**DIGITAL ACCESS TO
SCHOLARSHIP AT HARVARD**

DASH.HARVARD.EDU

HARVARD LIBRARY
Office for Scholarly Communication

Modeling risk for severe adverse outcomes using angiogenic factor measurements in women with suspected preterm preeclampsia

The Harvard community has made this article openly available. **Please share** how this access benefits you. Your story matters

ORIGINAL ARTICLE

Modeling risk for severe adverse outcomes using angiogenic factor measurements in women with suspected preterm preeclampsia

Glenn E. Palomaki[1,2], James E. Haddow[1,2], Hamish R. M. Haddow[2], Saira Salahuddin[3,4], Carl Geahchan[5], Ana Sofia Cerdeira[5,6], Stefan Verlohren[7], Frank H. Perschel[8], Gary Horowitz[4,9], Ravi Thadhani[4,10], S. Ananth Karumanchi[3,4,11,12] and Sarosh Rana[3,4,13]*

[1]Department of Pathology and Laboratory Medicine, Women & Infants Hospital/Alpert Medical School at Brown University, Providence, RI, USA
[2]Savjani Institute for Health Research, Windham, ME, USA
[3]Division of Maternal Fetal Medicine/Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA
[4]Harvard Medical School, Boston, MA, USA
[5]Center for Vascular Biology, Beth Israel Deaconess Medical Center, Boston, MA, USA
[6]Gulbenkian Programme for Advanced Medical Education, Porto, Portugal
[7]Department of Obstetrics, Campus Virchow-Clinic, Charité University Medicine, Berlin, Germany
[8]Department of Laboratory Medicine, Clinical Chemistry, and Pathobiochemistry, Charité University Medicine, Berlin, Germany
[9]Clinical Chemistry Laboratory, Beth Israel Deaconess Medical Center, Boston, MA, USA
[10]Division of Nephrology/Department of Medicine, Massachusetts General Hospital, Boston, MA, USA
[11]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA
[12]Howard Hughes Medical Institute, Chevy Chase, MD, USA
[13]Division of Maternal Fetal Medicine/Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL, USA,
*Correspondence to: Sarosh Rana. E-mail: saroshrana@gmail.com

ABSTRACT

Introduction Preeclampsia (PE) is a pregnancy-specific syndrome associated with adverse maternal and fetal outcomes. Patient-specific risks based on angiogenic factors might better categorize those who might have a severe adverse outcome.

Methods Women evaluated for suspected PE at a tertiary hospital (2009–2012) had pregnancy outcomes categorized as 'referent' or 'severe', based solely on maternal/fetal findings. Outcomes that may have been influenced by a PE diagnosis were considered 'unclassified'. Soluble fms-like tyrosine kinase (sFlt1) and placental growth factor (PlGF) were subjected to bivariate discriminant modeling, allowing patient-specific risks to be assigned for severe outcomes.

Results Three hundred twenty-eight singleton pregnancies presented at ≤34.0 weeks' gestation. sFlt1 and PlGF levels were adjusted for gestational age. Risks above 5 : 1 (10-fold over background) occurred in 77% of severe (95% CI 66 to 87%) and 0.7% of referent (95% CI <0.1 to 3.8%) outcomes. Positive likelihood ratios for the modeling and validation datasets were 19 (95% CI 6.2–58) and 15 (95% CI 5.8–40) fold, respectively.

Conclusions This validated model assigns patient-specific risks of any severe outcome among women attending PE triage. In practice, women with high risks would receive close surveillance with the added potential for reducing unnecessary preterm deliveries among remaining women. © 2015 The Authors. *Prenatal Diagnosis* published by John Wiley & Sons Ltd.

INTRODUCTION

Preeclampsia (PE), a syndrome characterized by hypertension and proteinuria, is suspected in 10% of pregnancies but confirmed in only 2 to 3%.[1] In developed countries, PE is a leading cause of medically indicated preterm births.[2] Annually, a half million US babies are delivered before 37 weeks' gestation; 25% are induced for medical or obstetric indications. Nearly half are attributable to a PE diagnosis, and some may be avoidable. Our current clinical[3] and laboratory tests do not

accurately predict adverse outcomes,[4,5] and confusion arises from underlying diseases that mimic PE.[6–9]

The American Congress of Obstetricians and Gynecologists (ACOG) endorses immediate delivery in women with PE at and beyond 37 weeks.[10] Expectant management is recommended when symptoms occur earlier, with the goal of reaching 34 weeks among patients with severe features.[10] Current clinical and laboratory criteria cannot reliably distinguish between women requiring early induced delivery as a result of imminent severe

maternal/fetal morbidity and those that can be managed safely to a later date.[11,12] Thus, providers may over-utilize laboratory, ultrasound and clinical services, delivering some pregnancies earlier than necessary with potential preterm delivery complications. Accurately determining the risk of serious outcomes among women evaluated for PE could reduce the rate of preterm delivery, improve resource allocation and reduce spending.[13] It would also define a group with high risks that could be candidates for newer potential treatment modalities.[14]

