

Validation of a comorbidity index for use in obstetric patients: A nationwide cohort study

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Abstract

Introduction: A previously developed Obstetric Comorbidity Index has been validated in highly selected cohorts. Validation of the index in an unselected population as well as in other health registers is, however, of high importance to determine external validity.

Material and methods: Using nationwide registers, we formed a nationwide cohort including completed pregnancies (both live- and stillborn) in Denmark from 2000 through 2014. Maternal age and 20 comorbid conditions were assessed and weighted. Outcomes were maternal end-organ injury or death within 30 days postpartum. The index's predictive and discriminative ability was estimated by Brier score and the area under the receiver operating characteristic curve (AUC), respectively. Logistic regression analysis was used to estimate odds ratios (OR) with 95% confidence interval (CI).

Results: In 876 496 completed pregnancies by 527 079 women, 1.40% (n = 12 314) experienced an outcome. The majority of women (64.1%) did not have any record of a condition included in the index and only 0.3% (n = 3044) had a score >6. The incidence of an outcome increased with increasing comorbidity score from 0.9% (95% CI 0.8-0.9) in women scoring 0% to 10.4% (95% CI 7.6-13.9) in women scoring 9-10. Compared with women scoring 0, a score of 1-2 yielded an OR of 2.34 (95% CI 2.25-2.44), 3-4 an OR of 5.16 (95% CI 4.81-5.54), 5-6 an OR of 4.84 (95% CI 4.31-5.44), and 8-9 an OR of 7.97 (95% CI 6.54-9.72) for experiencing the outcome. The index had a Brier score of 0.01 and an AUC of 0.64.

Conclusions: Despite potential weaknesses in the outcome definition, the Obstetric Comorbidity Index showed a moderate ability to discriminate and predict end-organ injury and death in a nationwide cohort in Denmark, in accordance with previous findings. These results suggest that the index may be a useful tool to control for confounding in health research and clinically to identify women at high risk for adverse maternal outcomes.

KEYWORDS

adverse maternal outcomes, comorbidity, obstetric comorbidity index, prediction, reproduction, validation

1 | INTRODUCTION

Maternal mortality remains high in developing countries.¹ Even in some high-income countries, such as the USA, maternal deaths have not decreased in the last 30 years and severe morbidity in relation to childbirth has increased.² Severe maternal morbidity during pregnancy may affect the health of the fetus, the newborn, and the mother. Identification and prediction of maternal comorbidity is important to take appropriate action.²

A predictive index to score comorbidity in obstetric patients may serve two purposes. First, it holds clinical value to identify women of high obstetric risk in order to triage to facilities equipped to handle complications and heightening surveillance around the time of delivery. Secondly, it can serve as a tool to control for confounding in health service research. Bateman et al have developed a maternal comorbidity index to predict severe maternal morbidity and mortality.³ They determined predictors of severe maternal morbidity and mortality by diagnoses and age and summarized the burden of comorbidity into a single numerical score in obstetric patients. The Obstetric Comorbidity Index has, until now, only been validated within highly selected cohorts derived from Medicaid, a health insurance program for low-income individuals in the USA (<https://www.medicaid.gov/basic-health-program/index.html>) and from one small geographic area of Canada.^{3,4} Validation of the index in an unselected population as well as in other health registers is, however, of high importance to determine external validity, should the Obstetric Comorbidity Index be used to inform the care of pregnant women.⁵⁻⁷ The Danish health registers, with complete data on all obstetric patients, due to free access to health services, are unique sources for such an assessment in a complete and unselected study population. We therefore aimed to validate the Obstetric Comorbidity Index by examining its ability to predict morbidity, defined as incidence of acute end-organ injury or mortality, and its ability to discriminate between low- and high-risk obstetric patients in prediction of maternal end-organ injury and death.

2 | MATERIAL AND METHODS

2.1 | Data sources

This study was a population-based cohort study based on the Danish Medical Birth Registry⁸ and the Danish National Patient Register.⁹ The Medical Birth Registry contains information on all births in Denmark, both hospital and homebirths, since 1973.⁸ The registry includes data on the mothers (age, height, weight, parity, tobacco use, etc.), and the newborn (date of birth, gestational age, weight, Apgar score, etc.), and reports information on pregnancy complications and procedures performed during the delivery. The registry relies mostly on data from the Danish National Patient Registry but supplemented with information from birth reports on home births and stillborn children. The Danish Civil Registration System informs the birth registry on death of either mother or child up to 6 month after delivery.¹⁰

Key message

This validation of an obstetric comorbidity index in an unselected cohort found the index a valid tool to identify women with a high risk of adverse maternal outcomes. The index may be useful to control for confounding in health research.

