ORIGINAL RESEARCH

A Study of soluble fms like Tyrosine Kinase 1 as a marker of Preeclampsia in Primigravida

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Abstract
Background: Soluble fms liketyrosinekinase1 (sFlt-1) antagonizes vascularendothelial functionsleadingtohypertensive disorders of pregnancy. **Aims:** The aim of this studyis tofindtheassociationbetweensoluble fms liketyrosinekinase1and incidence of preeclampsia amongprimigravida. **Materials and Methods:** This cross sectional study was conducted at Raja Mirasudar Hospital, Thanjavur, during the period of June 2016 to December 2016. Study population total of 90 cases primigravida. Blood sample were assessed for ALT, AST,Creatinine, Platelet count and sFlt-1. Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 20. Descriptive statistics, chi square tests, relative risk and ANOVA were used, appropriately to calculate the statistical significance. P value of < 0.05 was considered as statistically significant. **Results:** sFlt levels were normal and elevated in 78.9% and 21.1% of cases, respectively and there were 5.6% and 18.9% of cases with eclampsia and pre-eclampsia, respectively. We found statistically significant association with relative risk (RR) of 23.7 between sFlt levels and presence or absence of preeclampsia and eclampsia. The mean difference in sFlt levels among preeclampsia and eclampsia cases were found to be statistically significant. **Conclusion:** From this study,it is found that the primigravida with increasedserums Flt levels haddeveloped Preeclampsia in the laterpregnancy and few of themdeveloped Eclampsia. serum sFlt levels can be used to predicttheoccurrenceofbothpreeclampsiaandprogression toeclampsia.

Key words: sFlt-1, preeclampsia, eclampsia, primigravida

Introduction

One of the important causes for maternal morbidity, mortality and perinatalmorbidity and mortality is Gestationalhypertension.WHOsays,about16% of maternal death in developed countries is secondary to hypertensivedisorders occurring during pregnancy[1]. This is significantly higher than othercauses of maternalmortality like haemorrhage (13%), abortion(13%) and sepsis (2%). Gestational hypertension is a significant factor accounting for 10 to38% maternal deaths in South Asia. In India, the maternal and perinatal mortalitydue to Preeclampsia has been reported to be 12% and 4.76% respectively[2,3]. Evenin developed countries the case fatality rate has been reported to be 1.8%withEclampsiaandfurther35%ofwomendevelopmajorcomplications.[4] Gestational hypertension is a disorder commonly occurs during the 12th week of gestation due to the abnormal placentation. Ischemia which occurs in the placenta leads to endothelial dysfunction which eventually results in development of complications. "Gestational hypertension"refers to blood pressure ≥ 140/90 mmHg for the firsttimeduring thepregnancy[20 weeks] butproteinurianotidentified[5]. Among the cases with gestational hypertension, about half of the proportion of cases develops Preeclampsiawhich is characterized by proteinuria, thrombocytopenia and signsofend organs damage. In order to reduce the impact of the same, early diagnosis and adequate treatment will help to reduce the burden in terms of morbidityand mortality in both mother and child. The biochemicalfactors for abnormal angiogenesis are "Placental growth factor" and "Soluble fms like tyrosine kinase 1". These biochemical parameters are reported to be more specific than bloodpressure and proteinuria[6]. "Soluble vascular endothelial growth

receptor 1" also called "solubleFMSliketyrosinekinase1"antagonises the endothelial functions which eventually results in development of hypertensive disordersof pregnancy[7].

Aims and Objectives

The aim of this study is to find the association between soluble fms liketyrosinekinase1and incidence of preeclampsia amongprimigravida.

Materials and Methods

This cross sectional study was conducted by the Department of Biochemistry at Raja Mirasudar Hospital, Thanjavur, a tertiary care teaching hospital during the period of June 2016 to December 2016. Study population includes primigravida mothers who attended the department of Obstetrics and Gynecology during the study period. Primigravida mothers aged between 20-45 years, who attended the outpatient department for routine visit during their gestational age of 16-20 weeks were included in the study. Cases with known history of diabetes mellitus, hypertension, edema, proteinuria, oliguria, hepatic diseases and chronic illnesses involving major organs were excluded from the study. A total of 90 cases of antenatal mothers were included in the study. All participants were thoroughly explained about the study and its need in their native language and informed written consent were obtained from them. Principal investigator collected the demographic and clinical details about the patients, all their blood samples were collected. Five mlofblood samples were collected by venepuncture
Understrict aseptic precaution as per the inclusion criteria. The samples were centrifuged and serum separated. One part of the sample was taken and analysis of ALT, AST, Creatinine and Platelet count were done immediately. Remaining part of the sample was stored for analysis of at - 70º C. Enzyme-linked immunosorbent assays (ELISA) for sFlt 1was performed with commercially-available kits. In sterile tubes urine samples were collected and tested for protein with dipstick method. The serum collected was used for the estimate on of soluble fms like tyrosine kinase1by Elisa method, serum Aspartate Transaminase-Modified IFCC Method, serum Alanine Transaminase-Modified IFCC Method, serum Creatinine-Modified Jaffe'sMethod, Platelet count- cell counter. Urine protein was assessed by dipstick method, Blood pressure measured by sphygmomanometer and weight was checked using digital weighing scale. Gestational Hypertension - defined as diastolic blood pressure ≥90mmHg and systolic blood pressure ≥140mmHg Normotensive patients after 20weeks of pregnancy atleast
Two consecutive measurements 6hrs apart urine protein measured by dipstick method in a random urine sample. All details of the patients were entered in a proforma.