A decade ago, alterations in circulating soluble fms-like tyrosine kinase (sFlt1) and placental growth factor (PlGF) were observed to be associated with PE.[15–17] Circulating anti-angiogenic protein sFlt1 is elevated, while free concentrations of pro-angiogenic protein PlGF are reduced. These changes occur before clinically overt findings.[18–20] The combination of sFlt1 and PlGF has high sensitivity and specificity to predict certain adverse outcomes.[19–21] Preliminary studies have explored the clinical validity of these markers among women with suspected PE.[22–24] We reported that over 95% of selected adverse outcomes in women with suspected preterm PE were associated with significant abnormalities in angiogenic factors.[23] Rates of adverse outcomes among women with sFlt1/PlGF ratios <85 were low and generally unrelated to PE,[25] and others have reported similar findings.[22,24,26,27] However, many such studies defined adverse outcomes with direct ties to the diagnosis of PE or excluded certain adverse outcomes not related to PE or the angiogenic factors. Soluble endoglin (sEng), another anti-angiogenic protein, is also associated with PE-related adverse outcomes.[28]

In addition to the varying definitions of severe outcome, the use of an sFlt1/PlGF cutoff of ≥85 as a predictor has potential drawbacks based on implicit assumptions: (1) The relationship between sFlt1 and PlGF and adverse outcomes is constant by gestational age, (2) the strength of association is similar for both markers, (3) absolute levels of the two markers are unimportant, (4) confounding variables influence each marker in a similar way, (5) the cutoff of 85 is optimal, (6) prior risk factors are unimportant and (7) a categorical result (positive/negative) is sufficient for clinical decision-making. The present study addresses the issue of optimizing the interpretation of these angiogenic factors for prediction of impending severe adverse pregnancy outcomes that are defined using only maternal and fetal outcomes that are both comprehensive and not related to the diagnosis of PE. The setting is for 'high risk' women being evaluated for PE in triage; the results, therefore, may not be applicable to screening in the general population. The intent of such testing is to repeat testing every 2 weeks and update risk estimates.

METHODS

Study participants

Women presenting at the obstetric triage unit for PE evaluation at Beth Israel Deaconess Medical Center (BIDMC) between July 2009 and June 2012 were eligible (BIDMC approval 2009P-000084). Women provided written informed consent. Subjects presenting before October 2010 have been reported earlier, but a different definition of adverse outcome was

used.[23,28] Current analyses were limited to singleton pregnancies first evaluated at ≤34.0 weeks with angiogenic marker measurements, pregnancy outcomes and delivery information. The majority of pregnancies seen at triage were first evaluated after 34.0 weeks, and these were not considered in our analyses. Hypertensive disorders of pregnancy (chronic, gestational hypertension, PE and superimposed PE) were defined according to the 2002 ACOG Bulletin[29] with minor modifications as defined previously.[23,25]

Relevant findings for the woman and the fetus

Clinical findings, results of physical examinations, blood pressures, standard laboratory tests and ultrasound findings within 2 weeks of the initial presentation were stored along with information from subsequent outpatient and inpatient visits.[23,25] Table 1 lists maternal findings used to classify pregnancy outcomes. Fetal and neonatal findings (e.g. gestational age at delivery, birth weight, neonatal death) were abstracted from patient charts and were also used to classify outcomes (Table 1).

Table 1 Relevant maternal and fetal findings and the definition of three pregnancy outcome categories

Code	Within 2 weeks[a]	Finding
Maternal		
M0	No	None of the following maternal findings
M1	Yes	Severe hypertension (BP ≥ 160/110)
M2	Yes	Elevated liver function test(s) (LFT)
M3	Yes	Disseminated intravascular coagulation (DIC)
M4	No	Placental abruption
M5	Yes	Pulmonary edema
M6	Yes	Cerebral hemorrhage
M7	Yes	Maternal death
M8	Yes	Eclampsia
M9	Yes	Acute renal failure
M10	No	HELLP syndrome
Fetal		
F0	No	None of the following fetal findings
F1	No	Small for given gestational age (<5th centile)
F2	No	Pre-term delivery (≤34.0 weeks)
F3	No	Very pre-term delivery (≤32.0 weeks)
F4	No	Neonatal death
Pregnancy outcome		
Referent	—	'Normal' group – (M0 AND F0 throughout pregnancy)
Severe	—	Severe adverse outcome – (M3 through M10) OR (F3 through F4) OR (F1 AND F2 AND BP ≥ 140/90)
Unclassified	—	All remaining pregnancies

[a]The finding was recorded within 14 days following the initial presentation at the triage clinic. In practice, the intent is for women to be retested and reinterpreted every 2 weeks.

Sample collection and measurement of angiogenic factors

Residual blood samples from clinical testing were stored at 4 °C for 48 h, collected and centrifuged at 3000 rpm for 10 min. Plasma was aliquoted and stored at −80 °C; these analytes are stable for 10 years.[18] Samples had not been thawed prior to testing. Testing for sFlt1 and PlGF on samples collected through October 2010 was performed on an automated platform (Elecys, Roche Diagnostics, Indianapolis, IN).[23,30] Remaining samples (through June 2012) were tested on the same platform at BIDMC. Inter-assay coefficients of variation for sFlt1 and PlGF were 2.6 to 3.0% and 2.0 to 2.4%, respectively. Laboratory personnel were blinded to clinical information, and physicians were unaware of test results.

