , the difference is statistically significant p-value < 0.05. Urinary tract infection and upper respiratory tract infections were found to be common. The study therefore suggests that infection could as well be the factor in the pathogenesis of eclampsia [15].

Several morphological changes in malaria placentae have been reported to include an accumulation of parasitized and non parasitized erythrocytes in maternal villous space, leukocyte accumulation (villitis), malaria accumulation in phagocytes, its deposition in villous spaces and wide spread fibrinoid necrosis of villi and basement membrane thickening.

A case control study was done which included 144 pre eclampsia/ eclampsia and 144 controls, all being primigravidae. Among the cases

35% were patients with eclampsia and 65% were pre eclamptics. Although the definition of preeclampsia/eclampsia includes proteinuria 2+ by dipstick method, in this study proteinuria was found to be 1+ in 25(17.4%), 2+ in 83(57.6%) and 3+ in 36(25%) of cases. This finding coincides with other researchers . Sibai et al in one of the study found out that 29% of eclamptic mothers had no proteinuria [17].

The study population had patients with the age ranging from 14 – 39 years. Majority of them were within the age group 15 – 24 years contributing to more than 80% of the study population. (83% of the cases and 85% of the controls). This finding reflects the fact that majority of primigravidae in Muhimbili National Hospital labor ward are within the age group 15 - 24 years.

Pre eclampsia/eclampsia has a high predisposition of premature deliveries as shown in many studies. This study revealed that 28.5% of cases delivered before gestational age of 37 weeks. Kiwale who studied only eclamptic patients found that 52.5% of them delivered before 37 weeks gestational age[12] .

Compared with the controls the risk of premature delivery is high in pre eclamptics/eclamptics (28.5% and 18.5% in cases and controls respectively) OR = 1.81 95% confidence interval 1,3.28.

The study aimed at finding the association between malaria and preeclampsia/eclampsia. Histological diagnosis of placental parasitization has been used in this study because it results in a higher rate of detection of placental malaria infection than placental smear diagnosis [28] . Ibhanesebhor SE, Okolo AA in the study about placental malaria and pregnancy outcome found that 57.69% of placental malaria when histological diagnosis was used and 44.68% when placental smear diagnosis was used [10].

Generally 57.3% of the study population had malaria parasites in their peripheral blood. More than 90% of patients who had malaria had parasites concentration below 50MPS/200WBC. The prevalence of peripheral malaria parasitaemiia in this study coincides with the findings in other studies though the prevalence varies.

In different studies prevalence in malaria has been found to be high in primigravidae, gestational age below 20 weeks, enrollment in rainy season or post rainy season, maternal age below 25 years, seropositivity to Human Immunodeficincy Virus (HIV), and no use of antimalaria prophylaxis and treatment [32].

Studies done in different parts of Africa show wide range of prevalence in peripheral malaria parasitaemia in primigravidae from as low as 20%

in parts of Nigeria to as high as 74% in Muheza Tanzania [21].

The study found out that there is no association between peripheral malaria parasites and pre eclampsia/ eclampsia.
Among cases 54.9% had malaria parasites in blood compared to 60.4% of controls. The difference between cases and controls is no statistically significant p - value = 0.405.

Among the study population 11.1% had malaria parasites in the placenta while 9% were positive for placental malaria pigments and 7.29% had both placental malaria parasites and pigments.
Ibhanesebhor SE reported malaria parasitaemia of placenta to be 45.19% [10].
Mutabingwa in his study where he supervised malaria chemoprophylaxis found out that 78% of placenta studied had no evidence of active or past malaria infection while 14% had signs of passed infections and 8% had signs of active infections [22].

Moshi found out that 20% of the pregnant mothers had placental malaria infections and overall 42% had malaria parasites either in their blood, placenta or cord blood [19].

Overall this study has found out that the presence of malaria parasites and/or pigments in the placenta has been high in cases than controls.

Placental malaria parasites in cases was 12.5% compared with 9.7% in controls and placental malaria pigments has been found to be 11.1% in cases and 6.9% in controls while the presence of both placental malaria parasites and pigments was 9.02% and 5.6% in cases and controls respectively. The differences in cases and controls are not statistically significant.

Therefore the study shows that there is no association between the precence of placental malaria parasites, pigments and both parasites and pigments and occurrence of pre eclampsia /eclampsia. However these results of persistent high levels of placental malaria parasites, pigments and both parasites and pigments in cases than controls imply that there is clinical significance which is not statistically demonstrable by this study. This finding may be attributed by seasonality, the use of malaria chemo prophylaxis and treatment which was not controlled in this study and sampling of placental tissues.

CONCLUSSION

The study shows that there is high prevalence of placental malaria parasites and pigments in the preeclampsia /eclampsia than controls. Although the study has failed to show statistical significant association between placental malaria parasitaemia and preeclampsia/eclampsia

these persistent high clinical values are alarming and need farther research . The study therefore has provided preliminary data for future research.

RECOMMENDATIONS

A bigger study is still needed to assess further the relationship between malaria and preeclampsia/eclampsia.