Statistical Analysis

Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 20. Descriptive statistics, chisquare tests, relative risk and ANOVA were used, appropriately to calculate the statistical significance. P value of < 0.05 was considered as statistically significant.

Results

In the present study, there were 58.8% of cases who were in the age group between 21-25 years of age and 42.2% of cases who were between the age group 25-30 years of age. Mean age of the study participants was found to be 24.9±2.3 years (Mean± SD).Mean maternal weight was found to be 59.7±4.5 kgs, 59.7±4.5 kgs, 65.9±4.1 kgs and 65.9±4.1 kgs during the gestational weeks of 17-20 weeks, 21-28 weeks, 29-36 weeks and 36-40 weeks, respectively. Mean weight gain during pregnancy was found to be 12.3±2.0 kgs, in this study. Mean systolic blood pressure was found to be 117.6±6.9 mmHg, 116.8±14.3 mmHg, 116.8±14.3 mmHg and 120.9±15.4 mmHg during the gestational weeks of 17-20 weeks, 21-28 weeks, 29-36 weeks and 36-40 weeks, respectively. Mean diastolic blood pressure was found to be 82.2±3.8 mmHg, 74.9±11.3 mmHg, 82.9±8.7 mmHg and 84.6±10.8 mmHg during the gestational weeks of 17-20 weeks, 21-28 weeks, 29-36 weeks and 36-40 weeks, respectively. Mean Alanine Aminotransferase (ALT) levels were found to be 26.8±3.8 IU/L, 29.3±5.1 IU/L, 28.9±10.1 IU/L and 29.7±10.1 IU/L during the gestational weeks of 17-20 weeks, 21-28 weeks, 29-36 weeks and 36-40 weeks, respectively. MeanAsparate Transaminase (AST) levels were found to be 27.3±3.8 U/L, 28.6±6.2 U/L, 29.1±10.1 U/L and 29.3±9.9 U/L during the gestational weeks of 17-20 weeks, 21-28 weeks, 29-36 weeks and 36-40 weeks, respectively. Mean serum creatinine levels were found to be 1.2±0.1 micromol/L, 0.9±0.1 micromol/L, 0.9±0.1 micromol/L and 0.9±0.1 micromol/L during the gestational weeks of 17-20 weeks, 21-28 weeks, 29-36 weeks and 36-40 weeks, respectively. Mean platelet count was found to be 159.9±68.7× 10^9/L, 153.7±93.0× 10^9/L, 150.1±18.5× 10^9/L and 149.0±18.3× 10^9/L during the gestational weeks of 17-20 weeks, 21-28 weeks, 29-36 weeks and 36-40 weeks, respectively. Also the mean soluble FMS like tyrosine kinase 1 was found to be 188.5±176.0 pg/ml (Table 1).

Table 1: Mean maternal parameters at different gestational age groups

Parameter	Gestational weeks			
	17-20 weeks	21-28 weeks	29-36 weeks	36-40 weeks
Maternal weight (in kgs)	59.7±4.5	60.9±4.2	65.9±4.1	71.9±3.8
Systolic blood pressure (in mmHg)	117.6±6.9	116.8±14.3	116.4±13.9	120.9±15.4
Diastolic blood pressure (in mmHg)	82.3±3.8	74.9±11.3	82.9±8.7	84.6±10.8
ALT (IU/L)	26.8±3.8	29.3±5.1	28.9±10.1	29.7±10.1
AST (U/L)	27.3±3.8	28.6±6.2	29.1±10.1	29.3±9.9
Serum creatinine (micromol/L)	1.2±0.1	0.9±0.1	0.9±0.1	0.9±0.1
Platelet count ($\times 10^9$/L)	159.9±68.7	153.7±93.0	150.1±18.5	149.0±18.3

On assessing the urine protein levels at different gestational periods, there were 76.7% and 23.3% of cases with nil and trace levels of urine protein, respectively during the gestational age of 17-20 weeks, 90%, 4.4%, 1.1% and 4.4.% of cases were reported with nil, trace, one plus and two plus levels of urine protein, respectively during the gestation age of 21-28 weeks, 82.2%, 2.2%, 3.3%, 8.9%, 1,1% and 2..2% of cases were reported with nil, trace, one plus, two plus, three plus and four plus levels of urine protein, respectively during the gestational age of 29-36 weeks and 76.7%, 5.6%, 5.6%, 6.7% and 5.6% of cases were reported with trace, one plus, two plus, three plus and four plus levels of urine protein, respectively, during the gestational age of 36-40 weeks (Table 2).

