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Examining the effect of maternal obesity on outcome of labor induction in patients with preeclampsia

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Abstract

OBJECTIVE—The objective of this investigation was to evaluate the effect of maternal obesity, as measured by prepregnancy body mass index (BMI), on the mode of delivery in women undergoing indicated induction of labor for preeclampsia.

STUDY DESIGN—Following IRB approval, patients with preeclampsia who underwent an induction of labor from 1997–2007 were identified from a perinatal information database, which included historical and clinical information. Data analysis included bivariable and multivariable analyses of predictor variables by mode of delivery. An artificial neural network was trained and externally validated to independently examine predictors of mode of delivery among women with preeclampsia.

RESULTS—Six hundred and eight women met eligibility criteria and were included in this investigation. Based on multivariable logistic regression (MLR) modeling, a five unit increase in BMI yields a 16% increase in the odds of cesarean delivery. An artificial neural network trained and externally validated confirmed the importance of obesity in the prediction of mode of delivery among women undergoing labor induction for preeclampsia.

CONCLUSION—Among patients who are affected by preeclampsia, obesity complicates labor induction. The risk of cesarean delivery is enhanced by obesity, even with small increases in BMI. Prediction of mode of delivery by an artificial neural network performs similar to MLR among patients undergoing labor induction for preeclampsia.

Keywords

Obesity; severe preeclampsia; cesarean delivery; body mass index

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Among women who are diagnosed with preeclampsia, the risk of cesarean delivery increases with increasing prepregnancy BMI.

Introduction

Preeclampsia complicates 3–4% of all pregnancies and increases the morbidity and mortality for both the mother and fetus following clinical diagnosis.¹ Despite prior investigations of putative causative mechanisms for preeclampsia, the underlying pathophysiology is still uncertain. As the cause of preeclampsia is unknown, the clinical interventions for prevention or treatment are also lacking.² Currently, the only known cure for preeclampsia requires delivery of the fetus and placenta.³ Many of these curative deliveries result in iatrogenic preterm births and account for 15% of the total preterm births in the United States annually.¹

Prior research efforts have focused on identification of those mothers at greatest risk of labor complications. Women with preeclampsia requiring an induction of labor have an increased risk of cesarean delivery.^{4–7} Recently, several investigators have demonstrated that cesarean delivery increases the risk for future pregnancy complications including miscarriage, stillbirth, uterine rupture, and repeat cesarean surgical complications.^{8–10} Strategies directed at reducing the rate of cesarean delivery, and thus cesarean-related complications have been suggested.^{11, 12} However, the rate of cesarean delivery in the United States in 2006 was 31%, the highest on record.¹³ Proposed mechanisms for the increase in cesarean rates include increased attention to pelvic floor protection, maternal demand for cesarean, legal awards for birth injury in vaginal delivery, and increased incidence of pregnancy comorbidities.^{14, 15}

Obesity is a well known risk factor for cesarean delivery.^{16–18} Mothers who are obese at the time of delivery have increased risks for labor dystocia, fetal macrosomia, and fetal distress. Each of these factors has been identified to contribute to an increased cesarean delivery rate in obese patients.^{19, 20} As obesity becomes epidemic in the United States, the cesarean delivery rate is anticipated to continue to rise.

Obesity is also associated with an increased risk of maternal preeclampsia.^{16, 17} Obese women have more than a three-fold increased risk of preeclampsia when their BMI exceeded 30 kg/m².^{21, 22} The increased risk of preeclampsia secondary to maternal obesity is also noted to be a potentially reversible risk factor. One investigation suggested that a 4.5 kg (10 lbs) weight reduction prior to pregnancy may result in a 50% reduction in preeclampsia risk assuming no unmeasured confounding existed in this investigation.²³ Thus, both prepregnancy and antepartum counseling of obese women concerning optimal weight management and pregnancy weight gain could impact the risk of preeclampsia complicating pregnancy and possibly reduce the rate of cesarean delivery. Unfortunately, little has been described in the literature concerning pregnancy risk in obese women who develop preeclampsia. Additional information is needed to better counsel obese women concerning adverse pregnancy outcome when obesity and preeclampsia coexist. The purpose of this investigation was to examine the impact of BMI on mode of delivery among women undergoing induction of labor for the indication of preeclampsia after controlling for important confounders using traditional regression and artificial neural network analyses.

