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BASELINE PLACENTAL GROWTH FACTOR LEVELS FOR THE PREDICTION OF BENEFIT FROM EARLY ASPIRIN PROPHYLAXIS FOR PREECLAMPSIA PREVENTION

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Abstract

Objective—Placental growth factor (PIGF) levels early in pregnancy are lower in women who ultimately develop preeclampsia. Early initiation of low-dose aspirin reduces preeclampsia risk in some high risk women. We hypothesized that low PIGF levels may identify women at increased risk for preeclampsia who would benefit from aspirin.

Study Design—Secondary analysis of the MFMU High-Risk Aspirin study including singleton pregnancies randomized to aspirin 60mg/day (n=102) or placebo (n=72), with PIGF collected at 13w0d–16w6d. Within the placebo group, we estimated the probability of preeclampsia by PIGF level using logistic regression analysis, then determined a potential PIGF threshold for preeclampsia prediction using ROC analysis. We performed logistic regression modeling for potential confounders.

Results—ROC analysis indicated 87.71 pg/ml as the threshold between high and low PIGF for preeclampsia-prediction. Within the placebo group high PIGF weakly predicted preeclampsia (AUC 0.653, sensitivity/specificity 63/66%). We noted a 2.6-fold reduction in preeclampsia with aspirin in the high-PIGF group (12.15% aspirin vs 32.14% placebo, $p = 0.057$), but no significant differences in preeclampsia in the low PIGF group (21.74% vs 15.91%, $p = 0.445$).

Conclusions—Unlike other studies, we found that high rather than low PIGF levels were associated with an increased preeclampsia risk. Low PIGF neither identified women at increased risk of preeclampsia nor women who benefitted from aspirin. Further research is needed to determine whether aspirin is beneficial in women with high PIGF, and whether the paradigm linking low PIGF and preeclampsia needs to be reevaluated.

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Keywords

Aspirin; MFMU; placental growth factor (PIGF); preeclampsia

INTRODUCTION

Preeclampsia, a major cause of maternal and fetal morbidity, affects 0.4–2.8% of pregnancies worldwide.^{1, 2} With growing evidence supporting early initiation of low-dose aspirin (LDA) in high risk women for prevention of preeclampsia, great emphasis has been placed on the identification of serum biomarkers which may predict preeclampsia and identify women who may benefit from LDA.

One such potential biomarker is placental growth factor (PIGF), a mediator of placental vascular development produced by placental trophoblasts³ which was shown to be significantly lower in pregnancies that go on to develop preeclampsia as early as 11 weeks gestation.^{4–8} PIGF is thought to induce non-branching angiogenesis leading to a low-resistance placental vascular network.⁹ In pregnancies complicated by preeclampsia, limited angiogenesis early in pregnancy with shallow vascular invasion of maternal spiral arteries leads to subsequent placental under perfusion. It is thought that placental blood flow may be further decreased by a number of factors including activation of the coagulation cascade, platelet aggregation, and endothelial dysfunction, (in part due to an imbalance of prostacyclin and thromboxane A2).^{10–12} In vascular conditions such as chronic hypertension, a baseline increase in systemic inflammation is also thought to predispose women to the development of preeclampsia.¹³

Aspirin, as a modulator of platelet aggregation and inflammation,^{14–16} has been studied as a potential target for the prevention of preeclampsia. In low doses (60–150mg), aspirin is associated with a reduction in preeclampsia risk in high risk women when initiated at 16 weeks of gestation or less.¹⁶ The American College of Obstetrics and Gynecology recommends early initiation of LDA only for women with a history of early preeclampsia in a prior pregnancy (resulting in delivery prior to 34w0d), or preeclampsia in more than one pregnancy. Currently there are no clear strategies for the prevention of preeclampsia in other high-risk and low-risk women, and it is not yet clear why some women benefit from LDA while others do not. If PIGF levels early in pregnancy were found to be useful in identifying women at increased risk for preeclampsia and those likely to benefit from LDA use, the use of LDA prophylaxis could potentially be expanded to women without clinical risk factors for preeclampsia.

