Noninvasive assessment of maternal hemodynamic function by electrical impedance cardiography (EIC) and correlation with uterine and umbilical vascular resistance in mid-pregnancy

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Introduction: Maternal vascular adaptation to pregnancy involves the coordinated augmentation of both systemic and uteroplacental circulation, with the concomitant development of a new fetoplacental circuit. Disturbances of maternal hemodynamic adaptation in early pregnancy are often associated with compromise in the other circulations, although the assessment of maternal vascular function by conventional means is cumbersome and expensive.

Objectives: We sought to assess maternal hemodynamic function with a noninvasive cardiographic monitor, and to correlate the findings to both uteroplacental and fetoplacental vascular resistance.

Methods: We measured cardiac output and index (CO, CI), systemic vascular resistance (SVR), mean arterial pressure (MAP) and an index of contractility (ICON) with a novel electrical impedance cardiograph (Aesculon EIC System, Cardiotronic, USA) that provides a volume independent estimate of cyclical blood flow velocity. We enrolled high-risk subjects between 22 and 25 weeks who were referred for assessment of fetal growth and uterine artery Dopplers due to abnormalities of serum screening analytes or other risk factors for preeclampsia. Doppler measurements of blood flow in the uterine arteries (pulsatility index, PI) and umbilical artery (systolic:diastolic ratio, S/D) were obtained by ultrasound (Voluson E8, GE Healthcare, Inc.), along with the fetal weight percentile (FW%). Data were expressed as medians (+/-range), and analyzed with Spearman's correlation coefficient, R. Statistical significance was set to p=0.05.

Results: Electrical impedance cardiography (EIC) data was collected from seventeen subjects. There were no measurement failures. The median gestational age was 24.3 weeks and the BMI was 26.4 (21-47). The median PI, S/D and FW% were 0.96 (0.47 – 2.1), 3.3 (2.6-7.1), and 53% (6% - 82%). EIC results and their relationship to uterine and umbilical Dopplers and fetal growth are shown in Table 1. There were no significant correlations between maternal systemic hemodynamic parameters and uterine artery PI. On the other hand, maternal cardiac function was strongly related to the umbilical artery S/D ratio, and SVR was uniquely related to the FW%.

Table 1

EIC Hemodynamic Parameter	Median (range)	Correlation with Dopplers and growth (Spearman R; *=p<0.05)		
		Uterine PI	Umbilical S/D	FW %
CO	7.5 (4.0-0.1)	-0.29	-0.72 *	0.24
CI	4.4 (2.3 – 5.2)	-0.46	-0.69 *	0.21
SVR	823 (469 – 2028)	0.34	0.89 *	-0.57 *
MAP	78 (10-109)	0.36	0.53 *	-0.77 *
ICON	66 (22-100)	-0.32	-0.54 *	0.16

Conclusion: Maternal systemic hemodynamics can be conveniently acquired by EIC at the same time as routine obstetrical imaging. Our data suggest that maternal cardiovascular adaptation more closely reflects the fetoplacental circulation than the uteroplacental circulation in women at moderate risk of preeclampsia. EIC may be a useful adjunct in assessing risk of fetal compromise.

Relationship between mid-pregnancy Placenta Growth Factor and hemodynamics in the mother, fetus, and uterus.

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Introduction: Placental Growth Factor (PlGF) is an angiogenic and vasoregulatory peptide member of the vascular endothelial growth factor family. Reduction of free, circulating PlGF is associated with preeclampsia and fetal growth restriction, and precedes the clinical manifestations of disease by several weeks. It is not known whether aberrant PlGF is related for alterations in endothelial vascular function that cause or exacerbate the placental syndromes of pregnancy.

Objectives: We sought to determine if mid-pregnancy PlGF was related to, and possibly mediating, measures of maternal, fetal, or uterine hemodynamic function in women at risk for placenta-mediated complications of pregnancy.

Methods: We measured free plasma PlGF (Triage PlGF Assay, Alere, Inc.) between 22 and 25 weeks in high risk subjects referred for assessment of fetal growth and uterine artery Dopplers due to abnormalities of serum screening analytes or other risk factors for preeclampsia. Maternal hemodynamic parameters including mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance (SVR) and index of contractility (ICON) were measured in recumbent position with noninvasive electrical cardiography (Aesculon EC System, Cardiotronics, Inc.). Doppler measurements of blood flow in the uterine arteries (pulsatility index, PI) and umbilical artery (systolic:diastolic ratio, S/D) were obtained by ultrasound (Voluson E8, GE Healthcare, Inc.), along with the estimated fetal weight (EFW). PlGF was expressed as the log concentration, plotted against the hemodynamic measurements, and analyzed with Spearman's correlation coefficient, R. Statistical significance was set to p=0.05.