Methods

The Institutional Review Board approved this retrospective cohort investigation prior to data acquisition and analysis. All patients with a singleton gestation complicated by preeclampsia who delivered at the Medical University of South Carolina, a tertiary referral center, from July 1997 to June 2007 were identified using a perinatal research database of linked maternal-neonatal variables. Preeclampsia and severe preeclampsia were diagnosed according to definitions provided by the American College of Obstetrics and Gynecology

(ACOG).²⁴ Briefly, over the time period of this study, patients received a diagnosis of preeclampsia if 300 mg or greater of protein was excreted in a 24 hour urine collection with elevation of blood pressure of greater than 140 mmHg systolic or greater than 90 mmHg diastolic obtained on two assessments at least six hours apart. Inclusion criteria included only those patients with a singleton gestation who underwent an induction of labor for the indication of preeclampsia. Patients were excluded for the following indications: prior cesarean section for desired or medically indicated repeat surgical delivery, placenta previa, abruption, fetal malpresentation, aneuploidy, maternal human immunodeficiency virus, and nonreassuring fetal status at presentation as these indicators would have contraindicated an induction of labor. Covariates were obtained from the perinatal research database for each patient as follows: maternal age at the time of delivery (years); maternal race (African-American, Caucasian, Hispanic); nulliparity; gestational age at delivery (weeks); neonatal birth weight (grams); prepregnancy BMI (kg/m^2) calculated by height and self-reported prepregnancy weight; cervical ripening (use of misoprostol or dinoprostone during induction); severe preeclampsia; intrauterine growth restriction (IUGR) as defined by ultrasound estimated fetal weight $< 10^{\text{th}}$ percentile for gestational age; chronic hypertension defined as hypertension prior to the onset of pregnancy or diagnosed by systolic or diastolic blood pressure greater than 140 or 90 respectively on two occasions prior to 20 weeks gestation; diabetes (pregestational Type 1 or Type 2 diabetes); fetal oligohydramnios defined as a four quadrant amniotic fluid index of < 5 cm or absence of a 2 cm pocket of amniotic fluid; maternal fever during labor defined as a oral body temperature of $\geq 100.4^{\circ}\text{F}$; epidural use; maternal smoking defined as any use of cigarettes during pregnancy; and excessive weight gain in pregnancy defined as greater than 50 lbs documented weight gain in pregnancy.²⁵

Statistical Analysis

Bivariable analysis was conducted using the Wilcoxon rank sum test for examination of continuous variables (maternal age, BMI, gestational age at delivery, fetal birth weight) by mode of delivery. Proportions were compared by mode of delivery using chi-square tests or Fishers exact test as appropriate. Unadjusted and adjusted odds ratios and associated 95% confidence intervals were calculated for each covariate based on fitted simple and multiple logistic regressions for the outcome cesarean delivery. A multiple logistic regression was conducted to estimate the effect of prepregnancy BMI on the risk of cesarean delivery with the following additional variables included in the model: maternal age, nulliparous, cervical ripening, IUGR, diabetes, chronic hypertension, maternal fever, epidural use, and excessive weight gain in pregnancy. These variables were selected based on prior publications and clinical observations.^{11, 15, 26} Continuous variables were assessed for linearity in the logit and transformed as necessary. Model adequacy was assessed using the Hosmer Lemeshow goodness-of-fit (GOF) test. The area under the receiver operator characteristic (ROC) curve was used to assess the predictive accuracy of the fitted multivariable model. All statistical tests were two-sided with alpha set to 0.05 to control for Type I error. Data analysis was performed with SAS v.9.1.3 (SAS, Cary, NC).

A feedforward artificial neural network (ANN) was utilized on a Matlab v. 7.0.1 platform (Mathworks Inc, Natick, MA). This ANN was programmed and deployed as open source code for use in classification problems.^{27, 28} The outcome of interest was defined as mode of delivery (vaginal delivery or cesarean delivery). The ANN algorithm required that the data be divided among three subgroups: a training dataset, a testing dataset, and an external validation dataset. The training dataset comprised observations from half the subjects who underwent induction of labor for preeclampsia and was used to train the ANN. The testing dataset made up 25% of data observations from subjects undergoing induction of labor for preeclampsia and was responsible for the early stopping procedure to prevent overfitting of

the ANN model. The remainder of subjects observations (25%) were then used for external validation of the ANN model in classification of patients into predicted mode of delivery (vaginal delivery-successful induction or cesarean delivery). This allocation algorithm has been suggested as providing optimal training of the ANN by our lab and prior authors.^{27,28, 29} The allocation of patients between the three groups (training, testing, or external validation) was performed at random using a computerized randomization algorithm in Matlab v 7.0.1 (Mathworks Inc, Natick, MA). Modeling using this ANN algorithm was repeated for 25 iterations to determine stability of performance using unique randomized training, testing, and external validation groups with each model. Variable selection was completed for each model to determine the variables most sensitive to the prediction of mode of delivery among patients undergoing induction of labor for preeclampsia. The number of variables needed to achieve maximum prediction accuracy was determined by plotting the inclusion of variables in order of sensitivity to the outcome (mode of delivery) against achieved area under the ROC curve. Area under the ROC curve was reported for each of 25 optimally trained ANN models and summarized across models using median and interquartile range.