The interaction between LDA and low baseline PIGF levels in preeclampsia prevention has not yet been evaluated. Nonetheless, early pregnancy PIGF measurement is being marketed in many parts of world specifically to identify women who should receive LDA.¹⁷ Given the association between low PIGF in early pregnancy and preeclampsia later in gestation, and preeclampsia risk reduction with LDA initiated early in pregnancy, we sought to determine whether certain high-risk women with low PIGF might benefit from early LDA prophylaxis.

MATERIALS AND METHODS

This is a retrospective cohort study performed as a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network High Risk Aspirin preeclampsia prevention study (HIRA) database of released variables. The HIRA study was a randomized placebo-controlled trial performed at twelve medical centers within the United States (1991–1995) designed to determine whether LDA (60mg/day) initiated at 13–26 weeks improved pregnancy outcome in women at high risk for preeclampsia.¹⁸ From 1992–1995, an ancillary observational study was performed involving the collection of serum biomarkers including placental growth factor (PIGF). This secondary analysis was approved by the Colorado Multiple Institutional Review Board (COMIRB).

We identified women who were enrolled between 13w0d and 16w6d and who met criteria for enrollment based on pre-existing diabetes mellitus, chronic hypertension, or a history of preeclampsia in a previous pregnancy. Enrollment in the primary HIRA study was stratified by high-risk sub-group. Chronic hypertension was defined by the use of an anti-hypertensive agent, or a resting blood pressure of greater or equal to 140/90 mmHg on two occasions at least 4 hours apart, either prior to pregnancy or during pregnancy prior to 20 weeks gestation. Women with hypertension and diabetes were included in the diabetes group. A history of preeclampsia was determined by review of the medical record (with new onset proteinuria and hypertension), or by an oral history of preeclampsia with delivery prior to 37 weeks. Further details of enrollment criteria and exclusion criteria are published elsewhere.¹⁸

Our primary study outcome was preeclampsia at any time point in pregnancy. Our secondary outcomes were late-onset preeclampsia (delivery on or after 34w0d), early-onset preeclampsia (delivery <34w0d), delivery of a small-for-gestational age neonate (SGA, <10%), or a composite outcome (early preeclampsia or SGA). Preeclampsia was defined as the development of hypertension (either systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg on two occasions at least four hours apart) plus one of the following: proteinuria, thrombocytopenia, or pulmonary edema. Proteinuria was defined as a 24h urine collection with $\geq$ 300 mg or a dipstick test with 2+ proteinuria ($\geq$ 100mg per deciliter) on two occasions at least four hours apart, without evidence of a urinary tract infection. Thrombocytopenia was defined as a platelet count of $<$ 100,000 per cubic millimeter. Eclamptic seizures and HELLP also satisfied the diagnostic criteria for preeclampsia. In women with preexisting hypertension or proteinuria, the criteria for diagnosis of preeclampsia differed slightly, as previously described.¹⁸ An infant was considered small for gestational age at birth if its weight was below the 10th percentile for gestational age based on normative birth weights for singletons.^{18, 19}

Sample collection was performed at study entry. Sample handling and PIGF analysis was previously described.²⁰

We compared demographics characteristics and outcome variables between women randomized to LDA vs. placebo and between women with high vs. low baseline PIGF using

exact chi-square tests for categorical variables, and t-tests for continuous measures. Within the placebo group, we performed logistic regression analysis to estimate the probability of preeclampsia by PIGF level, and then performed a non-directional ROC analysis to determine a potential PIGF threshold for the prediction of preeclampsia. Using the chi-square test we compared preeclampsia rates by treatment group (LDA or placebo) overall and within each PIGF category (high or low). We estimated a logistic regression model to compare the odds of preeclampsia by treatment group, PIGF category, and their interaction, and adjusted for potential confounds and precision variables (maternal age, gestational age at randomization, high-risk subgroup (chronic hypertension, diabetes, history of preeclampsia in a prior pregnancy), race or ethnicity, tobacco use, parity, and history of miscarriage). We defined significance as an alpha of < 0.05 , and used SAS software to perform the statistical analyses.