Definition of three pregnancy outcome categories

Samples were obtained prospectively, but angiogenic factors were tested after delivery. Thus, the women were subject to the current care standards. A 'referent' category included all pregnancies with no adverse maternal or fetal findings (Table 1). Importantly, PE was not considered as a maternal finding. This referent group was used to define the gestational age relationships for angiogenic factors and to define the false positive rate. The 'severe' category contained those pregnancies with an adverse outcome for the mother, fetus or both (Table 1), usually occurring within the next 2 weeks. This group was used to determine the detection rate. Our aim was to avoid arbitrary classifications that would be biased toward abnormal angiogenic factor measurements or toward a PE diagnosis. Delivery prior to 32.0 weeks was hypothesized to be because of severe disease with accompanying complications. Remaining pregnancies were placed in a third heterogeneous 'unclassified' category with the assumption that a PE diagnosis may have influenced delivery in our observational study. The 2-week limit on measuring outcomes reflects the intent that such testing be repeated in these pregnancies every 2 weeks until they reach 34.0 weeks' gestation.

Statistical analysis

Included pregnancies were randomly assigned to a modeling or validation subset. Within the modeling dataset, measurements from referent samples were used to derive median levels between 20 and 34 weeks' gestation. Modeling was based on validated approaches used for prenatal Down syndrome screening.[31] Assay results were converted to multiples of the median (MoM) and weight adjusted.[32] Data were further examined to determine whether parity, smoking or other factors might influence measurements. Bivariate discriminant analysis was used to model the ability of angiogenic factors to differentiate severe and referent outcomes. The discriminant function provided the likelihood of a pregnancy being in a given outcome category. The risk of a severe outcome was calibrated using the dataset's observed risk of a severe outcome (e.g. the model's average risk equals risk in the dataset). Risks were arbitrarily stratified into 'low' (more than a 10-fold reduction from baseline), 'high' (more than a 10-fold increase) or 'moderate' (all intervening risks) groups. Individual risks were capped at 100-fold increase or decrease. This preliminary model was then applied to the validation dataset and its performance compared. If the

performance was consistent in the two datasets, a final model would be produced using the entire cohort.

Approximately 15 pregnancies with severe outcomes are required for each of the independent factors considered (i.e. 30 severe outcomes in the modeling and validation datasets for sFlt-1 and PlGF), for a total of 60 cases. Approximately 30% of our originally published cohort presented ≤34.0 weeks, and adverse outcomes occur in about 30%. Thus, about 670 women (60/0.3/0.3) attending a PE triage clinic would be sufficient for reliable modeling. The entire cohort consisted of 1141 evaluated women, but this included twin pregnancies and multiple enrollments for the same woman, along with many women presenting after 34 weeks' gestation. Thus, the entire cohort would be needed for the analyses.

RESULTS

Creating the datasets

Table 1 shows how maternal and fetal findings define three outcome categories. The findings do not include diagnosis of PE or relate to whether the outcome might be related to angiogenic abnormality. Figure 1 shows that 328 of 1141 women (29%) enrolled ≤34.0 weeks of gestation and had a singleton pregnancy. These were allocated into the modeling ($N = 163$) and validation ($N = 165$) datasets with approximately equal numbers in each of the outcome categories. Demographic characteristics in the two datasets did not differ (Supplemental Data Table 1).

Converting to multiples of the median (MoM)

sFlt1 and PlGF measurements from referent pregnancies in the modeling dataset ($N = 69$) were used to compute medians between 20 and 34 weeks (Figure 2) that were used to convert each woman's individual analyte measurements into MoM levels.

Potential covariates of angiogenic factors

Laboratory results expressed as MoM were examined against potential covariates (Supplemental Data Table 2) using regression analysis. In referent pregnancies, maternal weight had a significant negative association with sFlt1 ($p = 0.037$) and PlGF ($p = 0.0056$) and the levels were adjusted using a fitted reciprocal weight equation. The sFlt1/PlGF ratio was also significantly associated with maternal weight but was not adjusted. For primiparous pregnancies, sFlt1 and the ratio tended to be higher ($p = 0.16$, $p = 0.19$, respectively), but only the ratio reached statistical significance ($p = 0.017$, Supplemental Table 2). The corresponding levels for PlGF were significantly lower ($p = 0.034$). Both sFlt1 and PlGF were adjusted for parity. Smoking and maternal age were not strongly related to any of the analyte levels, and no adjustments were made.