Results

Of 893 patients identified with preeclampsia, 608 patients met eligibility criteria and were included in the analyses. Demographic and outcome information for these pregnancies is shown in Table 1. (Table 1). Of note, patients who ultimately had a cesarean section (n=195) were more likely to be nulliparous, diabetic, have excessive weight gain in pregnancy, or have a higher BMI relative to women experiencing a vaginal delivery (n=413). It was also noted that patients who had a successful vaginal delivery after induction of labor had a higher incidence of epidural use (72% cesarean and 85% vaginal, $p<0.001$). There were no significant differences between cesarean delivery and vaginal delivery groups with respect to maternal age, maternal race, gestational age at delivery, birthweight, cervical ripening, severe preeclampsia, IUGR, chronic hypertension, oligohydramnios, smoking, or maternal fever.

Multiple Logistic Regression Model

In order to assess the effect of maternal, prepregnancy BMI on the odds of having a cesarean delivery among women with preeclampsia, a multiple logistic regression analysis was performed. Model fit and predictive accuracy were found to be adequate by Hosmer-Lemeshow GOF ($p=0.5$) and area under the ROC curve ($AUC=0.74$), respectively. Results of this analysis are presented in Table 2. (Table 2) After adjusting for all covariates, the association of increased maternal BMI and increased risk of cesarean delivery remained statistically significant. Specifically, a 5 unit increase in prepregnancy BMI yields a 16% increase in the odds of cesarean delivery relative to vaginal delivery ($OR = 1.16$, 95% CI = 1.04 to 1.31; $p = 0.01$). Patients with maternal fever, diabetes, chronic hypertension, a growth restricted fetus, severe preeclampsia, or nulliparity were noted to have an increased risk of cesarean delivery. Interestingly, patients who choose to have an epidural for labor anesthesia were noted to have a reduction in the odds of cesarean delivery when undergoing induction of labor for preeclampsia.

Feedforward Artificial Neural Network Model

608 eligible patients who were used for MLR modeling were included in the ANN model. The patients were randomly assigned to either the training (n=304), testing (n=152), or external validation (n=152) groups by random allocation. Twenty-five independent models were trained, tested, and externally validated using this allocation. In each model, the external validation dataset was not used for testing or training of that same ANN model. To

determine the number of variables needed by each model to provide the greatest area under the receiver operator curve, a plot of the variables included in order of sensitivity to the outcome against area under the receiver operator curve was examined. A summary of variables used in the twenty five optimized ANN models for classification of mode of delivery are provided in Table 3 (Table 3). For these optimized feedforward ANN models, the median performing ANN had an area under the receiver operator curve of 0.75 (Q1: 0.74, Q3: 0.77).

Comment

As obesity becomes an epidemic in the U.S., studies of populations that are affected adversely by this change will be increasingly important. Realizing that two-thirds of the U.S. population is currently overweight or obese, this investigation is applicable to a large group of women who will both plan and complete pregnancy while either being classified as overweight or obese.^{17, 30, 31} Prior investigations have suggested that maternal obesity has an adverse pregnancy effect through both increased risk of preeclampsia and increased risk of cesarean delivery.^{17, 22} This investigation sought to evaluate the impact of maternal obesity on the mode of delivery among women undergoing an induction of labor for the diagnosis of preeclampsia. In this population, even small increases (5 units) in BMI was associated with a 16% increased odds of cesarean delivery. This increase in cesarean delivery is both statistically and clinically significant. Increased cesarean delivery results in increased healthcare costs and has also been associated with adverse future pregnancy outcomes. Clinicians need additional data to counsel patients on methods for improved pregnancy outcome and this investigation adds to the expanding volume of literature associating maternal obesity with adverse pregnancy outcomes. When assessing the results of this model performed in the population described, a modest weight reduction that results in a 5 point decrease in BMI would be anticipated to reduce the risk for cesarean delivery by 14% ($1/1.16=0.86$). If there were a 10 point decrease in BMI, the risk for cesarean delivery would be reduced by 25% ($1/1.34=0.75$). These suggested reductions in cesarean delivery are limited to the population studied in this model and may not apply to the general population as unaccounted variability exists in this model as shown in the receiver operator characteristic curve.