Results: Data from seventeen fully studied patients were analyzed. The median gestational age was 24.3 weeks. PlGF concentration ranged from 25 to 1180 with a median of 235 pg/ml. PlGF was positively related to maternal cardiac index (R=0.56, p=0.02) and ICON (R=0.51, p=0.04) and negatively related to SVR (R=-0.48, p=0.05). There was a non-significant negative correlation with MAP (R=-0.41, p=0.10). PlGF showed a positive correlation to EFW (R=0.52, p=0.03) and a negative relationship to umbilical artery S/D ratio (R=-0.42, p=0.06). There was no correlation between maternal PlGF and uterine artery Doppler PI (R=-0.19, p=0.46).

Conclusions: The concentration of circulating free PlGF at mid-pregnancy is related to both maternal systemic hemodynamic function and fetal umbilical artery resistance (and growth) in high risk pregnancies prior to the onset of preeclampsia. It is not, however, related to vascular resistance in the uterine artery. PlGF may play a role in modulating the general vascular function of the fetus and mother after establishment of the uteroplacental circulation.

Placental Growth Factor, Uterine Dopplers, Electrocardiometry (PLUDEC) in High Risk Pregnancies

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Introduction

Placental Growth Factor (PLGF) is an angiogenic peptide produced by the normal, healthy placenta which is secreted in large quantities into the circulation during pregnancy and acts on endothelial cells to alter maternal vascular function. Low concentrations of PLGF in pregnancy have been recently linked to preeclampsia, a syndrome of maternal endothelial dysfunction, and to various other adverse obstetrical outcomes related to placental dysfunction such as fetal growth restriction and preterm birth. Additionally, high concentrations of anti-angiogenic factors such as soluble VEGF receptors SFLT-1, which are released by the placenta under hypoxic conditions, can bind PLGF and prevent its angiogenic effects on the endothelium, thus contributing to adverse obstetrical outcomes. Many clinical and biochemical risk factors for preeclampsia have been previously identified, but none are directly implicated in the pathogenesis of the disease. Some of these risk factors include abnormal concentrations of serum analytes from 1st and 2nd prenatal screening tests (such as PAPP-A, AFP, HCG, and inhibin2) maternal age and 3) obesity. These risk factors are, in effect, early pregnancy markers of suboptimal placental or maternal vascular function, although the mechanisms linking these factors to the syndrome of preeclampsia are uncertain. We hypothesize that PLGF mediates maternal vascular function, and that many risk factors for preeclampsia act through alterations in the circulating level of this angiogenic growth factor. This study examines the correlation between PLGF and serum analytes, maternal BMI, and maternal age.

Methods

In order to assess the concentration of circulating PLGF in a cohort of high risk women with risk factors for preeclampsia, a target cohort of 21 maternal subjects were enrolled at the UCSD Placenta Clinic. Patients at this clinic were evaluated at 22-25 weeks. There, the subjects were interviewed and plasma and urine samples were collected from the subjects. Additionally, 2 control subjects, who were recruited during routine prenatal sonograms at the same site, were enrolled in the study. The blood and urine samples were collected, prepared and frozen on site at – 80C. Samples were assayed in a batch for PLGF using the Alere Triage Platform, an automated immunoassay for PLGF developed by Biosite, Inc. Assays were performed anonymously by Biosite, Inc in San Diego, as part of a research agreement with Dr. Douglas Woelkers, the study's PI. Ultimately, multivariable models of analysis were examined to search for independent associations between PLGF and serum analytes, maternal BMI, and maternal age. For these analyses, the concentration of PLGF was log-transformed for normality, and reported as medians +/- interquartiles. Correlations with continuous variables were performed using Pearson's r coefficient. Spearman's rank R coefficient as appropriate, with statistical significance defined as $p = 0.05$. A sample-size calculation based on the detection of a correlation of > 0.50 between PLGF and cardiac output determined that 30 subjects would need to be enrolled to achieve 80% power.

Results

Twenty one subjects were enrolled in this study at the UCSD Placental Clinic. One patient was excluded because her gestational age was beyond 25 weeks. The average maternal age was 31.7 years, and the average gestational age was 24.5 weeks. PLGF concentrations were measureable in 19 of 21 subjects, with a mean concentration of 322 pg/ml (range 24.8 to 1180 pg/ml). One subject was below the limit of detection (low cutoff 12 pg/ml) and one declined to provide blood or urine samples. Out of the 21 maternal subjects, 17 subjects had a complete quad screen test, which measure alpha-fetal protein levels (AFP), estriol, inhibin-A, and human chorionic gonadotropin (HCG). One subject was not evaluated using a quad screening test. Four subjects were evaluated without PAPP-A results.