RESULTS

Of the 1358 women in the Maternal-Fetal Medicine Units Network multicenter High Risk Aspirin ancillary biomarker study (2002–2005), we identified 174 women with a singleton pregnancy who enrolled between 13w0d and 16w6d. When comparing the LDA and placebo groups, we found no significant differences in demographic characteristics including baseline PIGF levels or distribution of high-risk subgroups (diabetes, hypertension, or preeclampsia in a prior pregnancy), Table 1. The majority of subjects in both treatment groups were obese and African American. The “low PIGF” and “high PIGF” groups differed significantly in three aspects: gestational age at enrollment (106 v 111d), high-risk subgroup distribution (with more women with diabetes in the low PIGF group and more women with chronic hypertension in the high PIGF group), and race/ethnicity distribution, Table 1. Of women in the low PIGF group, 49.6 % were Caucasian and 40.6% were African American. Of women in the high PIGF group, 19.7% were Caucasian and 72% were African American.

Within the placebo group, the threshold PIGF value for the prediction of preeclampsia (collected at enrollment, between 13w0d–16w6d) was 87.71 pg/ml, above which there was a higher rate of preeclampsia. Preeclampsia was seen in 21.3% of women with “high” baseline PIGF (mean 163 pg/ml) and in 19.3% of women with “low” PIGF (mean PIGF 58.7 pg/ml). The receiver operator curve yielded an area under the curve (AUC) of 0.653 (0.51–0.80) with sensitivity and specificity of 63% and 66% for prediction of preeclampsia.

There were no statistically significant differences in our primary outcome of preeclampsia with LDA treatment in either the low PIGF or high PIGF groups (Table 2, Figure 1). We found the highest rate of preeclampsia in women with high baseline PIGF who were randomized to placebo (32.14%). In contrast, women with high PIGF randomized to LDA had a relative 2.6 fold decrease in the rate of preeclampsia vs placebo (12.12 vs 32.14 %), with odds ratio of 0.291 (95% CI: 0.078–1.082). Among the high PIGF group the rate of any outcome (late preeclampsia, early preeclampsia and/or SGA) was higher with placebo than with aspirin (43% vs 12%).

In contrast, within the low PIGF group preeclampsia was more common in women randomized to LDA than placebo (21.74% v 15.91%, $p=0.445$), Table 2. There were no significant differences in baseline PIGF levels in pregnancies later diagnosed with preeclampsia and small for gestational age birth weight. The relationship between PIGF and LDA was similar in significance and magnitude when we adjusted for potential confounders and precision measures including high-risk sub-group, gestational age at enrollment and ethnicity. In sensitivity analyses, when we included gestational age at enrollment with PIGF and LDA treatment group in a logistic regression model of preeclampsia, the magnitude and significance of estimates were similar.

There were no significant differences in any of our secondary outcomes (late preeclampsia, early preeclampsia, small for gestational age, and compound of early preeclampsia or SGA) by treatment group in either the low or high PIGF groups. Early preeclampsia was seen only in the low-PIGF LDA-treated group.

COMMENT

Within this secondary analysis of the MFMU High Risk Aspirin study, we did not find low levels of baseline PIGF to be associated with an increased risk of preeclampsia. We found a trend towards lower odds of preeclampsia with early initiation of LDA in women with high PIGF levels at enrollment. This was contrary to our hypothesis, as low PIGF neither identified a group at increased risk of preeclampsia nor identified women that would benefit from LDA.