Bivariate analyses of markers

Figure 3 shows the bivariate relationships for sFlt1, PlGF and the ratio, among women in the referent and severe outcome categories. In general, within-outcome correlations between markers were low ($r < 0.4$ (except for PlGF and the sFlt1/PlGF ratio where the correlations were relatively high ($r = 0.56$ and 0.73 in referent and severe categories, respectively). The relative
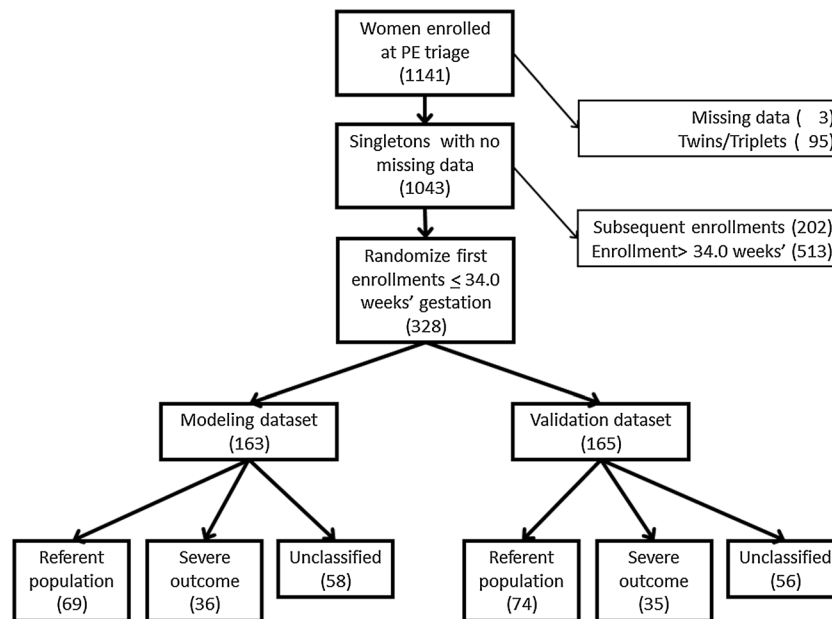
Figure 1 Defining the study datasets and pregnancy outcomes. Women were excluded, if initial visit was after 34.0 weeks' gestation, records indicated multiple gestations, data were from a subsequent enrollment, or records had important missing data. A total of 328 unique women attending the clinic and enrolling prior to 34 weeks of gestation were randomized into a modeling (163) or validation (165) dataset. The last line shows the numbers of women in the three outcome categories (referent, severe and unclassified), as defined in Methods. The model was designed to differentiate between pregnancies in the referent population and those having a severe adverse outcome

independence of sFlt1 and PlGF suggested that combining the two would improve testing over one or the other.

Developing the model

The model relied on weight- and parity-adjusted sFlt1 and PlGF MoM levels with the outcome (referent or severe) as the dependent variable. Population risk, expressed as odds of a severe outcome, was $1:2$ (33%). Figure 4A shows the patient specific risks (x-axis) versus the gestational age at delivery in the modeling dataset. All 36 severe outcomes occurred at or prior to 37.0 weeks. Of these, 27 (75%) were classified as high risk ($\geq 4.6:1$), 4 (11%) as low risk ($<1:20$) and the remaining 5 (14%) as moderate risk. The four severe outcomes classified as low risk by our model included two cases of acute renal failure (patients ID #164 and #328, refer to Supplemental Tables 3 and 4), a delivery prior to 32 weeks of gestation (#234) and a neonatal death (#33). All 69 pregnancies in the referent category, by definition, delivered after 37.0 weeks. Of these, the model classified 59 (86%) as low risk, 9 (13%) as moderate risk and 1 (1%) as high risk (#307, normal term delivery with BP 143/105). The observed (and median assigned) odds for the high, moderate and low risk groups were $26:1$ ($40:1$), $1:2$ ($1:7$) and $1:15$ ($1:200$). Using a lower risk cutoff of $1:2$, detection of adverse outcomes improved from 75 to 83%, but the false positives increased from 1 to 4%.

Applying the sFlt1 and PlGF model to the validation dataset

The model derived in the first dataset was then applied to the separate validation dataset with 35 severe and 74 referent pregnancies (Figure 4B). In the high, moderate and low risk categories, the observed numbers of severe to referent pregnancies were $25:0$, $7:18$ and $3:56$, respectively. The three

outcomes classified as severe but assigned low risk included one acute renal failure (#185), one placental abruption (#166) and one delivery occurring at 29 weeks (#93). Using a lower risk cutoff of $1:2$, detection was 83% with a 5% false positive rate. Using a $5:1$ cutoff, detection was 71%, with a 0% false positive rate. The positive likelihood ratios for the modeling and validation datasets at the $1:2$ cutoff levels were 19 (95% CI 6.2–58) and 15 (95% CI 5.8–40), respectively. At the cutoff level of $5:1$, the likelihood ratios were 51 (95% CI 7.3–362) and >52 (87.4 to 374), respectively ($p = $ NS, one false positive was assumed to allow for computations).