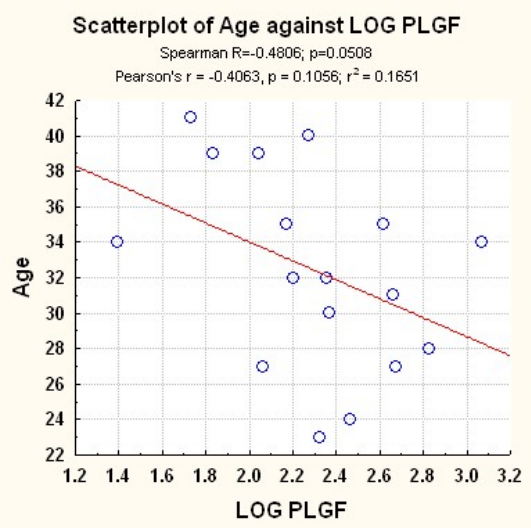
1) As a result of this investigation, no statistically significant correlations were found between mid-pregnancy PLGF and serum analytes used for the first and second trimester prenatal screening: PAPP-A, AFP, HCG, and inhibin.

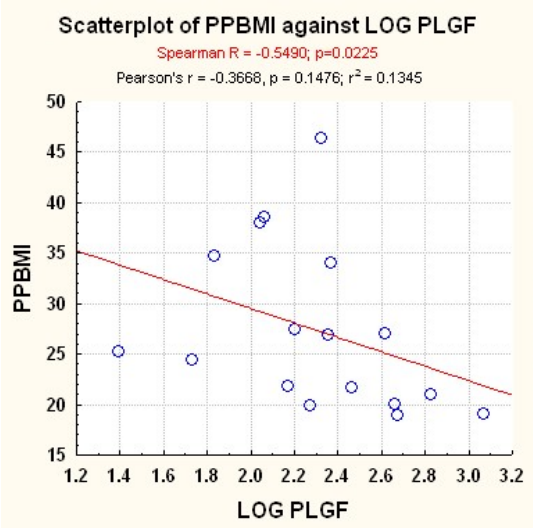
2) PLGF was related to some of the demographic characteristics of patients. For instance, PLGF appeared to be lower in older patients (p= 0.0508). Also, PLGF appeared to be lower in more obese women (p= 0.0166). Meanwhile, PLGF was not related to gestational age in this study, but all subjects were within a narrow gestation age window.

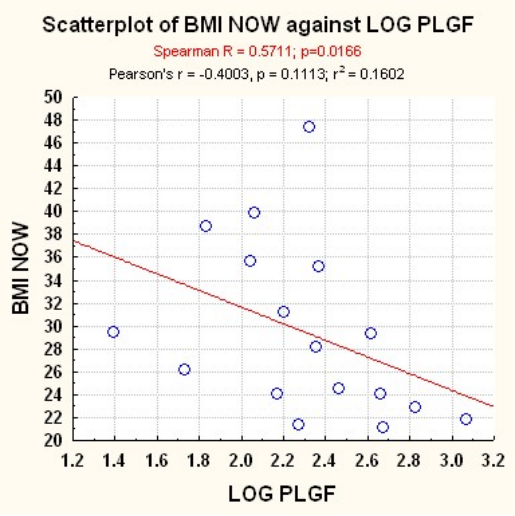
3) There were also no statistically significant correlations between PLGF and pre-pregnancy risk factors for preeclampsia including chronic hypertension and pre-gestational diabetes, but the number of subjects is too low for reliable analysis.

PlGF vs Demographics

	Spearman Rank Order Correlations (Data 10_17_11.s MD pairwise deleted Marked correlations are significant at p <.05000 Exclude cases: 10,13,17			
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value
Age & P PLGF	17	-0.480641	-2.12280	0.050824
PPBMI & P PLGF	17	-0.549020	-2.54405	0.022461
GA & P PLGF	17	-0.294018	-1.19139	0.252012
BMI NOW & P PLGF	17	-0.571078	-2.69435	0.016646