The primary strength of this analysis is the basis in a well-designed multi-center double-blinded randomized controlled trial in which the outcomes were thoroughly vetted with strict diagnostic criteria, and high-risk inclusion criteria were well defined. All samples in the study were analyzed in a blinded fashion and the inter-assay variability for the measurement of PIGF factor was within acceptable limits and similar to that presented in other studies.²⁰ Our results were limited by the secondary nature of this analysis which did not allow us to distinguish potentially relevant outcomes (such as mild vs severe preeclampsia, and constitutionally small vs pathologically small neonatal growth parameters). The sensitivity and specificity estimated by our ROC analysis for the prediction of preeclampsia using baseline PIGF levels were modest (63 and 66%). Our threshold PIGF level from the ROC analysis was determined for the entire cohort. While we understand that PIGF levels increase throughout the second trimester,⁵ our small sample size did not allow for the use of gestational-age specific thresholds. Biomarker data for the High Risk Aspirin MFMU study was published in 2010 by Powers, et al,²⁰ over ten years after sample collection (1992–1996). The duration of time that serum samples were frozen prior to analysis was not described however samples were known to have been stored at -80°C and thawed either one (74%) or two times (26%).²⁰ In prior analysis PIGF serum samples were stable through six freeze-thaw cycles²¹ and following storage at -80°C for greater than 36 months.²² In addition we faced sample size limitations owing to our restrictive inclusion criteria (gestational age at enrollment $<17\text{w}0\text{d}$ with concurrent enrolled in the MFMU High-Risk Aspirin ancillary biomarker study) which may have affected our subset analysis. We limited our analysis to women enrolled only through 16 weeks gestational age (instead of

26w as in the original High-Risk Aspirin study) based on subsequent meta-analysis data suggesting a reduction in preeclampsia and SGA birth weight with initiation of LDA at 16 weeks of gestation or less.¹⁶ Inclusion of women with multiple gestations may have allowed for a larger sample size, however we excluded this subgroup due to their higher baseline PIGF levels and our hope of identifying a predictive PIGF threshold within singleton gestations.²⁰

Our original hypothesis involved a potential interaction between baseline PIGF levels and LDA. As a marker of placental hypoperfusion, we suspected that low PIGF was a sign of poor placental development early in pregnancy⁹ which could lead to secondary vasoconstriction and platelet aggregation – a process which may be lessened by the thromboxane-limiting effects of LDA,¹¹ potentially reducing the risk for preeclampsia later in pregnancy. Instead, we found that women with low PIGF had a non-significant increased risk for preeclampsia with LDA vs placebo (22 v 16%). Perhaps low PIGF is a sign of poor trophoblastic invasion in early pregnancy which leads to subsequent placental dysfunction not surmountable by any potential LDA effect.

Counter to our hypothesis, our findings suggest that high PIGF levels may be predictive of a reduction in preeclampsia risk with early initiation of LDA. PIGF has pro-inflammatory properties which are responsible for activation of monocytes and lymphocytes, involving Flt-1 binding with subsequent recruitment and activation of mediators of inflammation.²³ Higher levels of systemic inflammation are thought to predispose women to the development of preeclampsia.¹³ It is conceivable that high levels of PIGF-associated inflammation may be pathogenic, and that LDA (an anti-inflammatory drug) may play a role in mediating this effect.

We are not aware of a prior study evaluating the relationship between baseline PIGF levels and pregnancy outcome by LDA use. In Kleinrouweler's comprehensive meta-analysis of circulating biomarkers for prediction of preeclampsia,⁷ baseline PIGF levels were lower in women who ultimately developed preeclampsia. Kleinrouweler analyzed women considered both high- and low-risk for the development of preeclampsia including women receiving LDA for preeclampsia prophylaxis.^{6, 20} While we did not find a significant difference in baseline PIGF levels by pregnancy outcome within our own population of high-risk women, our analysis was limited by sample size