The Danish National Patient Register holds data on all inpatient hospital contacts in Denmark since 1977 and, since 1995, outpatient contacts have been included. The diagnostic codes used in the patient register are classified according to the Danish version of the International Classification of Diseases, version 8 (ICD8: 1977-1993) and, since 1994, version 10 (ICD10).

Data were linked by the unique identification number assigned to all residents in Denmark at birth or first immigration.¹¹ Virtually all medical care in Denmark, including completed pregnancies, is reported to the public health authorities, allowing true population-based studies, covering all inhabitants of Denmark. Data were obtained for the period of 1 July 2000 to 31 December 2014.

2.2 | Study population

All completed pregnancies (both live- and stillborn infants) in Denmark from 1 July 2000 to 1 December 2014 were included. Due to change in the coding practices in the Danish Medical Birth Register, completed pregnancies were defined as pregnancies with a minimum gestational age of 28⁺⁰ weeks until 31 March 2004 and a minimum gestational age of 22⁺⁰ weeks since 1 April 2004.⁸ The study unit was each pregnancy, allowing mothers to contribute to the cohort with more than one delivery. We omitted pregnancies with missing information on gestational age ($n = 13\,366$ [1.5%]) or day of admittance/discharge ($n = 880$ [0.1%]). For women giving birth at home, day of admittance and discharge was set to the day of delivery. Women who immigrated later than 180 days prior to the day of conception were excluded in order to have complete data to generate the Obstetric Comorbidity Index ($n = 21\,783$ [2.4%]). Day of conception was calculated by subtracting gestational age from date of birth.

2.3 | The Obstetric Comorbidity Index

We assessed maternal age and the 20 maternal conditions as defined by Bateman et al³ from the Danish National Patient Register to construct the Obstetric Comorbidity Index model. The ICD9 codes (which informed the original index model) were converted to ICD10 codes as specified by Metcalfe et al,⁴ who validated the Obstetric Comorbidity Index in a small study population based on ICD10 codes (Canadian version). As we aimed to validate the score as generated by Bateman et al, a few codes were changed to accommodate the Danish version of the ICD10 (the full list of comorbidities and their related diagnosis codes can be found in Table S1).

The concordance between the two versions of the ICD10 codes was confirmed by a skilled obstetrician (C.V.) and midwife (M.B.). For previous cesarean delivery, the code "O34.20" was determined to be insufficient in a Danish setting (due to coding practices) and information on a history of previous cesarean delivery was obtained from the Medical Birth Registry.

Presence of conditions diagnosed from 180 days prior to the day of conception through the delivery hospitalization was included in the model (Figure S1). Both primary and secondary diagnoses (A and B diagnoses) were included. A primary diagnosis is the main reason for each hospital contact. If relevant, secondary diagnoses may be added to identify additional diseases related to the hospital contact. Each condition was weighted as defined by Bateman et al and a summary score was generated. Maternal age was categorized as <20, 20-34, 35-39, 40-44, and >44 years at the day of delivery. The estimated scores of the maternal comorbidity index were evaluated on a continuous scale and stratified in the following seven categories: 0, 1-2, 3-4, 5-6, 7-8, 9-10, and >10.

2.4 | Study outcome

End-organ injury and maternal death were defined as a composite measure from the start of delivery admission to the hospital through 30 days postpartum (Figure S1). End-organ injury was defined as above according to Metcalfe et al's translation of Bateman et al's ICD9 codes to ICD10 codes (Table S2). We only deviated from the definition by Metcalfe et al by excluding ICD10 codes O99.4 and I50, since both diagnoses were represented in the definition of the comorbidity scores and we wanted to avoid including diagnoses in both the comorbidity and outcome definitions.