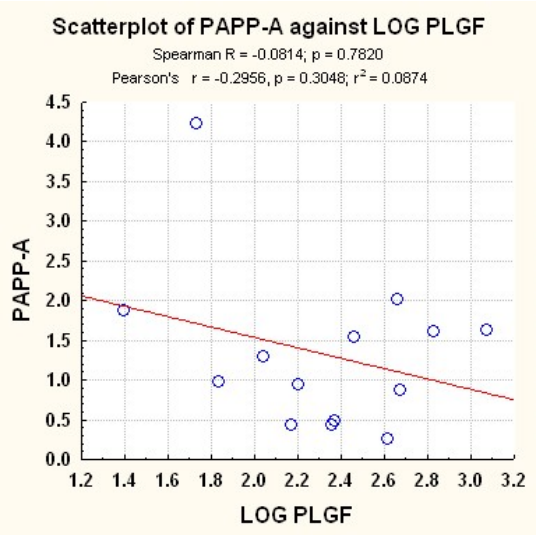


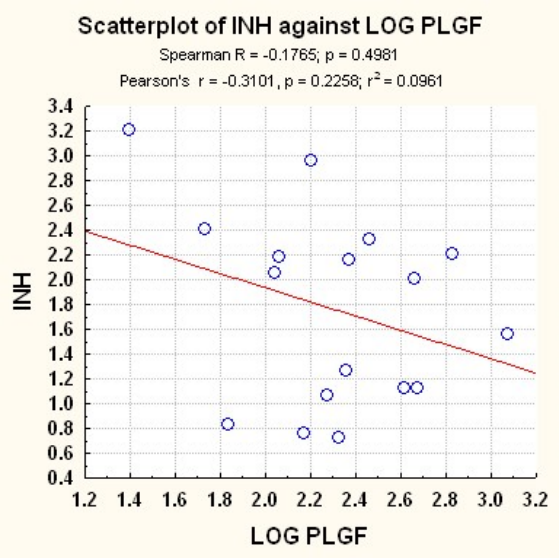




PlGF vs Analytes

Pair of Variables	Spearman Rank Order Correlations (Data 10_17_11.s MD pairwise deleted Marked correlations are significant at p <.05000 Exclude cases: 10,13,17 Valid N	Spearman R	t(N-2)	p-value
PAPP-A & P PLGF	14	-0.081408	-0.282945	0.782040
AFP & P PLGF	17	-0.017157	-0.066458	0.947891
HCG & P PLGF	17	-0.029412	-0.113961	0.910780
Ue3 & P PLGF	17	-0.051471	-0.199609	0.844467
INH & P PLGF	17	-0.176471	-0.694365	0.498068





Conclusion

Given a small sample size of 21 maternal subjects, statistically significant correlations were not determined between mid-pregnancy PLGF and serum analytes and maternal age. However, there were strong associations between PLGF and obesity which could have reached statistical significance given a larger sample size. Thus, the study would have required a larger sample size to detect statistically significant relationships and achieve a higher power. Of note, the relationship observed between PLGF and obesity is biologically analogous to the dilution effect: as the maternal BMI increases, lower concentrations of PLGF are detected and PLGF becomes diluted. This could explain why maternal obesity significantly increases the risk of preeclampsia.

Placental Growth Factor, Uterine Dopplers, Electrocardiometry (PLUDEC) in High Risk Pregnancies

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(Medical Student (II) at University of California, San Diego School of Medicine)

Introduction

Placental Growth Factor (PLGF) is an angiogenic peptide produced by the normal, healthy placenta which is secreted in large quantities into the circulation during pregnancy and acts on endothelial cells to alter maternal vascular function. Low concentrations of PLGF in pregnancy have been recently linked to preeclampsia, a syndrome of maternal endothelial dysfunction, and to various other adverse obstetrical outcomes related to placental dysfunction such as fetal growth restriction and preterm birth. Additionally, high concentrations of anti-angiogenic factors such as soluble VEGF receptors SFLT-1, which are released by the placenta under hypoxic conditions, can bind PLGF and prevent its angiogenic effects on the endothelium, thus contributing to adverse obstetrical outcomes. Many clinical and biochemical risk factors for preeclampsia have been previously identified, but none are directly implicated in the pathogenesis of the disease. Some of these risk factors include abnormal uterine artery Dopplers and small placental or fetal size.These risk factors are, in effect, early pregnancy markers of suboptimal placental or maternal vascular function, although the mechanisms linking these factors to the syndrome of preeclampsia are uncertain. We hypothesize that PLGF mediates maternal vascular function, and that many risk factors for preeclampsia act through alterations in the circulating level of this angiogenic growth factor. This study examines the correlation between PLGF and objective tests of placental and maternal vascular function in mid pregnancy such as uterine artery dopplers, umbilical dopplers, and fetal growth.