Baseline PIGF levels have been suggested to be a potential screening tool for identifying women at increased risk for preeclampsia. PIGF testing is currently marketed for this purpose outside of the United States (Roche – “Elecsys Preeclampsia Assay;” Perkin Elmer – “PIGF assay for first trimester preeclampsia screening”). This raises concern that some practitioners might use such measurements to identify women who should receive LDA, a strategy that our findings suggest could be without benefit or even harmful, given the increase (although non-significant) in preeclampsia seen in the low-PIGF group of women randomized to LDA. Before clinical application, further research is needed to better understand the interplay between early PIGF levels and aspirin response, and to determine whether alternative biomarkers may be more useful for the identification of appropriate candidates for early aspirin prophylaxis for preeclampsia prevention.

We identified a potential threshold for PIGF early in pregnancy for the prediction of preeclampsia using a process similar to the work of Kusanovic et al within a Chilean population that like our analysis included women with a history of preeclampsia in a prior pregnancy and chronic hypertension.⁴ Our predicted PIGF threshold at 13w0d–16w6d (87.71pg/ml) was similar to Kusanovic's thresholds identified at flanking gestational ages (at 6–15w: 28.04pg/ml; at 20–25w: 215.04pg/ml). The area under the curve for our ROC analysis (0.653) was also similar to Kusanovic's findings (0.653 and 0.65 respectively). The key difference in our results was a greater preeclampsia risk with PIGF values above this threshold, instead of below the threshold. This is a major difference in our findings which is of unclear etiology. One consideration is whether women in the Kusanovic cohort received aspirin, as our findings suggest that among women receiving LDA, women with low baseline PIGF levels appear to have a higher risk for preeclampsia than those with high baseline PIGF levels (21.7 v 12%). A second consideration is whether differences in the ethnic distribution of our population affected our findings given the large proportion of African-American women within our analysis (50% of our study group overall, and 72% of the "high-PIGF" group). While Kusanovic's study from Chile did not report ethnic/racial characteristics, we suspect that the contribution from individuals with African descent was minimal given the low prevalence within the Chilean population.²⁴ A genome-wide comparison of platelet aggregation phenotypes in African American and Caucasian American subjects identified several genomic regions (5q11.2) within the African American population which were linked to aspirin response factors, suggesting that ethnic variations in aspirin response may exist and could be driving our results.²⁵ On balance, our findings support the developing concept that preeclampsia may have fundamental pathophysiologic differences in different risk groups, and that extrapolating findings from one population to another should be done cautiously.^{26, 27}

While we did not find low PIGF to be predictive of benefit from LDA in women at increased risk for preeclampsia, early PIGF levels may be useful in the identification of appropriate candidates for LDA prophylaxis. The suggestion of benefit in women with high PIGF (as well as the possibility of harm to women with low PIGF), should be explored further in future research involving the prevention of preeclampsia.

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Figure 1.

We compared outcomes by aspirin treatment groups using a chi-square test overall and within baseline PLGF level categories. High PLGF: > 87.71 ; Low PLGF: ≤ 87.71 pg/ml. SGA = small for gestational age. Composite outcome = either early preeclampsia or SGA.