2.5 | Statistical analyses

The prevalence of death or end-organ injury (including each specific component of the combined outcome) was estimated at the level of pregnancy unit. The distribution of each potential predictor was assessed based on whether the outcome occurred. We tabulated the number of pregnancies assigned to each value of the Obstetric Comorbidity Index, and calculated the Brier score to evaluate the ability of the index to predict the outcome. The Brier score is calculated as the squared distance between the patient's observed outcome and the predicted probability. Zero represents perfect prediction.¹² The discriminative ability of the Obstetric Comorbidity Index was assessed by calculating the area under the receiver operating characteristic curve (AUC). Using logistic regression, odds ratios (ORs) and 95% confidence interval (CI) were calculated to examine the association between the derived Obstetric Comorbidity Index and the outcome using both the continuous Obstetric Comorbidity Index scale and the seven categories. We accounted for dependency between pregnancies (several pregnancies by the same mother) in all analyses by clustering the pregnancies by mothers using the sandwich estimator for variance.

As sensitivity analyses, we repeated the analysis with a subset of the outcomes most likely to be acute (^bmarked in Table S2) to reduce

the likelihood that the outcome is merely a confirmation of a pregnancy-related diagnosis given at a postpartum follow-up control. We also extended the outcome time frame from delivery hospitalization to 180 and 365 days postpartum. The study population was smaller in these analyses, as we excluded pregnancies without full follow up, leaving respectively 853 148 and 825 668 pregnancies in each cohort. Further, all analyses were repeated using Metcalfe et al's⁴ time frames for deriving the comorbidity index and outcome—ie, 90 days prior to conception to delivery and from delivery to 3 months postpartum, respectively.

As a supplementary analysis, we adjusted our main analysis for maternal body mass index (body mass index (BMI; kg/m²) prior to pregnancy (<18.5, 18.5-24.9, 25-29.9, ≥30 BMI units), smoking status in early pregnancy (nonsmoking, smoking 1-10, smoking ≥11 cigarettes per day), and parity (0, 1, ≥2 prior parity) in a subcohort with full information (n = 615 171) to examine whether adding these potential confounders would enhance the predictive validity of the comorbidity index.

All analyses were performed using STATA 15.0 (StataCorp LP).

2.6 | Ethical approval

The study was approved by the Danish Data Protection Agency (journal number 2015-57-0008). According to Danish law, ethical approval is not required for register-based studies. All personal-level data were pseudo-anonymized and handled at secure servers at Statistics Denmark.

3 | RESULTS

Among the 876 496 pregnancies by 527 079 women, giving birth in Denmark from 1 July 2000 through 1 December 2014, the incidence of the outcome was 1.40% (n = 12 314), and the most frequent components were acute liver disease (0.98%, n = 8573) and status asthmaticus (0.27%, n = 2326) (Table 1). During the 15-year study period, 35 women died during hospitalization and up to 30 days postpartum.

The most common conditions contributing to the Obstetric Comorbidity Index, apart from higher age, were previous cesarean delivery, multiple gestation, and chronic renal disease, present in respectively 91 322 pregnancies (10.4%), 39 917 pregnancies (4.6%), and 28 320 pregnancies (3.2%) (Table 2).

The vast majority of 828 766 of the study population had an Obstetric Comorbidity Index score <3 (94.6%), and 561 805 (64.1%) had no records of any of the conditions included in the index (Table 3; Figure S2). Only 3044 (0.3%) deliveries were associated with a score >6. In women with a score of null, 4854 (0.9%; 95% CI 0.8-0.9) experienced the composite outcome (end-organ injury or death). The risk increased with increasing comorbidity score and in women with a score >10, 11 women (10%; 95% CI 5.1-17.2) experienced a composite outcome (Figure 1; Table 3). The Obstetric Comorbidity Index showed a high ability to predict an outcome with a Brier score of 0.01 when calculated both on a continuous scale and categorically (Table 3). The discrimination ability was virtually the same when

TABLE 1 Distribution of composite outcome according to its specific morbidity component in Danish new mothers from 2000 through 2014

Outcome	All	%
Study population	876 496	
Any outcome (end-organ injury or death)	12 314	1.40
Components of any outcome ^a		
Acute heart failure	144	0.02
Acute liver disease	8573	0.98
Acute myocardial infarction	13	0.00
Acute renal failure	61	0.01
Acute respiratory distress syndrome/respiratory failure	47	0.01
Coma	18	0.00
Delirium	9	0.00
Disseminated intravascular coagulation/coagulopathy	296	0.03
Puerperal cerebrovascular disorders	467	0.05
Pulmonary edema	52	0.01
Pulmonary embolism	212	0.02
Sepsis	200	0.02
Shock	118	0.01
Status asthmaticus	2326	0.27
Status epilepticus	10	0.00
Death	35	0.00

^aNonexclusive as some experience more than one outcome.

calculated on a continuous and categorical scale with an AUC of 0.65 (95% CI 0.64-0.65) and 0.64 (95% CI 0.64-0.64), respectively.

