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Cost and resource implications with serum angiogenic factor estimation in the triage of preeclampsia

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Abstract

Objective—To analyze the economic and resource implications of using plasma soluble fms-like tyrosine kinase-1 (sFlt1) and placenta growth factor (PlGF) measurements in preeclampsia evaluation and management.

Design—Retrospective cost analysis of our prospective cohort study.

Setting—Boston, Massachusetts (USA).

Population—Women (n=176) presenting to the hospital at <34 weeks' gestation for evaluation of possible preeclampsia during 2009–2010. Cases without complete cost or outcome data (n=9) and re-enrollments (n=18) were excluded.

Methods—Modeled comparisons between the standard approach (combination of blood pressure, urinary protein excretion, alanine aminotransferase, and platelet counts) and a novel approach (ratio of plasma sFlt1 and PlGF) using actual hospital data converted to 2012 US dollars in accordance with Centers for Medicare and Medicaid Services.

Main outcome measures—Direct two-week costs and resource utilization by groups having true or false positive and negative test results for adverse outcomes according to approach.

Results—The improved specificity of the novel approach decreased the proportion of women falsely labeled as test-positive from 42.3% (34.4% – 50.2%) to 4.0% (0.85% – 7.15%) and increased the proportion correctly labeled as test-negative from 23.5% (16.7% – 30.3%) to 61.7% (53.9% – 69.5%). This could potentially reduce average per-patient costs by \$1,215. Substantial quantities of resources [47.2% (35.7% – 58.7%) of antenatal admissions and 72.5% (68.0% –

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Disclosure of Interests

None reported.

Contribution to Authorship

Conception and design of the study (WTS, DD, SJR, SR), acquisition of data (WTS, SS, SR), data analysis (WTS, DD, JW) and interpretation of data (WTS, DD, JW, SR), drafting the article (WTS, SR) and revising it critically for important intellectual content (WTS, DD, JW, SS, SJR, SR).

Details of Ethics Approval

The study was approved by the Beth Israel Deaconess Medical Center Institutional Review Board (IRB), and all patients provided written informed consent.

77.0%) of tests for fetal well-being] were unnecessarily used for women who were truly negative. A proportion of iatrogenic preterm deliveries among women with negative results was potentially avoidable representing further cost and resource savings.

Conclusions—Clinical use of the plasma sFlt1 and PlGF ratio improves risk stratification among women presenting for preeclampsia evaluation and has the potential to reduce costs and resource utilization.

Keywords

angiogenic factors; preeclampsia; costs; resource utilization

INTRODUCTION

After more than a century of investigation, preeclampsia remains a major public health problem affecting roughly 5% of pregnancies yet contributing to nearly 15% of direct maternal deaths and 25% of perinatal/neonatal deaths worldwide.[1] A disproportionate amount of resources and health care expenditure is dedicated to its identification and management. In 1992, approximately \$20 billion was spent in the United States to treat preeclamptic women and their neonates.[2 3] Simply establishing the diagnosis currently requires resource intensive measures such as hospital admission with close observation of maternal blood pressure, proteinuria, and laboratory trends. However, this approach fails to predict the most serious adverse outcomes (eclampsia and HELLP syndrome) in a substantial percentage of women.[4

The altered placental release of the anti-angiogenic factor soluble fms-like tyrosine kinase-1 (sFlt1) and the pro-angiogenic factor placenta growth factor (PlGF) has been proven integral to the pathogenesis of preeclampsia.[5] Measurement of these factors in the maternal circulation correlates well with disease onset and progression.[6–9] We have recently shown that the plasma sFlt1/PlGF ratio predicts adverse outcomes occurring within two weeks among women with suspected preeclampsia presenting at <34 weeks.[10] This ratio alone performed better than the standard battery of clinical diagnostic measures including systolic blood pressure, proteinuria, uric acid, alanine aminotransferase, platelet count and creatinine.[10] The growing body of evidence supporting this test's utility has led to its adoption into standard clinical practice within some European hospitals, however little is known about the impact of its use on resource utilization. This knowledge is crucial in determining its impact on public policy and implementation into practice in the United States.

Using data from a prospective cohort of women presenting with possible preeclampsia at less than 34 weeks gestation, we sought to determine the economic and resource implications of using sFlt1 and PlGF measurements as a means of stratifying risk and management strategies over the subsequent two-week period.