Table 1

Demographic Characteristics Based on Treatment Group and PlGF Strata

Characteristic	Aspirin		Placebo		p		Low PlGF		High PlGF		p
	n=102	N=72	n=102	N=72			n=113	N=61			
High Risk Group, n (%)											
Diabetes	38 (37.3)	26 (36.1)	0.46	51 (45.1)	13 (21.3)	0.01					
Hypertension	41 (40.2)	24 (33.3)		35 (31.0)	30 (49.2)						
History of Preeclampsia	23 (22.6)	22 (30.6)		27 (23.9)	18 (29.5)						
Gestational Age At Randomization (d)	107 (0.7)	109 (0.9)	0.06	106 (0.7)	111 (0.8)	<0.001					
Baseline PlGF level (pg/ml)	90.4 (8.7)	102 (10.2)	0.38	58.7 (1.5)	163 (15.3)	*					
Baseline Proteinuria > 300 mg/24h	12 (26.7)	8 (33.3)	0.59	13 (33.3)	7 (23.3)	0.43					
Maternal Age	27.2 (0.6)	27.5 (0.7)	0.78	27.4 (0.6)	27.2 (0.8)	0.88					
Nulliparous, n (%)	30 (29.4)	19 (26.4)	0.73	35 (31.0)	14 (23.0)	0.29					
Tobacco Use in Pregnancy, n (%)	16 (15.7)	11 (15.3)	0.99	13 (11.5)	14 (23.0)	0.16					
Body Mass Index (kg/m2), n (%)											
< 18.5	2 (2.0)	1 (1.4)	0.46	2 (1.8)	1 (1.7)	0.93					
18.5 – 24.9	25 (24.8)	25 (34.7)		34 (30.1)	16 (26.7)						
25 – 29.9	22 (21.8)	17 (23.6)		26 (23.0)	13 (21.7)						
30	52 (51.5)	29 (40.3)		51 (45.1)	30 (50.0)						
Predominant Race or Ethnicity, n (%)											
Caucasian	39 (38.2)	29 (40.3)	0.90	56 (49.6)	12 (19.7)	<0.001					
Hispanic	9 (8.8)	7 (9.7)		11 (9.7)	5 (8.2)						
African American	54 (52.9)	36 (50.0)		46 (40.7)	44 (72.1)						
Infant Birth Weight (g)	3164 (78.8)	3284 (85.9)	0.31	3224 (78.8)	3195 (80.5)	0.80					
Female Infant, n (%)	53 (52.0)	35 (48.6)	0.76	57 (50.4)	31 (50.8)	1.00					

Results are presented as mean (SE) unless otherwise stated. We used a t-test for continuous data and X² test for categorical data.

Low PlGF: 87.71 pg/ml; high PlGF: > 87.71.

Abbreviations: p, p-value; d, days; h, hours; SE, standard error.

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Table 2

Pregnancy Outcome Aspirin Treatment and Baseline PlGF Level

	Aspirin	Placebo	P-value
Overall	N=102	N=72	
Preeclampsia any time in pregnancy	19 (18.6)	16 (22.2)	0.56
"Late" preeclampsia, delivery ≥ 34w	14 (13.7)	16 (22.2)	0.144
"Early" preeclampsia, delivery < 34w	5 (4.9)	0	0.057
Small for gestational age (SGA)	3 (2.9)	4 (5.6)	0.387
Composite: "Early" preeclampsia or SGA	6 (5.9)	4 (5.6)	0.927
Subgroup = PLGF ≤ 87.71	N=69	N=44	
Preeclampsia any time in pregnancy	15 (21.7)	7 (15.9)	0.445
"Late" preeclampsia, delivery ≥ 34w	10 (14.5)	7 (15.9)	0.837
"Early" preeclampsia, delivery < 34w	5 (7.3)	0	0.068
Small for gestational age (SGA)	3 (4.4)	1 (2.3)	0.561
Composite: "Early" preeclampsia or SGA	6 (8.7)	1 (2.3)	0.167
Subgroup = PLGF > 87.71	N=33	N=28	
Preeclampsia any time in pregnancy	4 (12.1)	9 (32.1)	0.057
"Late" preeclampsia, delivery ≥ 34w	4 (12.1)	9 (32.1)	0.057
"Early" preeclampsia, delivery < 34w	0	0	*
Small for gestational age (SGA)	0	3 (10.7)	0.054
Composite: "Early" preeclampsia or SGA	0	3 (10.7)	0.054

Results are presented as n (%). We used the χ^2 test for comparison of outcomes.

Abbreviations: w, weeks; SGA, small for gestational age.

Low PlGF: ≤ 87.71 pg/ml; high PlGF: > 87.71