Combining the two datasets

Having found similar detection and false positive rates in the two datasets, we created a combined model, based on the total cohort. The revised medians (Supplemental Figure 1) and adjustment factors were nearly identical. This new model also accounted for the association of weight with severe outcomes. The risk of a severe outcome in women weighing ≥ 170 lb was significantly lower (OR = 0.37, 95% CI 0.17 to 0.83, $p = 0.011$) than that in lighter weight women (Supplemental Table 2). This was accounted for by multiplying patient-specific prior risks by 1.99 and 0.82, in lighter and heavier weight women, respectively. The risk of a severe outcome was lower in multiparous women (OR = 0.53, 95% CI 0.26 to 1.10, $p = 0.090$). Although not statistically significant, we chose to use our observed multipliers of 1.24 and 0.81 for prima and multi parity, respectively, as a result of this well-known association. The risks from the original dataset and the combined cohort were highly correlated ($r^2 = 0.96$, Supplemental Figure 2). The observed odds (severe: referent) in the high, intermediate and low risk groups were $55:1$, $8:31$ and $8:111$, respectively (Figure 4C, Supplemental
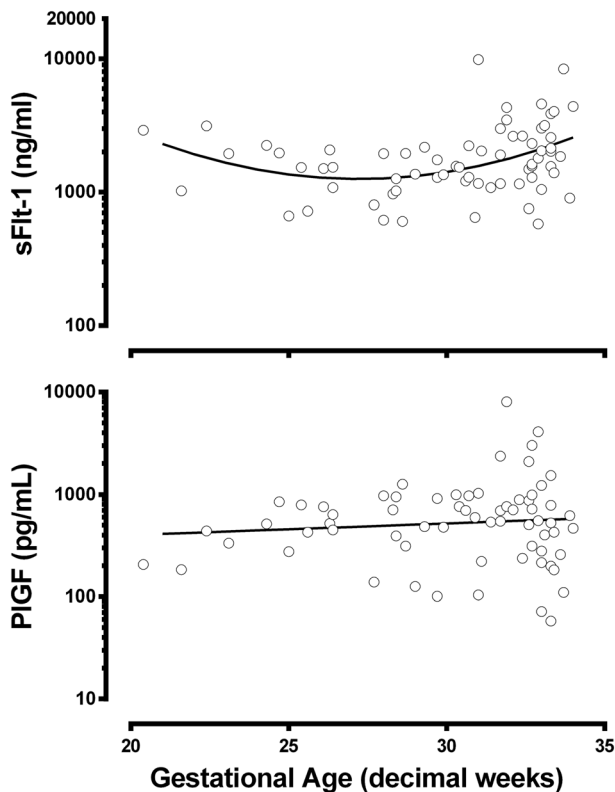
Figure 2 Gestational age-specific medians for SFlt1 and PlGF. These results are from the 69 referent women in the modeling dataset. The *x*-axis shows the gestational age at sample collection, up to 34.0 weeks of gestation. The logarithmic *y*-axes show sFlt1 and PlGF results. Solid lines/curves show the fitted regression equation indicating the reference (median) value by decimal gestational age (dGA). These equations are the following: $\text{median\_sFlt1} = 10^{((0.0067947653 \cdot dGA^2) + (-0.37004674 \cdot dGA) + 8.138)}$ and $\text{median\_PlGF} = 10^{((0.011431524 \cdot dGA) + 2.374)}$

was created to calculate patient-specific risks (screenshot available as Supplemental Data Figure 3).

Comparing the performance of the risk model with the sFlt1/PlGF ratio

Because the bivariate model and sFlt1/PlGF ratio are based on the same two angiogenic factors, test performance is expected to be similar (Figure 5). Among the 52 severe outcomes with elevated ratios, all were assigned high risks by the model. Among the remaining 19 severe outcomes with negative sFlt1/PlGF ratios, three, eight and eight had high, moderate and low assigned risks. Using the higher risk 5 : 1 cutoff, the detection and false positive rates for the model were 77 and 1%, as compared with 73 and 1% for the sFlt/PlGF ratio, alone (cutoff of 85).

Results in the unclassified outcome group

It was not possible to classify 114 pregnancies delivering between 34.1 and 37 weeks' gestation (Figure 1). It is likely that some portion was delivered early because of a diagnosis of PE, but it was not possible to determine which would have, in the absence of intervention, resulting in a severe or referent outcome. The model classified 51 of these pregnancies (45%) as low risk, and delivery occurred at an average of 34.9 weeks (five missing information, Supplemental Figure 4). Eight of the 51 (16%) had a diagnosis of PE. We assigned high risk to 29 pregnancies (25%), with delivery at an average of 33.3 weeks. Twenty (69%) had a PE diagnosis. Among the remaining 34 (30%) pregnancies with moderate risk, delivery occurred at an intermediate 34.6 weeks and 8 (24%) had a PE diagnosis. Overall, there was a positive association between assigned risk category and diagnosis of PE (X^2 test of trend, $p < 0.001$) as well as between assigned risk and earlier delivery (log linear regression, test of slope = 0, $p < 0.001$).

Usefulness of angiogenic factors: an example of renal failure

In our dataset, renal failure was diagnosed in seven pregnancies (Supplemental Data Table 5). Four had reduced risks of severe outcome (range 1 : 217 to 1 : 3) and negative sFlt1/PlGF ratios (0.5 to 16). The other three had increased risks (1 : 1 to 6 : 1). All three had negative but relatively high sFlt1/PlGF ratios (39 to 63). The four pregnancies with low risks

Data, Table 3). Using the lower risk cutoff of 1 : 2, detection was 86% with a 4% false positive rate. Using the 5 : 1 risk cutoff, detection was 77%, with a 1% false positive rate. These rates were not significantly different from the original modeling estimates indicating a robust model. Selected demographic, clinical and modeling results for patients are available (Supplemental Table 4). For research purposes, a spreadsheet
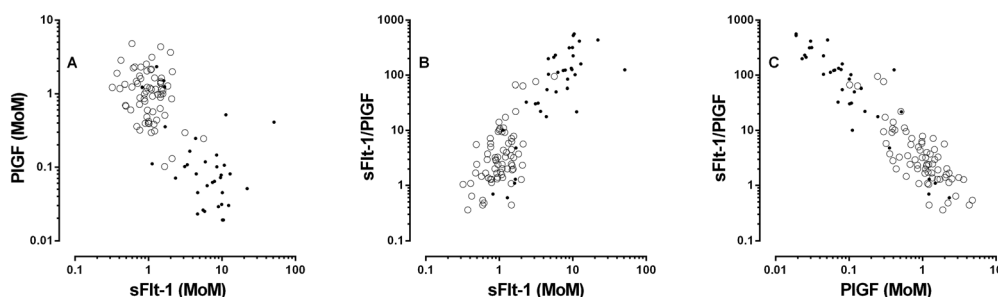