Methods

In order to assess the concentration of circulating PLGF in a cohort of high risk women with risk factors for preeclampsia, a target cohort maternal subjects was enrolled at the UCSD Placenta Clinic. Patients at this clinic are referred for abnormal concentrations of serum analytes, chronic hypertension, or a history of adverse pregnancy outcomes. They are evaluated at 22-25 weeks with a comprehensive fetal and placenta sonogram which includes measurements of the fetal size (estimated fetal weight, EFW and EFW %tile), placental length and width (L, W and L/W ratio), umbilical artery Doppler velocity (systolic to diastolic ratio, S/D ratio) and uterine artery Doppler velocity (pulsatility index, PI, and presence or absence of diastolic notching). While at the clinic, subjects were interviewed, and plasma and urine samples were collected for analysis of PLGF. The blood and urine samples were collected, prepared and frozen on site at – 80C. Samples were assayed in batch for PLGF using the Alere Triage Platform, an automated immunoassay for PLGF developed by Biosite, Inc. Assays were performed anonymously by Biosite, Inc in San Diego, as part of a research agreement with Dr. Douglas Woelkers, the study's PI, to search for independent associations between PLGF and early pregnancy risk factors. Additionally, 2 control subjects, who were recruited during routine prenatal sonograms at the same site, were enrolled in the study. For analyses, the concentration of PLGF was log-transformed for normality, and reported as

medians +/- interquartiles. Group comparisons were analyzed with student's t-test. Correlations with continuous variables were performed using Pearson's r coefficient or Spearman's rank R coefficient as appropriate, with statistical significance defined as p = 0.05. A sample-size calculation based on the detection of a correlation of > 0.50 between PLGF and cardiac output determined that 30 subjects would need to be enrolled to achieve 80% power.

Results

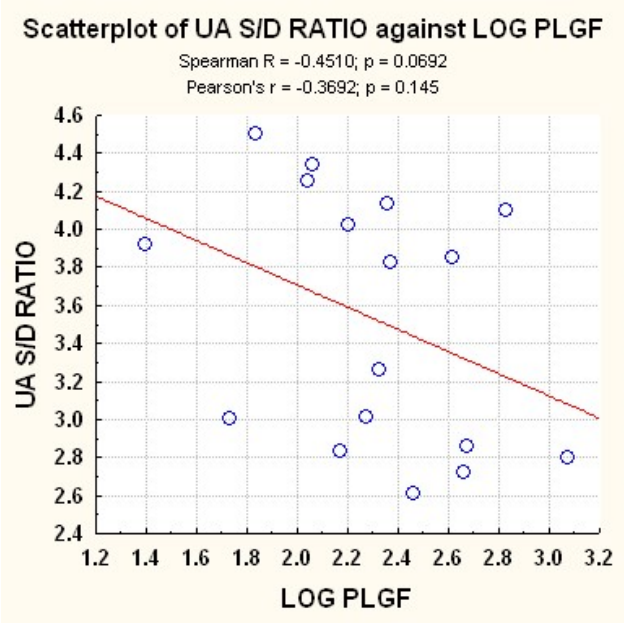
Twenty one subjects were enrolled in this study at the UCSD Placental Clinic and were evaluated with a comprehensive sonographic exam and uterine artery Doppler imaging, which was used to detect placental insufficiency. One patient was excluded because her gestational age was beyond 25 weeks. PLGF concentrations were measureable in 19 of 21 subjects, with a mean concentration of 322 pg/ml (range 24.8 to 1180 pg/ml). One subject was below the limit of detection (low cutoff 12 pg/ml) and one declined to provide blood or urine samples.

1) As a result of this investigation, no association was seen between PLGF and any of the Doppler indices, either as a correlation between PLGF and the PI, or when grouping subjects into those with notching or a high PI (>1.4).

2) There were also no statistically significant correlations between mid-pregnancy PLGF and sonographic findings for placental insufficiency, such as abnormal fetal (EFW, EFW%) or placental size (L/W Ratio). Nonetheless, a positive slope exists between PLGF and EFW% (p= 0.25) which is biologically plausible because a heavier fetus (larger EFW%) is more likely to have a robust placenta, which would secrete increased PLGF. There was also a strong and nearly significant negative relationship between PLGF and the umbilical artery S/D ratio (R=-0.45; p= 0.0692). It was observed that the higher the PLGF, the lower the S/D ratio, which would be expected from a healthy placenta with reduced vascular resistance.