METHODS

Study design of the prospective cohort

From July 2009 through October 2010, all women with singleton pregnancies who presented to the obstetric triage unit at the Beth Israel Deaconess Medical Center in Boston, MA, for evaluation of possible preeclampsia were offered enrollment. Indications for evaluation included elevated blood pressure, proteinuria, or any symptoms associated with preeclampsia such as headache, visual symptoms, right upper quadrant pain, or edema. Standard tests and evaluation measures were performed at the discretion of the patients'

attending physician. Discarded plasma samples from triage were collected from clinical lab, processed and stored at -80°C . Automated analysis was performed at the clinical laboratory of Charité Hospital (Berlin, Germany) with the commercially available assays on the Elecsys platform (Roche Diagnostics, Penzberg, Germany) as previously described.[11] All assays were performed after attainment of clinical data and the assay operators were blinded to the clinical information of the participants. The treating physicians were unaware of the sFlt1 and PlGF values.

All clinical outcomes were gathered over the subsequent two weeks and independently reviewed and adjudicated by two staff members prior to the availability of assay results. Adverse maternal outcomes were defined as the presence of hypertension plus one of the following: elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ($> 80 \text{ U/L}$), thrombocytopenia (platelet count $< 100 \times 10^9/\text{L}$), disseminated intravascular coagulation (DIC), abruption (clinical and/or pathological), pulmonary edema, cerebral hemorrhage, seizure (in a woman without an underlying seizure disorder), acute renal failure (creatinine $> 132.6 \mu\text{mol/L}$), or maternal death.[12] The adverse fetal/neonatal outcomes included iatrogenic delivery indicated for hypertensive complications of pregnancy as reported by the primary obstetrician, small for gestational age birth weight ($< 10^{\text{th}}$ percentile for gestational age), abnormal umbilical artery Doppler waveforms (absent or reverse flow), fetal death, and neonatal death.[12] Two study staff members blinded to assay results performed the adverse outcome determinations. Diagnoses and adverse outcomes were ascertained within two weeks of presentation. The Beth Israel Deaconess Medical Center institutional review board approved the study, and all women provided written informed consent.

Cost and resource determination

Participant re-enrollment was permitted among the cohort, however costs and resource determination was restricted to participants' initial study encounter. Direct antepartum and delivery-associated resources and costs were determined by review of participants' medical records and hospital administrative data. Actual institutional charges from all triage evaluations, maternal radiologic studies, fetal radiologic evaluations, tests of fetal well-being (including all combinations of biophysical profiles, non-stress tests, obstetric ultrasounds, and Doppler ultrasounds), laboratory evaluations, admissions, consultations, deliveries, and miscellaneous resources (intravenous tubing, intravenous fluids, etc.) were tallied over the two week period following enrollment. The reason for the two week window is due to the clinical utility of the test as described in the original study.[10] Study personnel blinded to the sFlt1, PlGF, and pregnancy outcomes extracted the data. All costs and charges were converted into 2012 US dollars using the conversion factor for 2012 (34.03) and the National Payment Amount for Geographic Practice Cost Index according to the Centers for Medicare and Medicaid Services. [13] The cost of the test was fixed at \$101.14 for measurement of both sFlt1 and PlGF and applied to groups in modeling the novel approach's budget impact.[14]

Statistical Analysis

The study is a cost analysis with a budget impact model.[15] Given that the data was collected in a prospective cohort and was not clinically used, we could not perform a traditional cost-effectiveness analysis. Comparisons in cost and resource utilization were made between the "standard evaluation approach" (including the combination of blood pressure, proteinuria, elevated transaminases: ALT or AST $> 80 \text{ U/L}$, and low platelet count: $< 100 \times 10^9/\text{L}$) and the "novel approach" (measurement of sFlt1 and PlGF). We used our previously defined sFlt1/PlGF ratio ≥ 85 as "test-positive" in the prediction of adverse maternal and fetal outcomes.[10] This value demonstrated the strongest test performance on

receiver operator characteristic (ROC) analysis within this cohort and among others.[11 16] Comparisons were made between testing strategies for groups of patients having both true and false positive or negative results. Costs for the novel approach included the \$101.14 per patient cost increase attributable to the addition of the plasma sFlt1 and PlGF. Two separate budget impact analyses were modeled: an “ideal” scenario and a “worst-case” scenario.