Figure 3 Bivariate comparison of angiogenic factor measurements in women with pregnancy outcomes classified as referent (69) or severe (36) from the modeling dataset. These figures show the relationships between two angiogenic factors (sFlt1 and PlGF) expressed as multiples of the median (MoM) that were selected for model development and the sFlt1/PlGF ratio. Values in pregnancies with severe outcomes are shown as small filled circles, while corresponding values in the referent pregnancies are shown as large open circles; for Figures 3A through 3C, the *r*-squared values in the referent and severe outcome groups are 0.02903, 0.4513; 0.3048, 0.2780; and 0.5649, 0.7341
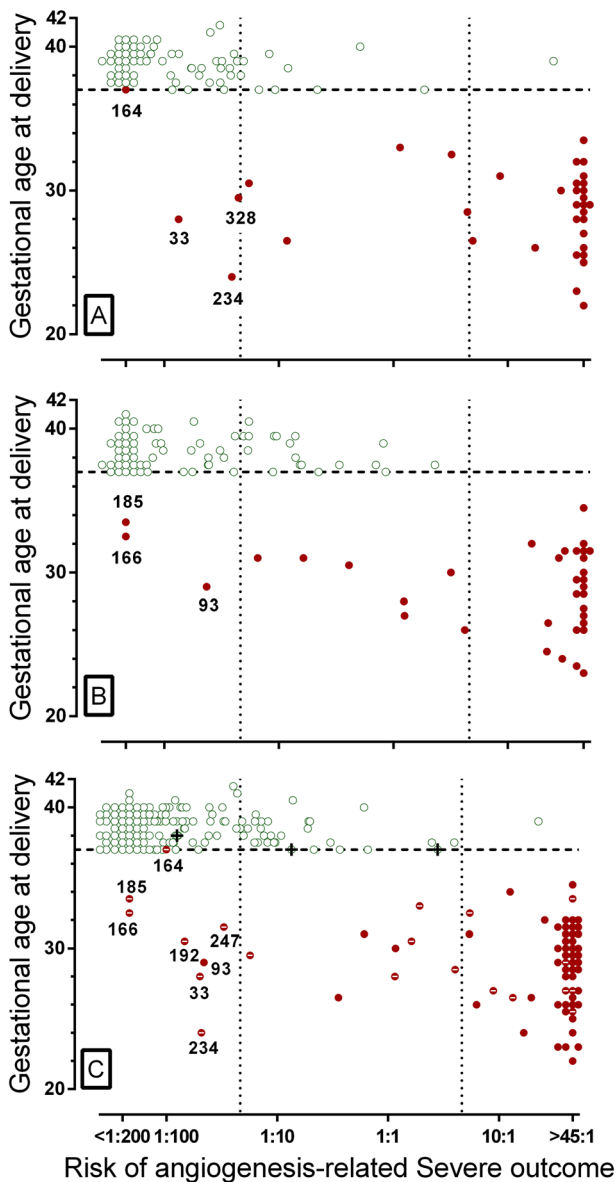
Figure 4 Patient-specific risk of an angiogenesis-related severe outcome versus gestational age at delivery. This figure shows the patient-specific risks assigned by the sFlt1 and PlGF model, applied to data from the referent and severe outcome groups. The model's risk of a severe outcome (logarithmic x-axis) is centered on the population baseline risk (1 : 2), with vertical dotted lines at 10-fold increases (right side) and 10-fold reductions (left side) in risk. From left to right, these three groups are considered to be low, intermediate and high risk. The decimal gestational age at delivery (y-axis) has a horizontal dashed line at 37.0 weeks, the cutoff used to delineate premature and term delivery. Severe outcomes are shown as small filled circles, while the referent pregnancies are shown as large open circles. Figure 4A shows results from the modeling dataset, Figure 4B from the validation dataset and Figure 4C from the combined dataset/model. In Figure 4C, a white dash (−) indicates those that are ACOG negative for PE among those with severe outcomes (filled red circles). A black plus (+) indicates an ACOG positive for PE among those with referent outcomes (open green circles)
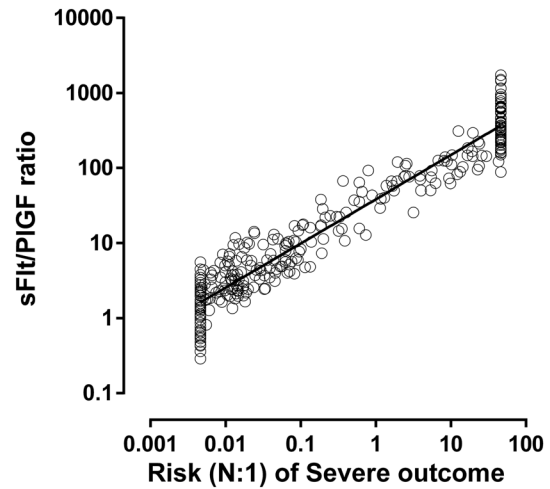

Figure 5 Comparison of the sFlt1/PlGF ratio with the patient-specific modeled risks based on sFlt1 and PlGF measurements expressed as multiples of the median (MoM). These data are from the entire cohort using the combined model. Risks are capped at 100-fold decrease (or increase) in the baseline risk ($r^2 = 0.93$)

delivered later (average 32 vs 29 weeks) had higher APGAR scores, and blood pressures were lower (average 165/103 vs 183/112). All three with increased risks but only one of four with decreased risks had a diagnosis of superimposed PE.