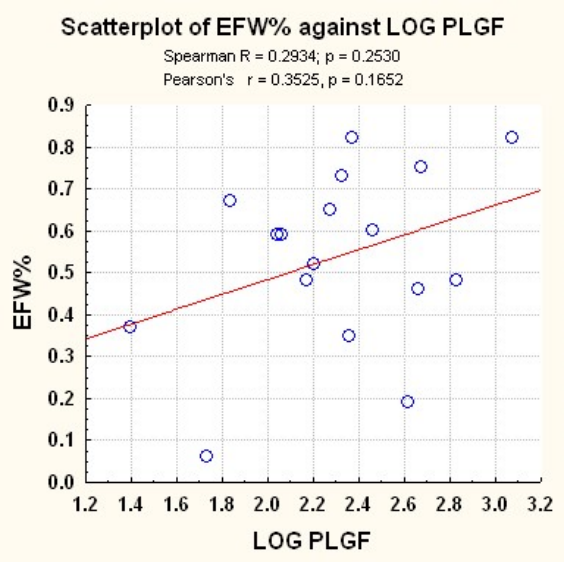
PLGF vs Fetal Doppler

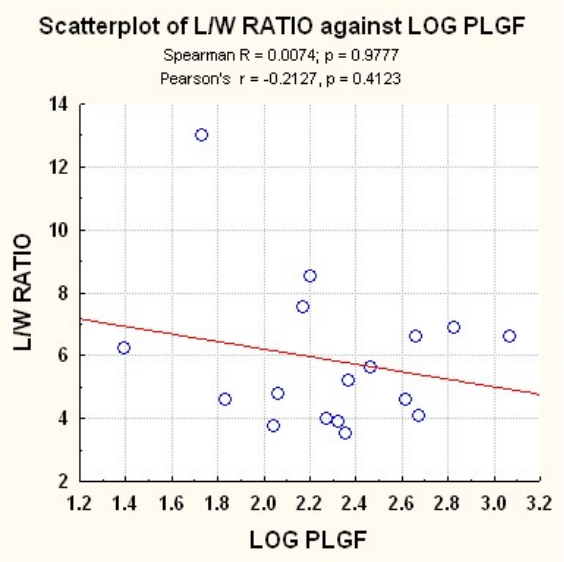
Pair of Variables	Spearman Rank Order Correlations (Data 10_17_11.s MD pairwise deleted Marked correlations are significant at p <.05000 Exclude cases: 10,13,17			
	Valid N	Spearman R	t(N-2)	p-value
UA S/D RATIO & P PLGF	17	-0.450980	-1.95694	0.069232
MCA RI & P PLGF	17	-0.002466	-0.00955	0.992505



PLGF vs Fetal/Placental Size

Pair of Variables	Spearman Rank Order Correlations (Data 10_17_11.s MD pairwise deleted Marked correlations are significant at p <.05000 Exclude cases: 10,13,17			
	Valid N	Spearman R	t(N-2)	p-value
Ave US Age & P PLGF	17	-0.156309	-0.612917	0.549112
EFW & P PLGF	17	-0.002451	-0.009493	0.992551
EFW% & P PLGF	17	0.293432	1.188788	0.253003
PL LEN & P PLGF	17	0.036765	0.142485	0.888593
PL WID & P PLGF	17	0.163090	0.640217	0.531690
L/W RATIO & P PLGF	17	0.007353	0.028479	0.977656





PlGF vs Uterine Artery Dopplers

Pair of Variables	Valid N	Spearman R	t(N-2)	p-value
SUP L PI & P PLGF	17	0.164216	0.64476	0.528823
SUP R PI & P PLGF	17	0.019620	0.07600	0.940422
SUP M PI & P PLGF	17	0.139706	0.54644	0.592801
R DCUB L PI & P PLGF	13	-0.396149	-1.43095	0.180235
L DCUB R PI & P PLGF	13	-0.137363	-0.45994	0.654517

Spearman Rank Order Correlations (Data 10_17_11.s
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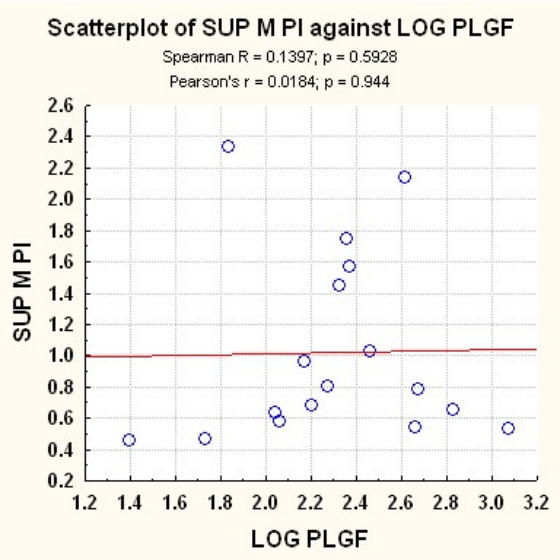
Marked correlations are significant at p <.05000
Exclude cases: 10,13,17