The ideal scenario modeled the budget impact of two variables: the redistribution of women into groups based on test performance of the sFlt1/PlGF ratio, and the proposed cost savings among the new “True Negative” group. Here, the assumed costs represented the average cost of the initial triage visit alone. We argue that subsequent testing and/or delivery of these patients in the following two weeks was not indicated and represented potential cost savings had the sFlt1/PlGF ratio been used clinically. The average cost of the enrollment triage visit represented the median two-week cost among women in the “True Negative” group with only one hospital evaluation and no antepartum admissions. The worst-case scenario model made no assumptions regarding changes to management decisions regarding resource utilization or cost. Its budget impact relied solely upon the redistribution of women into groups based on the test performance of the sFlt1/PlGF ratio. A sensitivity analysis was then performed whereby the sFlt1/PlGF ratio cut-off denoting test-positivity and the cost percentage were varied to assess the budget impact of the novel approach versus the standard approach.

The perspective undertaken for the analysis was the hospital/third party payer given that the large burden of costs associated with this disease lay with the payer. [15] Much of the data regarding indirect costs and patient resources were not available preventing an analysis from a societal perspective. Due to a short time horizon of two weeks after initial presentation, discounting was not undertaken. Sensitivity analyses were performed varying all costs from 50% to 200% of the baseline, including the cost of the test, in order to account for the variation in payment structure within the United States.

RESULTS

One hundred and seventy six encounters occurred among women less than 34 weeks' gestation during the study period. Of these, 3 were eliminated due to missing financial data, 6 were eliminated due to missing delivery data, and 18 were participant re-enrollments. 149 women provided complete cost and resource data for review. Within 2 weeks following the initial hospital triage visits, adverse outcomes occurred in 34.2% of participants (n=51). The distributions of participants by clinical outcome and test results for the standard approach and novel approach are shown in Figure 1. Demographic characteristics were relatively similar among groups defined by the novel approach; however comparison of the initial clinical triage parameters by group correlated with enhanced risk-stratification (Table 1). Women in the true positive group demonstrated significantly increased systolic and diastolic blood pressures ($p<0.0001$), proteinuria ($p<0.0001$), and laboratory findings associated with severe disease (Table 1).

The novel approach demonstrated improved specificity over the standard approach (93.9% vs. 35.7%). This decreased the proportion of women falsely labeled as test-positive (4.0% vs. 42.3%) and increased the proportion correctly labeled as test-negative (61.7% vs. 23.5%). Women demonstrating an sFlt1/PlGF ratio <85 without incurring any adverse outcomes over 2 weeks were categorized as truly negative and represented 61.7% of the total cohort (n=92) - an expansion of 38.2% over the standard approach (Figure 1). Costs and resource data reflected the clinical decision-making of physicians following the standard evaluation approach. However, by applying the novel approach and re-categorizing participants, we were able to evaluate potential savings.

The true negative group represented the population where cost and resource savings could be realized. Despite significantly fewer “high-risk” clinical parameters, these patients were managed over the entire two-week study interval with similar resources as the truly positive patients (Table 2). This group contributed 47.2% of the antepartum admissions, 72.5% of the tests for fetal well-being (including all combinations of biophysical profiles, non-stress tests, obstetric ultrasounds, and Doppler ultrasounds), 43.8% of maternal imaging studies (magnetic resonance imaging, magnetic resonance angiograms, chest X rays), and 40.2% of all serum and urine laboratory tests (serum chemistries, complete blood counts, coagulation studies, urinalyses, and urine dipstick analyses). Resources utilized during the initial work-up were inevitable, but we proposed that subsequent resources and costs over the two weeks following a sFlt1/PIGF ratio less than 85 were unnecessary.

The median two-week total cost for women in the true negative group who were evaluated only once in triage and were not admitted to the hospital was \$370 (n=46). Applying the cost of the novel test (\$101.14 added to all participants’ costs), the result (\$471) represents the ideal cost for women in the true negative group, and we employed this in our model’s ideal budget impact analysis (Table 3A). The improved specificity of the novel approach redistributed the participants and average cost-per-patient tallies of the groups. By more precisely defining the true positive group, this shift produced a cost-per-patient increase (\$4,325 vs. \$3,933). However, this increase was offset by cost savings from a reduction in the number and costs associated to false-positive participants (Figure 2). Most importantly, the implementation of the ideal cost upon the expanded true negative group contributed to a net savings of \$1,215 per patient and \$180,969 for the entire cohort.