DISCUSSION

The angiogenic factors sFlt1 and PlGF are strongly associated with adverse maternal and fetal outcomes in the early third trimester,[23,24,33] and the sFlt1/PlGF ratio is correlated with diagnosis and outcomes.[23,30,34,35] In our dataset, 73% of all severe outcomes were associated with an elevated sFlt1/PlGF ratio (≥85). False positive rates were similar. The current study is the first to create a validated risk-based model for predicting severe adverse pregnancy outcomes specifically calibrated for the PE triage setting. The detection rate increased to 77% using a validated model reporting patient-specific risks. Obstetricians are already familiar with the patient-specific risks widely used in prenatal for Down syndrome screening.[36] Our analyses demonstrate that a simple bivariate model can reliably predict an individual's risk of a severe adverse pregnancy outcome among women being evaluated for PE.

Patient-specific risks might be helpful in at least three ways. For high-risk patients, it informs decision-making regarding transfer to a higher level facility in anticipation of preterm delivery and betamethasone treatment, potentially reducing morbidity from delay in identification. These women might also be candidates for new treatments that address the underlying angiogenic imbalance.[14] For low-risk patients, the information aids in offering expectant management that could result in reduced hospital admission, outpatient evaluations and, perhaps, preterm deliveries. Subsequent testing every 2 weeks would be aimed at refining the risks as the pregnancy continues. Patient-specific risks could also aid management decisions involving patients with underlying disorders (e.g. renal disease, chronic hypertension, diabetes).[37,38] Modeling also addresses the difficulty in interpreting sFlt1/PlGF ratios that are negative but relatively high (e.g. 70) and can reduce the

anxiety associated with physician interpretation of raw numbers. A consistent risk estimate for severe outcomes may also reduce practice variation.

Another advantage of modeling is the ability to explicitly incorporate additional risk factors to aid in the prediction of severe outcomes associated with angiogenic dysfunction. For example, we found that lighter women (<170 lb) are twice as likely to have a severe outcome as heavier women. This might be because of the association between maternal weight and hypertension that increases the chance for heavier women to be referred to PE triage. However, the related severe adverse outcomes associated with angiogenic dysfunction actually appear to be less common in these heavier women; a preliminary finding that requires confirmation.

Our study has limitations. Data were collected from a single institution, but sufficient information was provided so our model could be applied to existing data from other high-risk cohorts. This could provide confirmation and transferability of our results. Because our study was observational, it was not possible to categorize all enrolled pregnancies as having a referent or severe outcome as a result of the potential impact of a PE diagnosis on delivery timing. Our analyses did not include a direct comparison with the diagnosis of PE because of this potentially strong bias. This may become even more of an issue with the new ACOG criteria.[10] Our model is not directly applicable to the general population, where the prior risks of PE are much lower. Lastly, it was not possible to serially follow all of the pregnancies every 2 weeks to look at longer term results, as only a subset of women were re-enrolled later in pregnancy.

Our study models late second through early third-trimester sFlt1 and PlGF measurements reported in MoM. In this respect, it is similar to the approach used in a large general population cohort of women at background risk for PE.[39] Our model, however, provides a validated patient-specific risk rather than a positive or negative interpretation and allows providers to incorporate additional information into decision-making. Enrollment for our high-risk cohort includes enrollment prior to 34 weeks, and we chose to predict severe adverse outcomes rather than the diagnosis of PE. Although these differences in design and analyses are important, both studies find that the angiogenic factors are capable of identifying women for whom more or less intensive interventions may be warranted. It is now time to undertake randomized trials that could avoid issues related to our unclassified category and provide for serial testing of women every 2 weeks until 34.0 weeks' gestation. Implementation of such a model in a practice setting could provide evidence that most severe outcomes can be identified and treated and that lower rates of preterm deliveries, improvement of resource allocation and reduced costs can be achieved.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Angiogenic factors are associated with preeclampsia (PE), a pregnancy-specific syndrome that can lead to severe adverse outcomes. The sFlt1/PlGF ratio has been shown to identify patients at risk for preeclampsia.

WHAT DOES THIS STUDY ADD?

- We define the disorder of interest as any severe adverse outcome among women with suspected PE. Angiogenic test results are combined into patient-specific risks to optimize translation to patient care to improve overall pregnancy outcomes.