Conclusion

In this small cohort size of 21 subjects, statistically significant correlations were not found between mid-pregnancy PLGF and maternal and fetal sonographic findings. Despite the lack of a statistical correlation, the slope of the relationship between PLGF and the fetal or maternal variables was nearly always in the direction anticipated by the hypothesis. The strongest relationship observed was that between PLGF and the fetal umbilical artery Doppler S/D ratio (-0.45), which may indicate that PLGF measured in maternal serum is a marker of angiogenesis on the fetal side of the placental circuit.

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Methods

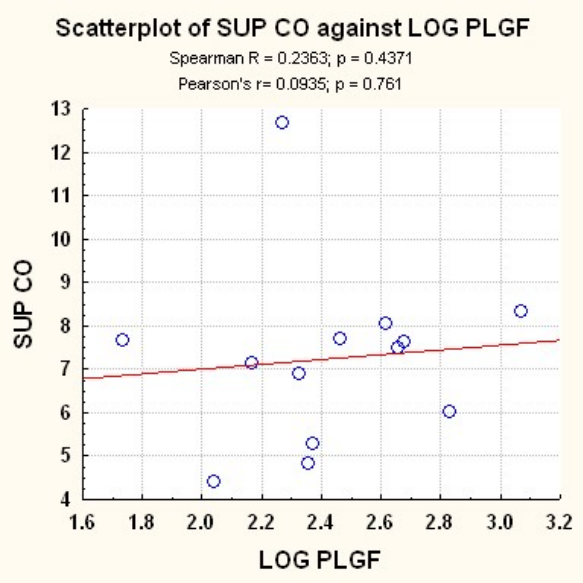
In order to assess the concentration of circulating PLGF in a cohort of high risk women with risk factors for preeclampsia, a cohort of maternal subjects were enrolled at the UCSD Placenta Clinic. Patients at this clinic were referred for abnormal concentrations of serum analytes, chronic hypertension, or a history of adverse pregnancy outcomes. They were evaluated at 22-25 weeks, during which plasma and urine samples were collected for analysis of PLGF. The blood and urine samples were prepared and frozen on site at – 80C. Samples were assayed in batch for PLGF using the Alere Triage Platform, an automated immunoassay for PLGF developed by Biosite, Inc. Assays were performed anonymously by Biosite, Inc in San Diego, as part of a research agreement with Dr. Douglas Woelkers, the study's PI, to search for independent associations between PLGF and mid-pregnancy markers of cardiovascular function. Concurrently, measurements of maternal hemodynamic function were taken using the EC, including blood pressure (mean arterial, MAP), cardiac output (CO), and systemic vascular resistance (SVR). For analyses, the concentration of PLGF was log-transformed for normality, and reported as medians +/- interquartiles. Group comparisons were analyzed with student's t-test. Correlations with continuous variables were performed using Pearson's r coefficient or Spearman's rank R coefficient as appropriate, with statistical significance defined as $p = 0.05$. A sample-size calculation based on the detection of a correlation of > 0.50 between PLGF and cardiac output determined that 30 subjects would need to be enrolled to achieve 80% power.