As anticipated, this study found an increased odds of cesarean delivery among women who were older, nulliparous, had diabetes or chronic hypertension, experienced fever in labor, severe preeclampsia, or had an IUGR fetus. Nulliparous women have long been recognized to be at risk for cesarean relative to women who have successfully delivered a prior child.³ These women are also considered a group at the greatest risk of experiencing preeclampsia (approximately 7%) complicating their pregnancies. Thus, women who are nulliparous and at risk for preeclampsia in future pregnancy, should be counseled during routine primary care visits that maintenance of normal weight reduces the risk for both preeclampsia and cesarean delivery.^{21, 32} Women with diabetes or hypertension complicating pregnancy have also previously been reported to have increased risk for cesarean delivery.²³ Women who enter pregnancy with diabetes may modify their risk by achieving a modest decrease in maternal obesity prior to pregnancy.³²

An important finding from our data includes the reduction in the odds for cesarean in women receiving an epidural during an induction of labor for preeclampsia. In this investigation, a 68% decrease in the odds for cesarean delivery was observed. This was striking, as this is a potentially modifiable risk factor at the time of labor induction for preeclampsia. Prior investigations have reported a reduction in uterine blood flow resistance as measured using Doppler velocimetry following epidural analgesia.^{33, 34} It is plausible that this effect may improve uteroplacental hemodynamics among women with

preeclampsia resulting in improved maternal support of the fetus during labor induction. However, this retrospective investigation is certainly limited in its ability to suggest causation for this effect. Population based cohorts need to examine the potential for epidural to improve the likelihood for vaginal delivery among women with preeclampsia.

The use of an artificial neural network as an independent model for prediction of mode of delivery among women undergoing induction of labor for preeclampsia is both novel and applicable to gaining a greater understanding of the relationship between cause and effect in labor induction outcomes among women with preeclampsia. In this investigation, the ANN was able to utilize as few as 3 to 5 variables to achieve 0.74 to 0.77 area under the receiver operator curve. This suggests that there are factors involved in determination of the mode of delivery that might be quite predictive even if only a few are utilized. Clinically, nulliparity and diabetes would be anticipated to influence the likelihood of cesarean delivery. The most often selected variables for inclusion in the optimal ANN model were similar to those selected by the MLR model (nulliparity, diabetes, epidural, BMI, maternal age, severe preeclampsia, and maternal fever). It is notable that the ANN selected epidural use as the third most sensitive predictor utilized in the prediction of mode of delivery. As ANN models are particularly applicable to classification problems when relationships between dependent and independent variables are either complex or unknown, there was distinct possibility that application of this technology to the prediction of labor induction outcome could allow better risk stratification for patients with preeclampsia. This methodology may also suggest potential modifiable factors (i.e. epidural use) that may improve success (vaginal delivery) among women undergoing labor induction. Those patients who had a low chance of achieving a vaginal birth might be preselected for cesarean delivery and avoid complications associated with failed induction of labor and cesarean delivery. Alternatively, those patients with a low likelihood of success with labor induction as predicted by the ANN might be further investigated in a prospective manner to identify interventions or modifiable risk factors that may improve success in labor induction.

The ANN is novel in that it can “learn” directly from the data and accommodate intrinsic nonlinear components of the biologic pathophysiology. In fact, prior investigations have found ANNs to outperform MLR modeling in up to one-third of cases.²⁹ In this investigation, the ANN model was found to be similar to that of the MLR model. This may be secondary to the scarcity of continuous variables utilized in the pool of predictor variables included in both models. However, strengths of the ANN model algorithm utilized in this investigation include the use of an early-stopping procedure to prevent overfitting of data.^{27, 28} In this ANN, the learning procedure requires continual adjustment of weights of the individual connections between layers until the resulting error is minimized. The error is defined by the application of testing data group to the ANN at different stages of learning. At the point when the ANN fails to improve prediction in the test data set, the learning of the ANN is halted. This early-stopping procedure prevents overfitting and defines the optimally trained, final ANN. Once an optimally trained ANN is completed, it is possible to deploy the model for independent validation or investigational use in clinical practice. Thus, ANN modeling can be applied in a bench to bedside manner in clinical obstetrics.

Clearly, obstetricians will face increasing rates of both preeclampsia and cesarean delivery due, in part, to the obesity epidemic in the United States.^{17, 22} Understanding the factors that increase the risk for cesarean delivery among women with preeclampsia may yield interventions that could reduce the cesarean delivery rate in this at risk population. As preeclampsia is a common complication of pregnancy, additional prospective studies should investigate novel interventions during a trial of labor to reduce cesarean delivery rates. The potential use of ANN modeling should also be further explored in obstetrical practice for both clinical outcomes prediction and risk stratification.