REFERENCES

1. Organization WH. World Health Report. Make every mother and child count. Geneva, 2005.
2. Friedman SA, Schiff E, Kao L, *et al.* Neonatal outcome after preterm delivery for preeclampsia. Am J Obstet Gynecol 1995;172:1785–8; discussion 1788–1792.
3. Thangaratinam S, Gallos ID, Meah N, *et al.* How accurate are maternal symptoms in predicting impending complications in women with preeclampsia? A systematic review and meta-analysis. Acta Obstet Gynecol Scand 2011;90:564–73.
4. Thangaratinam S, Ismail KM, Sharp S, *et al.* Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG 2006;113:369–78.
5. Thangaratinam S, Koopmans CM, Iyengar S, *et al.* Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in women with preeclampsia: a systematic review. Acta Obstet Gynecol Scand 2011;90:574–85.
6. Fisher KA, Luger A, Spargo BH, *et al.* Hypertension in pregnancy: clinical-pathological correlations and remote prognosis. Medicine (Baltimore) 1981;60:267–76.
7. Germain S, Nelson-Piercy C. Lupus nephritis and renal disease in pregnancy. Lupus 2006;15:148–55.
8. Catalano PM. Management of obesity in pregnancy. Obstet Gynecol 2007;109:419–33.
9. Powe CE, Thadhani R. Diabetes and the kidney in pregnancy. Semin Nephrol 2011;31:59–69.
10. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.
11. Ganzevoort W, Rep A, de Vries JI, *et al.* Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. Am J Obstet Gynecol 2006;195:495–503.
12. Menzies J, Magee LA, Macnab YC, *et al.* Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes. Hypertens Pregnancy 2007;26:447–62.
13. Schnettler WT, Dukhovny D, Wenger J, *et al.* Cost and resource implications with serum angiogenic factor estimation in the triage of pre-eclampsia. BJOG 2013;120:1224–32.
14. Thadhani R, Kisner T, Hagmann H, *et al.* Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation 2011;124:940–50.
15. Maynard SE, Min JY, Merchan J, *et al.* Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649–58.
16. Chaiworapongsa T, Romero R, Espinoza J, *et al.* Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. Young Investigator Award. Am J Obstet Gynecol 2004;190:1541–7; discussion 1547–1550.
17. Tsatsaris V, Goffin F, Munaut C, *et al.* Overexpression of the soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences. J Clin Endocrinol Metab 2003;88:5555–63.

18. Levine RJ, Maynard SE, Qian C, *et al*. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350:672–83.
19. Romero R, Nien JK, Espinoza J, *et al*. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. J Matern Fetal Neonatal Med 2008;21:9–23.
20. Kusanovic JP, Romero R, Chaiworapongsa T, *et al*. A prospective cohort study of the value of maternal plasma concentrations of angiogenic and anti-angiogenic factors in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia. J Matern Fetal Neonatal Med 2009;22:1021–38.
21. Cerdeira AS, Karumanchi SA. Angiogenic proteins as aid in the diagnosis and prediction of preeclampsia. Scand J Clin Lab Invest Suppl 2010;242:73–8.
22. Chaiworapongsa T, Romero R, Savasan ZA, *et al*. Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value in patients presenting to the obstetrical triage area with the suspicion of preeclampsia. J Matern Fetal Neonatal Med 2011;24:1187–207.
23. Rana S, Powe CE, Salahuddin S, *et al*. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation 2012;125:911–9.
24. Moore AG, Young H, Keller JM, *et al*. Angiogenic biomarkers for prediction of maternal and neonatal complications in suspected preeclampsia. J Matern Fetal Neonatal Med 2012;25:2651–7.
25. Rana S, Schnettler WT, Powe C, *et al*. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. Hypertens Pregnancy 2013;32:189–201.
26. Sibiude J, Guibourdenche J, Dionne MD, *et al*. Placental growth factor for the prediction of adverse outcomes in patients with suspected preeclampsia or intrauterine growth restriction. PLoS One 2012;7:e50208.
27. Chappell LC, Duckworth S, Seed PT, *et al*. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation 2013;128:2121–31.
28. Rana S, Cerdeira AS, Wenger J, *et al*. Plasma concentrations of soluble endoglin versus standard evaluation in patients with suspected preeclampsia. PLoS One 2012;7:e48259.
29. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 2002;99:159–67.
30. Verlohren S, Galindo A, Schlembach D, *et al*. An automated method for the determination of the sFlt-1/PlGF ratio in the assessment of preeclampsia. Am J Obstet Gynecol 2010;202:161.e1–11.
31. Haddow JE, Palomaki GE, Canick JA, Knight GJ. Prenatal screening for open neural tube defects and Down's syndrome. In *Fetal Medicine: Basic Science and Clinical Practice*, Rodeck CH, Whittle MJ (eds). Churchill Livingstone: London, 2009;243–64.
32. Neveux LM, Palomaki GE, Larrivee DA, *et al*. Refinements in managing maternal weight adjustment for interpreting prenatal screening results. Prenat Diagn 1996;16:1115–9.
33. Chaiworapongsa T, Romero R, Korzeniewski SJ, *et al*. Plasma concentrations of angiogenic/anti-angiogenic factors have prognostic value in women presenting with suspected preeclampsia to the obstetrical triage area: a prospective study. J Matern Fetal Neonatal Med 2014;27:132–44.
34. Verlohren S, Herraiz I, Lapaire O, *et al*. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol 2012;206:58.e1–8.
35. Verlohren S, Herraiz I, Lapaire O, *et al*. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. Hypertension 2014;63:346–52.
36. Palomaki GE, Haddow JE. Maternal serum alpha-fetoprotein, age, and Down syndrome risk. Am J Obstet Gynecol 1987;156:460–3.
37. Perni U, Sison C, Sharma V, *et al*. Angiogenic factors in superimposed preeclampsia: a longitudinal study of women with chronic hypertension during pregnancy. Hypertension 2012;59:740–6.
38. Rolfo A, Attini R, Nuzzo AM, *et al*. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. Kidney Int 2013;83:177–81.
39. Lai J, Garcia-Tizon Larroca S, Peeva G, *et al*. Competing risks model in screening for preeclampsia by serum placental growth factor and soluble fms-like tyrosine kinase-1 at 30–33 weeks' gestation. Fetal Diagn Ther 2014;35:240–8.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.