Table 2: Proportion of cases at different gestational age groups and urine protein levels

Urine protein	Gestational weeks			
	17-20 weeks	21-28 weeks	29-36 weeks	36-40 weeks
Nil	69 (76.7)	81 (90)	74 (82.2)	69 (76.7)
Trace	21 (23.3)	4 (4.4)	2 (2.2)	0
1+	0	1 (1.1)	3 (3.3)	5 (5.6)
2+	0	4 (4.4)	8 (8.9)	5 (5.6)
3+	0	0	1 (1.1)	6 (6.7)
4+	0	0	2 (2.2)	5 (5.6)

Among the study participants 78.9% of cases were reported with normal levels of sFlt whereas 21.1% of cases reported with elevated levels of sFlt, in this study. On assessing the medical conditions, there were 5.6% and 18.9% of cases with eclampsia and pre-eclampsia, respectively. Also there were 75.6% of cases with none of the medical conditions like preeclampsia and eclampsia (Table 3).

Table 3: Proportion of cases with sFlt levels and medical conditions

Parameter	Frequency	Percent
S Flt levels		
Normal (75to179pg/ml)	71	78.9
Elevated (>179pg/ml)	19	21.1
Medical condition		
Normal	68	75.6
Pre-eclampsia	17	18.9
Eclampsia	5	5.6

In this study, all the cases with normal blood pressure were found to have normal sFlt levels whereas among the cases with preeclampsia and eclampsia, there were 13.6% and 86.4% of cases with normal sFlt levels and elevated sFlt levels, respectively. On assessing the association between sFlt levels and presence or absence of preeclampsia and eclampsia, we found statistically significant association with relative risk (RR) of 23.7, in this study (Table 4).

Table 4: Proportion of sFlt levels and outcome with respect to preeclampsia and eclampsia

sFlt levels	Normal blood pressure	Pre-eclampsia & Eclampsia	Total	RR	P value
Normal	68(100)	3(13.6)	71(78.9)	23.7	0.000*
Elevated	0 (0)	19(86.4)	19(21.1)		
Total	68(100)	22(100)	90(100)		

*Significant; sFlt- Soluble fms-like tyrosine kinase

On assessing the mean sFlt levels among the cases with different medical conditions, mean sFlt was found to be 134.29±25.534 pg/ml, 220.94±72.994 pg/ml and 815.40±333.678 pg/ml among the cases without any associated medical illnesses, preeclampsia and eclampsia, respectively. Mean difference in sFlt among the cases without any associated medical illnesses, preeclampsia and eclampsia was found to be statistically different (p<0.0001) (Table 5).

Table 5: Mean sFlt levels in different medical conditions

Medical condition	N	Mean sFltlevel (pg/ml)	P value
Normal	68	134.29±25.534	<0.0001*
Pre-eclampsia	17	220.94±72.994	
Eclampsia	5	815.40±333.678	

*Significant

Discussion

Gestational hypertension usuallyoccurs after 20th week of gestation but the underlying mechanisms start as earlyas 8-18 weeks of pregnancy[8,9]. Gestational hypertension is one of the mostcommon conditions responsible for both maternal and perinatal morbidity andmortality[10].The working group of NHBPEP [National high blood pressure educationprograms2000] classified the disorders of hypertension during pregnancy intofourtypes[5] namely, firstly, preeclampsiaandeclampsiasyndrome,secondly,gestation alhypertension, thirdly, preeclampsiasyndromesuperimposed onchronichypertension and lastly, chronichypertension. Hypertensivedisorders of pregnancy occur in about 12-22% of pregnant womenwhich is more prevalent (25% of nulliparous women are complicated by hypertensive disorders)[11]. Gestationalhypertensionisincreased blood pressureoccurringduring pregnancyorwithinfirst24hoursofdeliverywithoutfeature sofPreeclampsia orpre-existinghypertension[12].Maternal andperinatalmorbiditiesare increased. Early onset gestational hypertension is often complicated bysevere Preeclampsia.Preeclampsia is considered primarily as a disease ofprimigravida[12]. Seizures canoccur either antepartum (38%) and intrapartum (18%) or postpartum (44%)Antepartumseizuresare more dangerousthanpostpartumseizures[13].Preeclampsia results in complications likeplacentalabruption,acuterenalfailure, hepaticfailure,disseminated intravascular coagulation,cardiovascular collapseandin fetus prematurity, “Intrauterine fetal growth retardation” (IUGR) andIntrauterine fetal death[14].Many Studies have shown that maternal and fetalmortality are significantly higher in nulliparous women with hypertensivedisorders[15]. sFlt-1 is produced by various tissues, including the trophoblastic layerofplacentaandcirculatingmonocytes[11].In Preeclampsia, trophoblastic invasion and inadequate vascular remodeling leads to hypoxiaand an increase in sFlt-1 production.This increase in circulatinglevelsofsFlt-1reducesthecirculatinglevelsofVEGFandpromotes endothelialcelldysfunction[14].