Although the analysis of the ideal budget impact used real cost data, it relied upon an assumption that physicians would manage women with an sFlt1/PIGF ratio < 85 without additional costs or resources beyond the initial triage visit. This represented a hypothetical cost-per-patient reduction of \$904 for the true negative group, and it greatly contributed to the reductions in total cohort and average per-patient costs (of note, the actual costs of standard management and delivery were applied to women in the false negative group within the model). Relinquishing this assumption, we calculated a “worst-case” scenario in which per-patient costs for each group in the novel approach matched the corresponding values from the standard approach plus the \$101.14 cost for the sFlt1/PIGF ratio (Table 3B). This scenario assessed the budget impact of improved characterization of participants without assumed changes in management strategy beyond the acceptance of the new risk characterization. Total cohort costs were reduced by \$80,351 and the cost-per-patient was reduced by \$540.

Sensitivity analysis was performed for cohort and per-patient costs in the novel versus standard approaches by the varying the cut-off sFlt1/PIGF ratio and retrieved percentage of cost. As demonstrated previously, the ratio of 85 demonstrated optimal balance of sensitivity and specificity (Table S1). [10 11 16] A net savings was predicted for both total cohort and per-patient costs with application of the novel approach utilizing ratios between 5 and 200. In addition, model costs were varied between 50% and 200%. Cost savings were predicted with clinical application of the novel approach utilizing all modeled cut-offs or cost percentages (Table 4).

Twelve women experienced adverse outcomes despite an sFlt1/PIGF ratio less than 85, and this group (false negatives) was predominantly obese with one half carrying a diagnosis of chronic hypertension (Table 1). Review of the clinical characteristics and outcomes of these women (Table S2) highlights the complex medical history and complaints that prompted preterm delivery in all of these women. The only adverse outcome was preterm delivery in ten of the twelve, and subjective concerns such as headache and physician or patient desire

was cited as the delivery indication in seven of the ten. Among the other three, two women were delivered due to non-reassuring fetal status with chronic HTN and the third woman was delivered secondary to acute fatty liver of pregnancy and elevated LFT's (a separate disease entity from preeclampsia). The two remaining adverse outcomes were one neonatal death in woman after experiencing chronic abruption and prolonged oligohydramnios from 16 weeks onward and other was acute renal failure in the setting of chronic hypertension and diabetic nephropathy. Since actual antenatal and delivery-associated data was used in the analysis of this group, no adjustment or speculation of the costs and resource utilization was performed to account for the potential implications of a "missed diagnosis".

Neonatal outcomes among live born infants experiencing iatrogenic preterm delivery within two weeks of study enrollment further demonstrate the sFlt1/PlGF ratio's ability to appropriately characterize risk (Table 5). 76.6% of the iatrogenic deliveries indicated for hypertensive complications of pregnancy occurred among women with a ratio greater than 85. The remaining 12 occurred among women in the false negative group as described above. All required admission to the neonatal intensive care unit, and the median length of stay was 17 days. Rates of additional morbidities were similar to neonates delivered of women from the true positive group (Table 5).

DISCUSSION

Main Findings

In this retrospective cost analysis, we demonstrated potential reductions in direct hospital costs and resource utilization with implementation of the plasma sFlt1/PlGF ratio for preeclampsia evaluation and management. Although current standard diagnostic tests are readily available and engrained into routine practice, they lead to significant misclassification and over-testing/treating of many women. Large quantities of resources and costs are erroneously allocated to many low risk women. Our results reveal that the increased specificity of this novel approach more-accurately defines the population at risk and could enable appropriate and reduced cost/resource expenditure. Ideal use of this novel approach potentially yields large per-patient cost savings (\$1,215); and even the "worst-case" scenario (or reduced percentages of the costs included in this model) could yield substantial per-patient savings (\$540).

Interpretation

The characteristics of this test highlight its potential to serve a diagnostic purpose rather than as a screening tool. Women in this study represented a "pre-selected" population in whom concerns for preeclampsia included varying degrees of hypertension or proteinuria which prompted hospital evaluation and an invitation to participate. This "screening" process is the basis of modern prenatal care and appears to work - demonstrating fair sensitivity in published reports and among our cohort.[17] Unfortunately, women with varied post-test odds for true adverse outcomes are undergoing similar management following initial identification, and our results among true negative participants demonstrated this. We envision that clinicians will use the sFlt1/PlGF ratio in the triage setting on women having already "screened-positive" by standard antenatal care criteria. A ratio less than 85 in the absence of other overt clinical concerns may identify a candidate for expectant management via routine prenatal care. Those with ratios greater than 85 represent women at significant risk for adverse outcomes and warrant the increased costs, resources, and potentially indicated delivery associated with heightened surveillance.