REFERENCES

1. Beek E.V,Peers L.L.H. Pathogenesis of pre-eclampsia. A comprehensive model. Obstetrical and Gynaecological survey.Review article Vol.53 number 4 1998.
2. Beischer NA, Mackay EV, Pre-eclampsia and eclampsia. Obs and the newborn. Sec. Ed. 1986. 169-177.
3. Bray.R.S,Malignant tertian malaria and pregnancy. Postgraduate Doctor Africa.1981.
4. Cunningham F, Mack Donald PC, Grant NF,et al. Hypertensive Disorder in Pregnancy. In: Williams Obstetrics, 20th edition. USA. Appleton and Lange 1997, 693-735.
5. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol 1988; 158:892-8
6. Ettling M, Malaria and mobidity : World health magazine,1990 April .
7. Fawcus S, Mbizwo MT, Lindark G, et al. Community based investigation of the causes of maternal mortality in Rural and Urban Zimbabwe ; Marternal Mortality Study Group.Central Africa J.Med.1995 April , 41 (4) :105-113
8. Galbraith RM, Fox H, Galbraith GMR et al. The Human Maternal

Fetal Relationship in Malaria. Histology, Ultrastructural and Immunopathological Studies of Placenta.Transactions of Royal Society of Tropical Medicine and Hygiene. 1980,74:61.

9. Gustaaf.P.Y,Robillard,Thomas. Immune maladaptation in the aetiology of pre-eclampsia . Obstetrical and Gynaecological survey. Review article Vol. 53 No. 6 1998

10. Ibhanesebhor SE, Okolo AA : Placental malaria and pregnancy outcome. International J.Obs/Gyne.1992. 37 (4): 247 - 52.

11. Jume O, Mamudo R, Ismail et al ; Massive Chronic Intervillositis of the Placenta Associated with Malaria Infection . Am J Surg Pathology 22 (8) : 1006- 1011, 1998.

12. Kiwale C,R Eclampsia : Magnitude, Related factors, and Outcome of pregnancy at Muhimbili Medical Centre _ Dar es salaam. A Dissertation in the partial fulfillment for the degree of medicine (Obs/ Gyn) University of Dar es salaam. 1999.

13. Lawson JB, Stewart DB. Malaria and Pregnancy. In Obstetrics and Gynaecology in the Tropics and Developing Countries. 1st edition London. Arnold Edward Publication, 1983; 59-72.

14. Lipyoga R.S.M . The association between malaria and abruptio placenta. A Dissertation in the partial fulfilment for the degree of

M.MED. (Obs & Gynae) University of Dar es salaam. 1995.

15. Machoki JMN, Mati JKG, Rogo KO, et al: Infection in the genesis of eclampsia in Nairobi, Kenya.East.Cent.Afr. J. Obst.Gyn.1989.8:83.

16.MacKay AP, Berg CJ, Atrask HK . Pregnancy related mortality from preeclampsia and eclampsia . B. J. Obstet/ Gynecol.2001, 97 (4) : 533-538.

17. Martin L,Penroll,Ralph C, et al Hypertensive states of pregnancy. Current Obs/Gynae Diagnosis and treatment.1987 340-352.

18.McDernott JM, Wirima JJ, Stekettee RW et al. The effect of placental malaria infection on perinatal mortality in rural Malawi. African J Trop Med& Hygiene.1996. Vol 55 No.1 61-65.

19. Moshi. E.C. Histochemical and immunohistochemical study of the placenta in malaria. A Dissertation for partial fulfillment for the degree of M.MED(Anatomical pathology.) of the University of Dar es salaam.

20.Muhimbili National Hospital . Obs / Gyn data base 2000.

21.Mutabingwa T.K. Malaria and pregnancy: Epidemiology, Pathophysiology and control options. ACTA TROPICA REVIEW ARTICLE Vol 57 1994

22. Mutabingwa TK, Eling WM, Kitinya JN, et al: Malaria chemosuppretion in pregnancy and Placenta malarial changes

among three different prophylaxis groups. Tropical and geographical medicine 1993;45(6):274-9.

23.National High Blood Pressure Education Working Group Report on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 19990; 163:1689-1712.

24.Ogweyo PA.A Pathological study on the pathogenic mechanisms in pre-eclampsia and eclampsia in Dar es salaam,Tanzania (unpublished report) 2001 5-18

25.Patric T,Robert .Current concept in pre-eclampsia. American Journal of Maternal child nursing year 2000

26.Playfair.J.H.L, Immunity to malaria. British Medical Bulletin. Vol.38. No.2 1982.

27. Roberts JM , Cooper DW, Hypertensive Diseases in Pregnancy . Review article . Lancet 2001 Jan; 357 (9249) : 53-56.

28. Reece AE, Hobbins JC, Makoney MJ, et al : Hypertensive Diseases in Pregnancy. In: Medicine of the Mother and Fetus. Washington. JB. Lippincoh Company. 1993; 925-940.

29.Schmutzhard,Gerstenbrand. F. Cerebral malaria in Tanzania. Epidemiology, clinical symptoms and neurological long term sequelae.Mnero hospital study. 1979-1981

30.Sullivan AD, Nyirenda T, Callinan T et al. Malaria infection during pregnancy : Intrauterine growth retardation and pre term delivery in Malawi. J. inf. Disease 1999. Vol.179 NO: 6 1850-3

31. Steketee RW, Wirima JJ.Slutsker L et al: Malaria parasites infection during pregnancy and at delivery in mothers, placenta and newborn: Efficacy of chloroquine and mefloquine in rural Malawi. AJ.Tropical med.hygiene. 1996. 55 (1suppl): 24 - 32 .

32.Udhayakumar Cellular immunologic Interaction Between Malaria and HIV during pregnancy. American Foundation for AIDS Research, June 2000.

33.Urassa EJN, Pregnancy outcome in patients presenting with hypertension in pregnancy in Muhimbili Medical Centre. J.Obst.Gyn. East. Cent. Afr.1984. No:3. 55-67.

34.Walter P.R Garite; Placenta pathological changes in malaria. A histology and ultrasound study. American journal of pathology. 82.Vol. 109.