VEGFRfamilymembersarehavingreceptortyrosinekinases(RTKs)whichcontainanextracellularligand ding regionwithseven immunoglobulin(Ig)- like domains, a transmembrane segment, and a tyrosinekinase(TK)domainwithin thecytoplasmicdomain[12].VEGFR1 is usually referred as decoyreceptor. It has been hypothesised that high levels of sVEGF-R1 antagonise theeffects of VEGF and PlGF on placental development, vascularisation andmaternal endothelial cell function, and thus the increase in sVEGFR1 inmaternal plasma has been postulated to inhibit VEGF-A. However, VEGF-Ainducesincreasedvascular permeability,vasodilatationandangiogenesis[11].The magnitude of the imbalance between angiogenic (VEGF) andantiangiogenic factor (sVEGFR-1) concentrations in maternal blood is greater inearly-onset(severe) than in late-onset(mild) Preeclampsia[16]. Sandrim*et al.*[17]study indicates that women with Preeclampsia havereducedplasma and wholeblood nitritelevels, whichnegativelycorrelate withthepotent VEGF inhibitor sFlt-1. Facemire *et al.*[18] demonstrated that inhibition of VEGF receptor type2(VEGFR2)resultsinhypertension through impairedNOsynthesisand contributestotheenhancedET1productionandelevationsin bloodpressureinresponseto sFlt-1-inducedhypertension inpregnant rats[19].Putra *et al.*[20] conducted a study to assess soluble FMS levels among normal and preeclampsic pregnant females and reported the mean soluble fms levels as 11231.00 ± 8390.3 pg/mL and 3981.62 ± 4921.5 pg/mL among the preeclampsia cases and normal pregnant females. This difference in mean soluble fms among the cases with and without preeclampsia and was found to be statistically significant. From their study they concluded that high levels of soluble FMS-like tyrosine kinase-1 (sFlt-1) in pregnancy were found to be a risk factor for preeclampsia.Bdolah*et al.*[21] performed a study and reported that among the females with nulliparity and multiparous pregnancies, serum sFlt1 levels were found to be 12732±832 and 10162±666, respectively. This difference in mean soluble Flt 1 among nulliparous and

multiparous pregnancies was found to be statistically significant.Thus they conclude that nulliparous pregnancies had higher circulating sFlt1 levels than multiparous pregnancies, suggesting an association with an angiogenic imbalance. Lumbanraja*et al.*[22] performed a study and found that maternal age, gestational age and levels of sFlt-1 appear to be strong predictors for poor clinical outcomes in patients with preeclampsia. Gurnadi*et al.*[23] conducted a study and reported that the median concentration of sFlt-1 in severe preeclampsia is higher compared with normal pregnancy. In contrast concentration of PlGF is lower in severe preeclampsia compared with normal pregnancy. They reported a significant negative correlation between the concentration of sFLt-1 and PlGF in normal pregnancy. Powers *et al.*[24] conducted a study and reported that odds of developing preeclampsia were significantly increased among women with multiple fetuses for each 2- fold elevation in sFlt1. They stated that the pattern of elevated concentrations of sFlt1 in high-risk pregnant subjects who develop preeclampsia is similar to that reported in low-risk pregnant women. Elbishry*et al.*[25] conducted a study and reported that cases with sFlt-1/PlGF ratio above the level of 85 were preeclamptic for whom close monitoring for the signs and symptoms of complications is needed. They concluded that sFlt-1/PlGF ratio can be used as a prognostic tool to assess the maternal and fetal outcomes among the cases with preeclampsia between 24-34 weeks of gestation.

Conclusion

This study reports that primigravidamothers those who reported with increasedserumsFlt levels were found to develop Preeclampsia during their later period of gestation and very few cases also developed Eclampsia.Hence we conclude that serum sFlt levels can be used as a predictor for diagnosing the cases with preeclampsiaandeclampsia.

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