The odds of the combined outcome increased by 41% (OR 1.41, 95% CI 1.39-1.42) with each one-point increase in the Obstetric Comorbidity Index. When the score was categorized, the logistic regression analysis showed a trend for ORs to increase from 2.34 (95% CI 2.25-2.44) to 12.75 (95% CI 6.20-26.23) in pregnancies with an Obstetric Comorbidity Index score of 1-2 and >10 compared with pregnancies with a score of 0. Between the categories of 3-4 and 5-6, the OR did not differ significantly: OR 5.16 (95% CI 4.81-5.54) and OR 4.84 (95% CI 4.31-5.44), respectively.

The sensitivity analysis defining outcomes as diagnoses most likely to reflect acute disease, yielded a slightly smaller proportion with an outcome within each category of comorbidity, yet the trend of increasing ORs was similar ranging from an OR of 1.59 (95% CI 1.52-1.67) for the category of 1-2 to and OR of 11.03 (95% CI 4.90-24.83) for the category of >10 compared with the category score of 0 (Table S3). Extending the time frame for having an outcome, from hospitalization to 180 and 365 days postpartum, respectively, yielded virtually the same results as the main analysis (Tables S4 and S5). When using the time frames as specified by Metcalfe et al,⁴ the distribution in comorbidity score categories (the stratification capacity) was very similar, and results showed an AUC of 0.64 for the continuous and

for the categorical scale (Table S6). When adjusting the main analysis for parity, BMI, and smoking in the subcohort with full information (n = 615 171), results remained very similar, although the associations were slightly weaker (Table S7). The AUC for both continuous and categorical exposures was 0.66 with a Brier score of 0.2.

4 | DISCUSSION

In an unselected cohort, representing all births in Denmark from 2000 through 2014, this validation study of the Obstetric Comorbidity Index proved a moderate ability to discriminate and to predict end-organ injury and death in a nationwide cohort in Denmark. The validity of the index proved to be robust in all sensitivity analyses. Including BMI, parity, and smoking in the analysis did not meaningfully enhance the predictive validity of the index.

The main strength of our study is the large nationwide cohort including all registered deliveries in Denmark, limiting selection bias. With linkage between registers, it holds a high degree of completeness of relevant data, enabling virtually full follow up.^{8,9,13}

Misclassification of some conditions and outcomes (excluding death) is possible, including less severe conditions such as gestational hypertension and also preeclampsia (especially severe preeclampsia), which are known to be underreported in administrative data.^{9,14-17} In identifying comorbidities, as well as end-organ injury, we only used main chapters and diagnoses (described by three or four characters in the ICD10 codes) (Table S1). Main chapters and diagnoses have higher validity compared with subclasses of diseases.^{9,16} Reviews of the Danish Medical Birth Register and the National Patient Registry report varying but generally high positive predictive values of diagnoses, depending on clinical speciality and severity. Overall, both registers are considered relatively complete and valuable tools for epidemiologic research.^{9,16} Due to the nature of the data, we expect any misclassification of conditions and outcome to be independent and thus any bias would be towards the null in the OR estimates and likely lead to smaller c-statistics. Coding practices may have varied during the long study period, and it is not known whether this affected the associations.