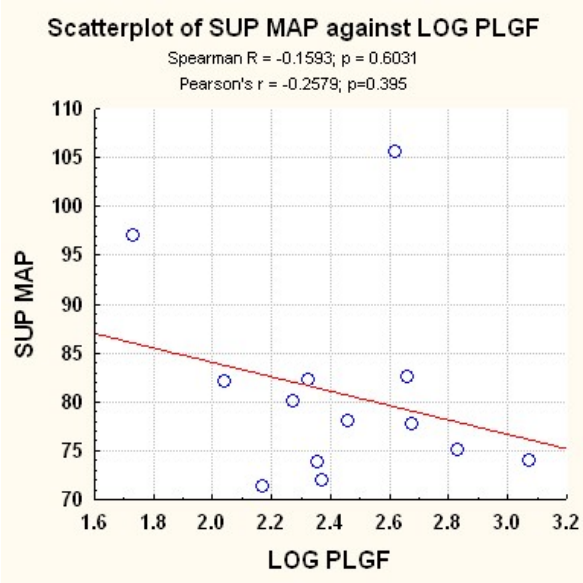
Results

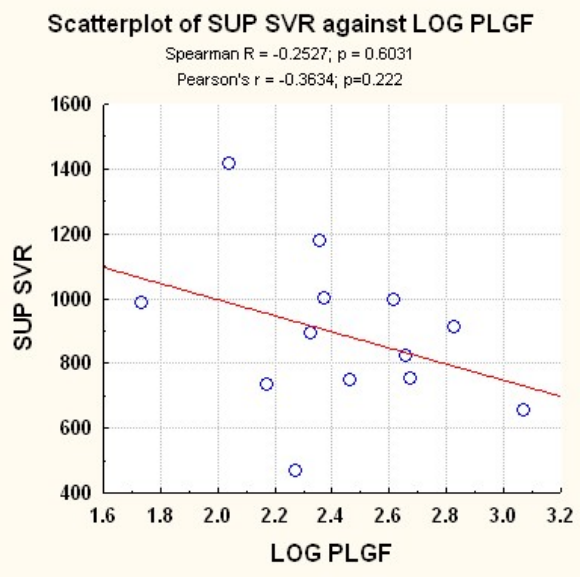
Twenty one subjects were enrolled in this study at the UCSD Placental Clinic. One patient was excluded because her gestational age was beyond 25 weeks. PLGF concentrations were measureable in 19 of 21 subjects, with a mean concentration of 322 pg/ml (range 24.8 to 1180 pg/ml). One subject was below the limit of detection (low cutoff 12 pg/ml) and one declined to provide blood or urine samples. Complete maternal cardiovascular function was measured using the cardiothoracic impedance plethysmography in 17 subjects.

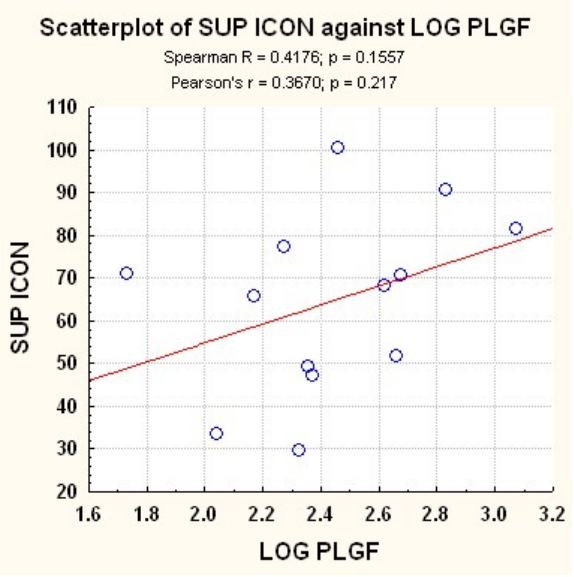
As a result of this investigation, no statistically significant correlations were found between mid-pregnancy PLGF and maternal hemodynamics as measured by the Cardiodynamics impedance plethysmography (CO, SVR, and MAP).

	Spearman Rank Order Correlations (Data 10_17_11.s MD pairwise deleted Marked correlations are significant at p <.05000 Exclude cases: 10,13,17			
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value
SUP CO & P PLGF	13	0.236264	0.806429	0.437084
SUP CI & P PLGF	13	0.377412	1.351698	0.203613
SUP SBP & P PLGF	13	-0.109890	-0.366685	0.720810
SUP DBP & P PLGF	13	-0.261348	-0.898005	0.388416
SUP MAP & P PLGF	13	-0.159341	-0.535313	0.603088
SUP SVR & P PLGF	13	-0.252747	-0.866398	0.404774
SUP SVRI & P PLGF	13	-0.153846	-0.516398	0.615799
SUP ICON & P PLGF	13	0.417582	1.524218	0.155675
R DCUB CO & P PLGF	13	0.192308	0.649944	0.529068
R DCUB CI & P PLGF	13	0.500000	1.914854	0.081864
R DCUB ICON & P PLGF	13	0.516484	2.000453	0.070749
L DCUB CO & P PLGF	13	-0.054945	-0.182508	0.858504
L DCUB CI & P PLGF	13	0.093407	0.311155	0.761500
L DCUB ICON & P PLGF	13	0.434066	1.598029	0.138342









Conclusion

In this small cohort size of 21 subjects, statistically significant correlations were not found between mid-pregnancy PLGF and markers of impaired maternal vascular adaptation. While the EC did show a positive correlation between PLGF and CO and a negative correlation between PLGF and SVR/MAP (as would be predicted by our hypothesis), the p values are not significant. This is possibly due to the small sample size. With a sample size of 13 subjects, there was only 20% power to exclude a type II error. The study would need 50 subjects to obtain 80% power.