Despite the potential major impact upon public health and health-care expenditure, few studies have addressed the economics of preeclampsia evaluation and management. Our

report utilizes actual costs and resources in comparing different approaches to preeclampsia evaluation and management. Hadker and colleagues developed a decision-analysis model that similarly assessed the economics of the addition of serum sFlt1 and PlGF measurement into standard obstetric practice of the United Kingdom National Health Service (NHS).[14] The authors demonstrated that the novel approach provided substantial cost savings for the NHS, but their model was built upon theoretical data and assumed test characteristics from other publications. They applied the sFlt1/PlGF measurement at 20 weeks to all women, an approach that has been shown to demonstrate poor predictive value.[18 19] Our application of the test to women with clinical signs and symptoms of preeclampsia parallels the approach by other studies where measurement of angiogenic factors has been shown to correlate strongly with diagnosis and outcome.[9 10 20] Thus, we propose that the assumed cost-savings demonstrated in the study by Hadker and colleagues could be magnified with a more appropriate application of this test to an at-risk population that undoubtedly has greater disease prevalence.

Strengths and Weaknesses

Strengths to this study include its use of actual direct hospital costs, clinical parameters, and outcomes gathered in a prospective fashion. This allowed for calculation of true test characteristics and implementation of these values into cost and resource analyses. Limitations of this work include its small sample size and generalisability of findings. Our data comes from a single tertiary care hospital in the United States representing the clinical practices of a single group of physicians. All costs are given in U.S. dollars. Whether the same cost and resource savings could be achieved in other settings is purely speculative.

The observational nature of this study and the blinding of treating physicians to sFlt1/PlGF ratios limited our ability to fully evaluate cost and resource implications without making assumptions. As such, we attempted to create “ideal” and “worst-case” scenario models to account for the lack of actual cost/resource data from true clinical use of the novel approach. However, we cannot fully account for the real-time clinical application of this test specifically with regard to using the cut off of 85 and the false negative diagnoses associated with this cut off. Although our data suggests that indicated preterm delivery based solely on a diagnosis of preeclampsia in the absence of an elevated sFlt1/PlGF ratio may not be warranted, we cannot account for the various additional rationale for preterm delivery. Additionally, implications of a “missed diagnosis” from the test’s lack of 100% sensitivity could not be assessed within the cohort undergoing standard management.

Another limitation was the retrospective nature of data collection. Assessment of indirect costs such as out-of-hospital costs, financial implications on participants’ activities of daily living, loss of income, childcare costs, long term implications on maternal and child health, and the social burdens associated with hospital admission are best attained with prospective data-collection tools employed by larger prospective studies.

CONCLUSION

Measurement of the serum sFlt1 and PlGF ratio improves risk stratification among women presenting for preeclampsia evaluation, and its clinical use has the potential to reduce hospital costs and resource utilization among patients at low risk for adverse outcomes. Whether the real-time use of the sFlt1/PlGF ratio in the triage and management of preeclampsia will result in reduction of iatrogenic preterm deliveries without increased adverse maternal, fetal, and/or neonatal outcomes (with consequent direct and indirect cost/resource implications) needs to be proven. Performance of larger prospective cohort or randomized studies using these angiogenic factors as clinical determinants of risk and management strategy in real time is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Standard Approach

Novel Approach

Figure 1. Categorization of participants into groups by outcome and evaluation approach
The proportion of falsely positive women decreased and the proportion of truly negative women increased substantially with utilization of the sFlt1/PIGF ratio rather than the standard approach of blood pressure, proteinuria, transaminases, and platelet counts.

Figure 2. Cost comparison among groups between standard and novel approaches

The decreased total cost over the subsequent two weeks following enrollment with the use of the sFlt1/PlGF ratio is driven by the improved specificity with few dollars devoted to falsely positive women.

Table 1
Demographic and clinical outcomes data of participants by group (as determined by novel approach).