Two validation studies of the Obstetric Comorbidity Index have previously been performed. Bateman et al used ICD9-CM data from Medicaid (representing 1 854 823 pregnancies) to develop the index based on two-thirds of the dataset, and validated the tool on the remaining one-third.³ Metcalfe et al validated the index in a cohort of 5595 Canadian women using ICD10-CA data.⁴ Overall, our results are consistent with the findings from these studies. In our nationwide cohort, the risk of experiencing end-organ injury was small (1.40%) and slightly lower than found by Metcalfe et al⁴ (1.7%). In comparison, Bateman et al report the risk of end-organ injury or death to be 1.16%.³ In total, 35 mothers in Denmark died within the first 30 days postpartum over a 15-year period. All conditions included in the comorbidity index were more prevalent in pregnancies with an outcome than in pregnancies without the outcome in the US study and in ours.³ Metcalfe et al did not report the distribution by

TABLE 2 Distribution of conditions in the maternal comorbidity index stratified according to the occurrence of the study outcome (end-organ injury or death) in deliveries in Denmark from 2000 through 2014

Variables	Weight*	All	%	Outcome	%
Study population		876 496		12 314	
Maternal age at delivery, y					
<20	—	11 893	1.4	136	1.1
20-34	—	695 872	79.4	9190	74.6
35-39	1	142 993	16.3	2494	20.3
40-44	2	24 636	2.8	465	3.8
>44	3	1102	0.1	29	0.2
Alcohol abuse	1	834	0.1	16	0.1
Asthma	1	7000	0.8	2333	18.9
Cardiac valvular disease	2	398	0.0	18	0.1
Chronic congestive heart failure	5	9	0.0	5	0.0
Chronic ischemic heart disease	3	160	0.0	7	0.1
Chronic renal disease	1	28 320	3.2	677	5.5
Congenital heart disease	4	4974	0.6	199	1.6
Drug abuse	2	1015	0.1	25	0.2
Gestational hypertension	1	11 982	1.4	300	2.4
Human immunodeficiency virus	2	148	0.0	<5	0.0
Mild/unspecified preeclampsia	2	19 535	2.2	647	5.3
Multiple gestation	2	39 917	4.6	1736	14.1
Placenta previa	2	5265	0.6	98	0.8
Preexisting diabetes mellitus	1	2559	0.3	95	0.8
Preexisting hypertension	1	7841	0.9	250	2.0
Previous caesarean delivery	1	91 322	10.4	1497	12.2
Pulmonary hypertension	4	16	0.0	<5	0.0
Severe preeclampsia	5	7862	0.9	333	2.7
Sickle cell disease	3	425	0.0	15	0.1
Systemic lupus erythematosus	2	336	0.0	10	0.1

*Weights according to Bateman et al.³

outcome. Most conditions were less prevalent in the Danish cohort than in the US cohort, possibly due to a healthier study population and differences in coding practice. The US cohort was identified in Medicaid, a healthcare insurance providing health coverage for

people with low income, and with administrative claims data from both inpatient and outpatient settings, whereas the Danish study population consisted of an unselected nationwide cohort with registration of hospital diagnoses only. Overall, differences in prevalence

TABLE 3 Validation of the maternal comorbidity index as derived by Bateman et al.³ in a nationwide cohort (n = 876 496) from 2000-2014

Bateman score	Stratification capacity		Distribution of outcome		Association		Discrimination ability		Calibration accuracy		
	n	%	n	%	OR	95% CI	AUC	95% CI	Proportion with outcome (%)	95% CI	Brier score
Continuous					1.41	1.39-1.42	0.65	0.64-0.65			0.01
0	561 805	64.1	4854	39.4	Ref.	—	0.64	0.64-0.64	0.9	0.8-0.9	0.01
1-2	266 961	30.5	5345	43.4	2.34	2.25-2.44			2.0	1.9-2.1	
3-4	34 409	3.9	1482	12.0	5.16	4.81-5.54			4.3	4.1-4.5	
5-6	10 277	1.2	416	3.4	4.84	4.31-5.44			4.0	3.7-4.4	
7-8	2540	0.3	165	1.3	7.97	6.54-9.72			6.5	5.6-7.5	
9-10	394	0.0	41	0.3	13.33	9.03-19.68			10.4	7.6-13.9	
>10	110	0.0	11	0.1	12.75	6.20-26.23			10.0	5.1-17.2	

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; OR, odds ratio.