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Table 1**Demographic Factors by Mode of Delivery**

	Cesarean Delivery (n=195)	Vaginal Delivery (n=413)	P value
Maternal age (years)	24 (20–29)	22 (19–28)	0.06 *
Maternal Race n (%)	108 (55)	248 (60)	0.74 †
Black	56 (29)	105 (25)	
White	28 (14)	55 (13)	
Hispanic	3 (2)	5 (1)	
Other			
Gestational age at delivery (weeks)	38 (36–39)	38 (36–39)	0.9 *
Birthweight (g)	3030 (2100–3500)	2830 (2400–3250)	0.06 *
BMI (kg/m ²)	34 (30–40)	32 (28–37)	0.001 *
	N (incidence CD/total)	% Cesarean Delivery	P value
Nulliparous	136 / 386	35.2%	0.03 †
Yes	59 / 222	26.6%	
No			
Cervical ripening	139 / 407	34.2%	0.12 †
Yes	56 / 201	27.9%	
No			
Severe preeclampsia	70 / 202	34.7%	0.34 †
Yes	125 / 406	30.8%	
No			
IUGR	12 / 27	44.4%	0.16 †
Yes	183 / 581	31.5%	
No			
Diabetes	42 / 86	48.8%	< 0.001 †
Yes	153 / 522	29.3%	
No			
Chronic hypertension	33 / 81	40.7%	0.07 †
Yes	162 / 527	30.7%	
No			
Oligohydramnios	9 / 25	36.0%	0.67 †
Yes	186 / 583	31.9%	
No			
Smoking	13 / 45	28.9%	0.63 †
Yes	182 / 563	32.3%	
No			
Maternal fever	12 / 26	46.2%	0.12 †
Yes	183 / 582	31.4%	
No			
Epidural	140 / 491	28.5%	<0.001 †
Yes	55 / 117	47.0%	
No			
Excessive weight gain in pregnancy	10 / 13	76.9%	0.001 ‡
Yes	185 / 595	31.1%	
No			

CD = cesarean delivery

BMI = body mass index

IUGR = intrauterine growth restriction (<10thile fetal growth for gestational age)

* Wilcoxon rank sum test

[†] Chi square test

[‡] Fisher exact test

Table 2

Unadjusted and Adjusted Odds Ratios for Cesarean Delivery Among Patients with Preeclampsia

Variable	Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95%CI)	P value *	Odds Ratio (95%CI) [†]	P value *
BMI (kg/m ²) (per 5 unit increase)	1.16 (1.05, 1.28)	<0.01	1.16 (1.04, 1.31)	0.01
Maternal age (years)	1.03 (1.01, 1.06)	<0.01	1.04 (1.01, 1.08)	0.01
Race	0.99 (0.85, 1.15)	NS	1.04 (0.84, 1.27)	NS
Severe preeclampsia (y/n)	1.69 (1.22, 2.34)	<0.01	2.00 (1.36, 2.94)	<0.001
Nulliparous (y/n)	1.70 (1.20, 2.34)	<0.01	3.06 (1.91, 4.88)	<0.001
Cervical ripening (y/n)	0.90 (0.66, 1.23)	NS	0.84 (0.58, 1.22)	NS
IUGR (y/n)	2.23 (1.14, 4.37)	0.02	2.61 (1.16, 5.85)	0.02
Chronic hypertension (y/n)	2.21 (1.45, 3.36)	<0.01	1.83 (1.07, 3.14)	0.03
Diabetes (y/n)	2.72 (1.79, 4.13)	<0.001	2.47 (1.50, 4.07)	<0.001
Epidural (y/n)	0.38 (0.26, 0.54)	<0.001	0.32 (0.21, 0.49)	<0.001
Maternal fever (y/n)	2.30 (1.05, 5.06)	0.04	3.36 (1.29, 8.76)	0.01

* Wald Chi square test

[†] Adjusted odds ratios and confidence intervals were adjusted for maternal age, body mass index, maternal race, severe preeclampsia, nulliparity, cervical ripening, IUGR, chronic hypertension, diabetes, epidural use, and maternal fever.

BMI = body mass index

IUGR = intrauterine growth restriction

Table 3

Variable selection frequency for the 25 optimal ANN models.

Variable *	% of models utilizing variable
Nulliparous	88
Diabetes	72
Epidural	68
Body mass index (BMI)	58
Maternal Age	54
Severe preeclampsia	54
Maternal fever	24

* A median of 4 variables (Quartile 1 = 3; Quartile 3 = 5) were selected across the 25 optimal ANN models.