Variable	True Positive	False Positive	True Negative	False Negative	p-value
N	39	6	92	12	
Triage Demographics					
Gestational Age (weeks)	30 (27–33)	31 (29–33)	31 (28–33)	32 (29–34)	0.47
Age (years)	32 (26–36)	34 (32–38)	32 (28–35)	31 (28–32)	0.53
Body Mass Index (kg/m ²)	29.9 (27.5–34.6)	27.8 (25.1–31.2)	33.9 (30.3–37.8)	36.8 (29.7–41.4)	0.002*
Nulliparous	22 (56.4)	6 (100.0)	48 (52.2)	7 (58.3)	0.15
Smoker (%)	4 (10.3)	0 (0.0)	8 (8.7)	0 (0.0)	0.60
Race (%)					0.24
<i>White/Caucasian</i>	24 (61.5)	5 (83.3)	50 (54.4)	6 (50.0)	
<i>Black/African American</i>	4 (10.3)	0 (0.0)	20 (21.7)	5 (41.7)	
<i>Asian</i>	4 (10.3)	1 (16.7)	5 (5.4)	0 (0.0)	
<i>Other</i>	7 (18.0)	0 (0.0)	17 (18.5)	1 (8.3)	
History of Preeclampsia (%)	7 (18.0)	0 (0.0)	18 (19.6)	4 (33.3)	0.39
History of Chronic Hypertension (%)	9 (23.1)	1 (16.7)	30 (32.6)	6 (50.0)	0.28
History of Diabetes (%)	1 (2.6)	0 (0.0)	11 (12.0)	3 (25.0)	0.09
Clinical Parameters in Triage					
Highest Systolic Blood Pressure (mmHg)	152 (144–164)	130 (124–147)	133 (123–143)	145 (139–148)	<0.0001*
Highest Diastolic Blood Pressure (mmHg)	97 (88–104)	86 (80–90)	83 (73–91)	93 (79–99)	<0.0001*
Proteinuria (>1+) (%)	29 (74.4)	1 (16.7)	17 (18.5)	7 (58.3)	<0.0001*
Alanine Aminotransferase (U/L)	25 (14–26)	17 (14–30)	16 (12–23)	17 (14–23)	0.01*
Creatinine (μmol/L)	61.9 (53.0–70.7)	53.0 (44.2–53.0)	44.2 (44.2–53.0)	53.0 (44.2–53.0)	0.0003*
Uric Acid (μmol/L)	374.7 (291.5–422.3)	333.1 (249.8–356.9)	243.9 (202.2–291.5)	279.6 (237.9–333.1)	<0.0001*
Platelet Count (× 10 ⁹ /L)	209 (143–240)	255 (167–315)	260 (227–298)	263 (195–357)	0.0002*
S/P ratio	348.0 (183.5–641.0)	145.3 (125.0–210.3)	4.0 (1.8–10.8)	12.1 (3.7–39.3)	<0.0001*

Variable	True Positive	False Positive	True Negative	False Negative	p-value
Delivery Data					
Time to Delivery from Triage (weeks)	0.3 (0.0–0.4)	4.2 (3.4–4.7)	6.4 (4.7–9.4)	0.6 (0.1–0.7)	<0.0001 *
Gestational age at delivery (weeks)	30 (27–32)	35 (34–36)	37 (36–39)	32 (29–34)	<0.0001 *
Birthweight (grams)	1,275 (780–1,575)	2,210 (1,795–2,390)	3,115 (2,568–3,490)	1,725 (1,278–2,175)	<0.0001 *

Tests of fetal well-being include all combinations of biophysical profiles, non-stress tests, obstetric ultrasounds, and Doppler ultrasounds. Data presented as n (%) and median (interquartile range) where appropriate

* Significant at $p < 0.05$

Table 2

Resource utilization by sFlt1/PlGF ratio (novel approach)