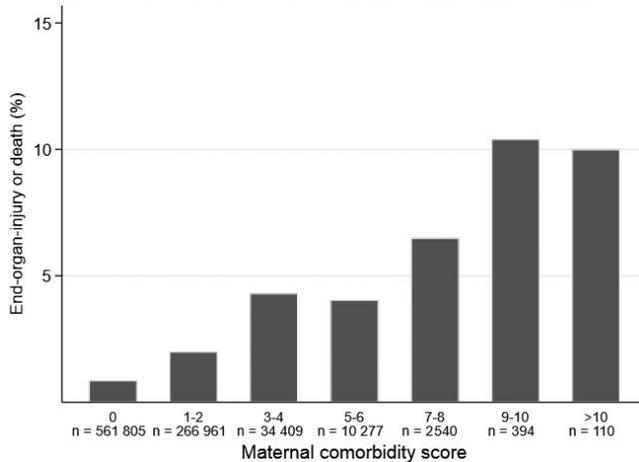


FIGURE 1 Observed incidence of outcome by maternal comorbidity index score in the Danish childbearing population, 2000-2014

of the conditions and outcomes across the three populations may be attributable to variation in disease patterns across countries, differences in coding practices and, for Metcalfe et al, the use of other time periods for generating the comorbidity score and identifying outcomes.

When deriving the index and the outcomes from the ICD10 codes following the translated specification from ICD9 to ICD10 by Metcalfe et al, we noticed that the ICD10 codes O99.4 and I50 were represented both in the generation of the comorbidity index and in the definition of the outcome. This likely inflated the *c*-statistics and measures of association reported by Metcalfe et al. We decided to exclude these codes from the outcome definition. More broadly, it may be uncertain whether the outcomes are truly picking up incident events or are just reflecting prevalent issues that were also captured by the comorbidities. In particular, the vast majority of outcomes were due to acute liver diseases and status asthmaticus. It is possible that coding of these conditions during the delivery hospitalization reflects coding of pre-existing conditions rather than true end-organ injury. To assess this, we repeated the analysis with a subset of the outcomes representing the diagnoses mostly likely to be incident and acutely occurring (Table S3). In this analysis, the odds of the combined outcome increased 1.33 with each one-point increase in the Obstetric Comorbidity Index, compared with 1.41 in the main analysis. Further, although the prevalence of an outcome was lower for all categories, the index still yielded a moderate ability to discriminate with an AUC of 0.60. All status asthmaticus cases disappeared when restricting the outcomes to the ones considered acute (as outlined in Table S3). Further, in 96.4% of deliveries with an asthma outcome, the mother had a diagnosis of asthma prior to 1 year before conception. Few patients experienced an end-organ injury from other causes. This may be explained by the healthy pregnant population in Denmark, high safety in maternity care leading to very low maternal mortality (estimated at 4/100 000 births by WHO¹⁸), and coding practices.

In our study, the Obstetric Comorbidity Index performed in accordance with previous findings. Our findings suggest an increase in

risk of the outcome with each one-point increase on the comorbidity scale similar to the increase found in the other studies,^{3,4} with an OR of 13.33 and 12.75 in women with pregnancies scoring 9-10 and >10, respectively, compared with women with pregnancies scoring 0. For comparison, Metcalfe et al found an OR for end-organ injury of 28.7 in the group of women with pregnancies with a score of 9-10.⁴ A logistic regression model predicting the outcome with the score as a continuous independent variable, yielded an OR per point increase of 1.37 in the study by Bateman et al,³ which was remarkably similar to our result of 1.41. All three studies had a comparable ability to discriminate with AUC between 0.64 and 0.70 for categorized scores (our findings and those of Metcalfe et al, respectively), and an AUC of 0.68 using the score as a continuous independent variable.³ In summary, despite some differences in prevalence of conditions and outcomes between the three cohorts, our results suggest that the Obstetric Comorbidity Index performs as expected, and in accordance with results from the USA and Canada, in an unselected nationwide cohort. Reassuringly for researchers not having access to information on parity, BMI or smoking (often considered confounders in reproductive epidemiology), adding these factors to the model did not enhance the quality of the model. This also suggests that the index can be used in other populations with a different health profile than the Danish. It must be noted though that *c*-statistics might not always be useful for assessing the value of additional variables in a prediction model.¹⁹

5 | CONCLUSION

Despite potential weaknesses in the outcome definition, the results suggest that the index may be a valid instrument for summary estimates of obstetric patients' burden of disease across different populations as well as a useful tool to control for confounding in epidemiologic and health services research. Finally, the index may potentially serve as a clinical screening tool for detecting high risk obstetric patients to identify women in need of a highly specialized hospital setting and, conversely, in a healthcare system stressed by economic constraints, to identify women of low risk who may need less obstetric surveillance during pregnancy.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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