Resource Utilization	True Positive (N=39)	False Positive (N=6)	True Negative (N=92)	False Negative (N=12)	p-value
Triage Visits	1 (1-1)	1 (1-1)	1 (1-2)	1 (1-2)	0.001 *
Cesarean Section (%)	33 (84.6)	4 (66.7)	55 (59.8)	8 (66.7)	0.05
Antepartum Admission (%)	25 (64.1)	4 (66.7)	34 (37.0)	9 (75.0)	0.005 *
Duration of Antepartum Admission (days)	3 (3-5)	3 (2-9)	4 (3-11)	3 (2-5)	0.41
Outpatient Visits (%)	0 (0.0)	3 (50.0)	45 (48.9)	3 (25.0)	<0.0001 *
Tests of Fetal Well Being	2 (1-3)	2 (0-2)	2 (1-4)	4 (2-5)	0.03 *
Magnetic Resonance Imaging (%)	1 (2.6)	0 (0.0)	6 (6.5)	1 (8.3)	0.71
Magnetic Resonance Angiogram (%)	2 (5.1)	0 (0.0)	6 (6.5)	0 (0.0)	0.74
Chest X ray (%)	8 (20.5)	0 (0.0)	2 (2.2)	1 (8.3)	0.003 *
Complete Blood Count	8 (5-11)	2 (1-3)	1 (1-3)	7 (3-9)	<0.0001 *
Coagulation Panel	8 (4-14)	1 (1-2)	2 (2-4)	5 (2-8)	<0.0001 *
Serum Chemistries	37 (22-66)	7 (6-9)	8 (5-20)	24 (16-26)	<0.0001 *
Urine Studies	1 (1-2)	2 (1-2)	2 (1-4)	3 (1-4)	0.001 *
Consultations	1 (1-2)	0 (0-0)	0 (0-0)	1 (1-2)	<0.0001 *

Data are presented as n (%) or median (interquartile range) where appropriate

* Significant at p<0.05

Table 3

A. Ideal budget impact by implementation of the novel approach

Cost resource	Standard Approach		Novel Approach		Budget Impact	
	N	Total \$	N	Total \$	Total Cohort	Per patient
True Positive	48	\$188,787	39	\$168,660	-\$20,127	\$392
False Positive	63	\$199,324	6	\$17,988	-\$181,336	-\$166
True Negative	35	\$48,137	92	\$43,345	-\$4,805	-\$904
False Negative	3	\$13,992	12	\$39,277	\$25,285	-\$1,391
Total	149	\$450,239	149	\$269,269	-\$180,969	-\$1,215

B. Worst-case budget impact by implementation of the novel approach

Cost resource	Standard Approach		Novel Approach		Budget Impact	
	N	Total \$	N	Total \$	Total Cohort	Per patient
True Positive	48	\$188,787	39	\$157,326	-\$31,461	\$101
False Positive	63	\$199,324	6	\$19,590	-\$179,734	\$101
True Negative	35	\$48,137	92	\$135,792	\$87,655	\$101
False Negative	3	\$13,992	12	\$57,180	\$43,188	\$101
Total	149	\$450,239	149	\$369,888	-\$80,351	-\$540

Costs are rounded nearest dollar increment. Cost of serum sFlt1 and PlGF measurement is \$101.14. Negative values represent cost savings.

Table 4

Budget impact of the novel approach in comparison to the standard approach by percentage of costs retrieved

Cost resource	Cost at 50%	Cost at 75%	Cost at 150%	Cost at 200%
True Positive	-\$12,036	-\$18,054	-\$36,108	-\$48,144
False Positive	-\$90,972	-\$136,457	-\$272,915	-\$363,887
True Negative	-\$7,055	-\$10,582	-\$21,165	-\$28,220
False Negative	\$12,036	\$18,053	\$36,107	\$48,143
Total	-\$82,957	-\$131,970	-\$279,011	-\$377,038
Cost per-patient	-\$557	-\$886	-\$1,873	-\$2,530

Costs are rounded nearest dollar increment. Cost of serum sFlt1 and PlGF measurement is included and fixed at \$101.14 throughout. Negative values represent cost savings.

Table 5

Neonatal outcomes among live born infants with an indicated delivery within two weeks of study enrollment. Comparisons between groups based on novel approach.

Neonatal outcomes	True Positive (N=36)	False Positive (N=0)	True Negative (N=0)	False Negative (N=12)
NICU Admission (%)	36 (92.3)	0 (0.0)	0 (0.0)	11 (91.7)
NICU Days	18 (11–56)	0 (0.0)	0 (0.0)	17 (10–22)
Respiratory Distress Syndrome (%)	22 (56.4)	0 (0.0)	0 (0.0)	6 (50.0)
Intraventricular Hemorrhage (%)	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Necrotizing Enterocolitis (%)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis (%):	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
O2 Requirement (%):	27 (69.2)	0 (0.0)	0 (0.0)	10 (83.3)
Perinatal Mortality (%):	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)

Data are presented as n (%) or median (interquartile range).